ELSEVIER
SAUNDERS

TEXTBOOK *of*
Veterinary Internal Medicine

SIXTH EDITION

STEPHEN J. ETTINGER
EDWARD C. FELDMAN

VOLUME 1

ABNORMAL LABORATORY FINDINGS

Robert M. Dufort

Chemistry Abnormalities:
Analyte

Alanine Aminotransferase (ALT or SGPTt)
Increased
Hepatocyte Damage
Drugs
Barbiturates
Carprofen
Cephalosporins
Glucocorticoids
Metronidazole
Thiacetarsamide
Trimethoprim/Sulfa
Endocrine Disease
Diabetes Mellitus
Hyperadrenocorticism
Hyperthyroidism
Hypoxia
Cardiopulmonary Disease
Thromboembolic Disease
Inflammation
Chronic Active Hepatitis (Doberman Pinschers)
Lymphocytic/Plasmacytic Hepatitis (Cats)
Enteritis
Pancreatitis
Peritonitis
Infection
Leptosporosis
Feline Infectious Peritonitis
Infectious Canine Hepatitis
Metabolic
Feline Hepatic Lipidosis
Storage Diseases
Neoplastic
Primary Neoplasms
Hepatocellular Adenomas
Biliary Carcinomas
Hemangiosarcomas
Hepatocellular Carcinomas
Metastatic Neoplasms
Assorted Carcinomas
Assorted Sarcomas
Toxic
Chemical
Copper
Carbon Tetrachloride
Petrochemicals
Heavy Metals
Arsenic
Lead
Mycotoxins
Trauma
Contusion
Herniation
Liver Lobe Torsion
Hepatocyte Regeneration
Hyperplastic Hepatic Nodules
Decreased
Decreased Liver Mass

Albumin
Increased
Dehydration (Increased Globulin and Total Protein)
Spurious
Decreased
Liver Failure
Atrophy
Fibrosis
Cirrhosis
Portosystemic Shunt
Renal Loss
Amyloidosis
Glomerulonephritis
Glomerulosclerosis
Malassimilation
Malabsorption
Maldigestion
Protein Losing Enteropathy
Exudative Skin Diseases
Vasculitis
Burns
Abrasions
Degloving Injuries
Neonates
External Blood Loss
Malnutrition
Dietary
Endoparasites
Compensatory
Chronic Effusions
Hyperglobulinemias
Multiple Myeloma

Alkaline Phosphatase (AP)
Increased
Cholestasis
Intrahepatic
Nodular Hyperplasia
Feline Hepatic Lipidosis
Cholangitis/Cholangiohepatitis
Extrahepatic
Cholangitis
Cholecystitis
Cholelithiasis
Biliary Neoplasia
Pancreatitis
Drugs (Canine)
Glucocorticoids
Anticonvulsants
Primadone
Phenobarbital
Bone Isoenzyme
Growth
Osteosarcoma
Hyperparathyroidism
Primary
Secondary
Renal Disease (Increase In Urine)
Endocrine
Hyperadrenocorticism (Canine)
Hyperthyroidism
Enteritis
Decreased
Analytical Artifact

Ammonia
Increased
Hepatic Failure
Cirrhosis
Portosystemic Shunt
Spurious
Hemolysis

Amylase
Increased
Pancreatic
Inflammation
Neoplasia
Necrosis
Pancreatic Duct Obstruction
Enteritis
Renal Disease (Decreased Filtration)

Anion Gap
Increased
Hyperglobulinemia
Metabolic Acidosis
Lactic Acidosis
Cardiac Arrest
Anoxia
Dehydration
Shock
Diabetic Ketoacidosis
Renal Failure
Hyperchloremic Acidosis
Gi Bicarbonate Loss
Toxic
Salicylate
Ethylene Glycol
Decreased
Hypoalbuminemia

Aspartate Aminotransferase (AST or SGOT)
Increased
Severe Hepatocyte Damage (Mitochondrial Enzyme)
Severe Muscle Insult
Erythrocyte Damage
Decreased
Cephalosporins (Canine)

Bicarbonate
Increased
Metabolic Alkalosis
Respiratory Acidosis
Drugs
Anesthetics
Narcotics
Cns Disease
Pulmonary Disease
Gastric Vomiting
Small Bowel Obstruction
Excessive Intravenous Bicarbonate Administration
Decreased
Metabolic Acidosis
Dehydration
Renal Failure
Respiratory Alkalosis
Panting
Tachypnea
Spurious
Delay in Analysis

Bile Acids
Increased
Decreased Liver Function
Cirrhosis
Portosystemic Shunt
Icterus
Cholerectics

Bilirubin, Direct
Increased
Prehepatic
Hemolytic Anemia
Cholestasis
Intrahepatic
Cirrhosis
Nodular Hyperplasia
Feline Hepatic Lipidosis
Cholangitis/Cholangiohepatitis
Extrahepatic
Cholangitis
Cholecystitis
Cholelithiasis
Biliary Neoplasia
Pancreatitis
Ruptured Gallbladder
Duodenal Perforation
Spurious
Hemolysis
Lipemia

Bilirubin, Indirect
Increased
Hemolytic Anemia
Severe Hepatic Disease

BUN
Increased
Prerenal Azotemia
High-Protein Diet
Dehydration
Heart Failure
Shock
Gi Hemorrhage
Increased Catabolism
Fever
Drugs
Tetracyclines
Renal Failure
Postrenal Azoternia
Urethral
Obstruction
Plant Awn
Urolith
Tear
Bladder
Obstruction
Urolith
Neoplasia
Polyp
Blood Clot
Rupture
Decreased
Diuresis
Polydipsia
Aggressive Fluid Therapy
Hemodialysis
Diabetes Insipidus
Hyperadrenocorticism
Drugs
Glucocorticoids
Liver Failure
Cirrhosis
Portosystemic Shunt
Urea Cycle Enzyme Deficiency
Low-Protein Diet
Malnutrition
Neonates

Calcium
Increased
Primary Hyperparathyroidism
Renal Secondary
Hyperparathyroidism
Toxic
Hypervitaminosis D
Over Supplementation
Calciferol Rodenticide
Jasmine Ingestion
Doronex Ointment (Calcipotriene)
Neoplasia
Lymphosarcoma
Multiple Myeloma
Anal Sac Adenocarcinoma
Carcinoma Bone Metastasis
Hemoconcentration
Hyperalbuminemia
Hypoadrenocorticism
Renal Failure (Chronic)
Osteolysis
Osteomyelitis
Osteoporosis
Granulomatous Disease
Acidosis
Spurious
Hyperalbuminemia
Decreased
Eclampsia
Renal Secondary
Hyperparathyroidism
Hypoalbuminemia
Hypomagnesemia
Hypoparathyroidism
Pancreatitis
Rhabdomyolysis
Dietary
Hypovitaminosis D
Excess Dietary Phosphorus
C-Cell Thyroid Tumors
Malabsorption
Hypercalcitoninism
Iatrogenic
Parathyroidectomy
Phosphate Enemas
Intravenous Phosphate Administration
Alkalosis
Ethylene Glycol
Spurious
Edta Contamination
Oxalate Contamination

Chloride
Increased
Dehydration
Metabolic Acidosis
Bromide Therapy
Decreased
Gastric Vomiting
Metabolic Alkalosis

Cholesterol
Increased
Cholestasis
Endocrine Disease
Hypothyroidism
Hyperadrenocorticoidism
Diabetes Mellitus
Postprandial
Dietary
Nephrotic Syndrome
Primary Hyperlipidemia
Idiopathic Hypercholesterolemia
Primary
Hyperchylomicronemia (Cats)
Lipoproteinlipase Deficiency (Cats)
Decreased
Protein-Losing Enteropathy
Portosystemic Shunt
Malassimilation
Malabsorption
Maldigestion
Lymphangiectasia
Starvation

ABNORMAL LABORATORY FINDINGS

Robert M. Dufort

Liver Failure
Hypoadrenocorticism

Cholinesterase
Decreased
Organophosphates
Carbamates

Cobalamin (B_{12})
Decreased
Bacterial Overgrowth

Creatinine
Increased
Azotemia
Prerenal
Renal
Postrenal
Decreased
Decrease Muscle Mass

Creatine Kinase (CK)
Increased
Muscle Inflammation
Immune Mediated
Eosinophilic Myositis
Masticatory Muscle Myositis
Endocarditis
Infectious
Toxoplasmosis
Neosporum Caninum
Nutritional
Hypokalemia (Polymyopathy)
Taurine Deficiency
Trauma
Exertional Myositis
Surgical
Intramuscular Injections
Hypothermia
Pyrexia
Prolonged Recumbency
Post-Infarct Ischemia
Cardiomyopathy
Disseminated Intravascular Coagulation

Fibrinogen
Increased
Inflammation
Pregnancy
Decreased
Liver Failure
Coagulopathies
Primary Hypofibrinogenemia

Folate
Increased
Bacterial Overgrowth

Fructosamine
Increased
Diabetes Mellitus
Decreased
Spurious
Hypoproteinemia
Anemia (False)

Gamma Glutamyltransferase (GGT)
Increased
Cholestasis
Intrahepatic
Extrahepatic
Drugs (Canine)
Glucocorticoids
Anticonvulsants
Primadone
Phenobarbital
Decreased
Spurious
Hemolysis

Globulin
Increased
Dehydration (Albumin and Total Protein)
Inflammation
Gammopathy
Monoclonal
Plasma Cell Myeloma
Ehrlichia
Dirofilariasis
Polyclonal
Chronic Inflammatory Disease
Feline Infectious Peritonitis
Dental Disease
Dermatitis
Inflammatory Bowel Disease
Parasitic Diseases
Immune-Mediated Diseases
Neoplasia
Decreased
Neonatal
Immunodeficiency
Congenital
Acquired
Blood Loss
Protein-Losing Enteropathy

Glucose
Increased
Endocrine
Acromegaly
Diabetes Mellitus
Hyperadrenocorticism
Pancreatitis
Stress (Cats)
Drugs
Intravenous Glucose Administration
Glucocorticoids
Xylazine
Progestagens (Ovaban and Others)
Decreased
Liver Failure
Endocrine
Hypoadrenocorticism
Hypopituitarism
Starvation
Neoplasia
Hyperinsulinism
Iatrogenic
Insulinoma
Idiopathic
Puppies
Toy Breed Dogs
Septicemia
Polycythemia
Leukemia
Glycogen Storage Disease
Artifact
Delayed Serum Separation

Iron
Increased
Hemolysis
Decreased
Chronic Blood Loss
Dietary Deficiency

Lactate Dehydrogenase (LDH)
Increased
Organ/Tissue Damage
Hemolysis
In Vivo
In Vitro
Hepatocytes
Muscle
Kidney
Spurious
Failure to Separate Serum From Rbcs

Lipase
Increased
Pancreatic Disease
Pancreatitis
Necrosis
Neoplasia
Enteritis
Renal Disease
Glucocorticoids

Magnesium
Decreased
Dietary
Diabetic Ketacidosis
Potential Causes:
Gastrointestinal
Malabsorption
Chronic Diarrhea
Renal
Glomerular Disease
Tubular Disease
Drugs
Diuretics
Amphotericin B
Others

Phosphorus
Increased
Reduced GFR
Renal
Acute
Chronic
Postrenal
Hemolysis
Hyperthyroidism
Neonates
Intoxication
Hypervitaminosis D
Jasmine Ingestion
Dietary Excess
Iatrogenic
Phosphate Enemas
Intravenous Phosphate Administration
Osteolysis
Hypoparathyroidism
Spurious
Delayed Serum Separation
Decreased
Hyperparathyroidism
Primary
Nutritional Secondary
Neoplasia
PTH-Like Hormone
C-Cell Thyroid Tumors
Insulin Therapy
Diabetic Ketoacidosis
Dietary Deficiency
Eclampsia
Hyperadrenocorticism

Potassium
Increased
Renal Failure
Distal RTA
Oliguric/Anuric
Postrenal
Obstruction
Ruptured Bladder
Spurious
Breed Idiosyncracy (Akitas)
Leukemias
Thrombocytosis
Collection In Potassium Heparin
Collection in Potassium EDTA
Hypoadrenocorticism
Acidosis
Diabetic Ketoacidosis
Diffuse Tissue Damage
Massive Muscle Trauma
Post-Ischemic Reperfusion
Dehydration
Hypoaldosterone
Drugs
Propranolol
Potassium-Sparing Diuretics
Ace Inhibitors
Decreased
Alkalosis
Dietary Deficiency (Feline)
Potassium-Free Fluids
Bicarbonate Administration
Drugs
Penicillins
Amphotericin B
Loop Diuretics
GI Fluid Loss (K^+-Rich)
Hyperadrenocorticism
Hyperaldosterone
Insulin Therapy
Renal
Postobstructive Diuresis
Renal Tubular Acidosis
Dialysis
Hypokalemic Periodic Paralysis
Burmese
Pit Bull
Renal Failure
Chronic Polyuria

Protein, Total
Increased
Dehydration (Albumin and Globulin)
Hyperglobulinemia
Spurious
Hemolysis
Lipemia
Decreased
Hemorrhage
External Plasma Loss
GI Loss
Overhydration
Liver Failure
Glomerular Loss

Sodium
Increased
Hyperaldosterone
GI Fluid Loss (Na^+-Poor)
Vomiting
Diarrhea
Diabetes Insipidus
Renal Failure
Dehydration
Insensible Fluid Loss
Fever
Panting
High Ambient Temperature
Decreased Water Intake
Limited Water Access
Primary Adipsia
Increased Salt Intake
Intravenous
Oral
Spurious
Serum Evaporation
Decreased
Hypoadrenocorticism
Diabetes Mellitus
GI Fluid Loss (Na^+-Rich)
Vomiting
Diarrhea
Hookworms
Burns
Chronic Effusions
Excess Adh
Diuretics
Hypotonic Fluids
Diet (Severe Sodium Restriction)
Psychogenic Polydipsia
Renal Failure (Polyuric)
Spurious
Hyperlipidemia

Thyroxine (T_4)
Increased
Hyperthyroidism
Anti-T_4 Autoantibodies
Decreased
Hypothyroidism
Nonthyroid Illness
Drugs
Corticosteroids
Phenobarbital

Triiodothyronine (T_3)
Increased
Hyperthyroidism
Anti-T_3 Autoantibodies
Decreased
Hypothyroidism

Trypsinogen-Like Immunoreactivity (TLI)
Increased
Pancreatitis
Postprandial
Decreased
Pancreatic Exocrine Insufficiency

CONTENTS

VOLUME I

SECTION I
Clinical Manifestations of Disease

General

Skin and Subcutaneous

Physique

Urogenital

Gastrointestinal

VOLUME II

SECTION XVIII Urinary System

SECTION XIX Hematology and Immunology

REFERENCES AND CLIENT INFORMATION SHEETS

SECTION I

Clinical Manifestations of Disease

"Tons de Rosa", pintado com a boca por Ruth Christensen

MAIO 2010

Sem	S	T	Q	Q	S	S	D
17						F	2
18	3	4	5	6	7	8	9
19	10	11	12	13	14	15	16
20	17	18	19	20	21	22	23
21	24	25	26	27	28	29	30
22	31						

ABRIL 2010

Sem	S	T	Q	Q	S	S	D
13				1	F	3	P
14	5	6	7	8	9	10	11
15	12	13	14	15	16	17	18
16	19	20	21	22	23	24	F
17	26	27	28	29	30		

JUNHO 2010

Sem	S	T	Q	Q	S	S	D
22		1	2	F	4	5	6
23	7	8	9	F	11	12	13
24	14	15	16	17	18	19	20
25	21	22	23	24	25	26	27
26	28	29	30				

General

CHAPTER 1

The Physical Examination of the Dog and Cat

Stephen J. Ettinger*

The physical examination begins long before the veterinarian ever touches the animal. The traditional teachings of *look*, *smell*, and *listen* are as important as ever. Excellent veterinarians avoid making diagnostic decisions driven by laboratory-derived data that bypass the physical examination, because correlation of all data is relevant to the determination of an appropriate diagnosis. This chapter is dedicated to the concept that veterinarians must bring together data from the history, physical examination, and diagnostic tests to care for an animal in the context of its life—including the life the owner envisions for the pet.

When possible, the animal's temperature and weight should be recorded before the veterinarian enters the examination room. This provides the nursing staff the chance to communicate with the animal's caretaker, gather pertinent information, note changes in weight, and identify the owner's concerns or requests.

This also is a good time for the staff to record any drugs currently administered, the prophylactic agents used (e.g., for heartworms and fleas), the animal's vaccination status, and its reproductive status (i.e., spayed, neutered, or last heat cycle).

The process should be as expeditious as possible, and every effort should be made to provide the client with an on-time, efficient examination. Reading material (magazines of interest to a wide variety of clients *and* their children) should be available if there is a likelihood of the pet's caretaker having to wait. Pet owners should be given an indication as to the doctor's schedule and the length of any delay. Providing the client with this information can offset frustration, anger, or anxiety. If the hospital has new client brochures about its methods and services, this is a good time to deliver these and to allow the client to browse through the material.

OBSERVING THE PET AND MEETING THE CARETAKER: THE HISTORY

Every veterinarian approaches a pet in his or her own way. With time, it becomes second nature. It is important to develop proper animal handling skills. Furthermore, clients observe a great deal during this process and may determine long before any recommendations are made just how trusting they will be. *Gentle care*, *compassion*, *concern*, and *attention* cannot be emphasized enough.

The process begins as the veterinarian enters the area where the owner and pet are waiting. A friendly greeting and a small but appropriate amount of banter are usually appreciated. An occasional client makes it clear that the veterinarian should get down to business immediately, and in such situations, it is wise to do so. People appreciate being greeted and particularly like being acknowledged. Asking owners about something specific to them assures that the veterinarian knows who they are. If the case is a referral, noting the distance traveled or offering a kind word about the trip acknowledges the client in an important way. It is not a technique easily taught, and it is not difficult to see whether the veterinarian "gets it" quickly and learns to communicate or simply turns away from such contact.

The importance of letting each client know that the veterinarian cares about him or her and the pet cannot be overemphasized. This must be done in a genuine way, reflected in dialog, attention, body language, and actions, and not in a lip service way, such as having "We care" or some other logo stamped on hospital leashes or stationery. Every successful veterinarian can relate tales about brilliant doctors whom clients dislike! The smartest veterinarian will never have the opportunity to demonstrate his or her skills if concern and caring are not expressed. In fact, clients are likely to be antagonistic toward veterinarians who fail to express compassion. Complaints are likely to be made much more frequently about an arrogant veterinarian than about one who is poorly trained or medically inadequate but friendly and compassionate. In a study comparing orthopedic surgeons, physicians with a disproportionately higher number of malpractice claims could be readily separated from those with fewer claims by evaluation of their examination room attitude. Not surprisingly, those with significant problems could consistently be identified.

A skilled veterinarian or physician understands that no part of the entire examination is as important as carefully listening to the client, therefore adequate time must be allowed for this in an environment that enhances the process. Examination rooms should be comfortable and inviting. Privacy for clients is necessary, because the situation may be a difficult one for them. Decisions that may seem routine and perhaps even minor to the veterinarian may not be perceived this way by the owner.

If there has been a delay, it is paramount that the doctor acknowledge this upon entering the room. The veterinarian should show clients the courtesy of recognizing that they have been waiting. Unnecessary interruptions should be minimized, and every hospital should have a policy in this regard. In a large critical care office, delays and interruptions do occur, but these must be limited. Phone calls should be restricted to those that are professionally relevant or urgent. When such

*The author wishes to acknowledge the assistance of Dr. Etienne Côté, Dr. Edward Feldman, Dr. Michael Schaer, and Ms. Linda Mills, who have reviewed this manuscript and made many favorable and helpful comments.

calls interrupt me with new clients, I explain that I need to speak with other owners about their hospitalized pet, yet I still make it clear that I am focusing on their pet's problems.

It is important to get the *owners'* version of the history and not one that has been "dictated" to them. For example, when questioned, the owners may acknowledge that a friend or family member told them about the supposed problem. Further questioning may determine that the owners have not noted any clinical signs that warrant such a concern.

There is no single technique for the examination process. Because this chapter is intended to explain my method of examination, I will delineate the regimen I follow, a process learned over decades of experience. When possible, I try to immediately make eye and physical contact with the pet. Even before beginning the process of taking a history, I try to welcome the pet. First, I make a brief attempt at greeting the animal by extending the back of my hand to its face. For this, cats and smaller dogs can be placed on the examination room table. Usually, with medium to large dogs, I kneel down on the examination room floor to greet the animal (I use a gardener's pad for my old, weakened, debilitated knees). Of course, some dogs and cats (those in cages, particularly) let me know beforehand that they are not ready for such a greeting. Then, I bypass the greeting and make a light comment to the owners about the pet not wishing me well (after all, I say, "Who likes going to the doctor?"). This begins a conversation with the owners that acknowledges the possibility of the pet being fearful and allows the owners to let me know how they feel about the process.

Clients are likely to want to tell the veterinarian what they know, think, or understand about the pet's problems. Regardless of how clearly and confidently clients relate their interpretation of the animal's difficulties, it is essential for the examiner to "go back to square one" and self-interpret the pet's problem. Nevertheless, the client's opinion should not be ignored, because this diminishes the trust being developed during this important part of the examination. I like to give clients a few minutes to express themselves, regardless of the relevance, because what they have to say is likely to be important to the ultimate outcome of the process. For example, clients may refuse to acknowledge how sick the pet is, or they may be worried about "cancer" or may focus on something that may not be pertinent. Clients' comments provide valuable insight into their concern and desire to care for the pet. There are different levels of owner commitment, and pets thus receive varied levels of medical attention.

Clients may offer information obtained from friends, breeders, or sources such as the Internet and may wish to have the veterinarian go over this material. A reasonable technique the veterinarian can use that precludes taking time away from the office call is to acknowledge the request and inform the caretaker that the material will be reviewed once the examination and early decision-making processes have been completed.

An owner's expectations may seem to convey that, "OK, you are the doctor, so you tell me what is wrong." A different tack then becomes necessary, and the approach changes from "Tell me what you have observed" to "It appears that your dog (or cat) has been losing weight; tell me, has this been a recent occurrence?" This may be all that is necessary to get the owners to begin talking about their pet.

Not every owner-veterinarian experience is informative. Valuable information is noted in the record. If the client refuses to provide a history or begins to attack another veterinarian, these comments should be noted in the record. The record provides not only a future legal defense but also a guide to further owner communication. Clients who have been dissatisfied with the results of prior care reasonably object when the same medications are prescribed for their pet. It suggests that the current veterinarian has not been listening. Inquiring in a unobtrusive manner about the owners' needs and desires helps define their wishes and permits the veterinarian to provide options from which the owners can choose.

Specifics about drugs currently being administered should be reviewed. The drug's name, dosage, and frequency of administration are significant. The veterinarian should also ask about prior drugs that may have been prescribed, including over-the-counter (OTC) products, prescriptions from other veterinarians, and holistic products. This is the time to inquire about the foods the animal is currently fed, prior diets provided, canned or kibbled formulations, supplements added, and treats given. The specifics of oral, topical, and injectable prophylactic products administered at home should be identified.

Information should be gathered regarding out of area travel and areas where the pet (or other pets in the family) previously may have lived. Clients should be questioned about the welfare of other pets currently living in the household. The vaccination history is needed for each pet in the household, particularly when laboratory tests for infectious diseases affected by prior exposure or vaccines are under consideration.

The history and the owner's story are equally important. These convey to the examiner the owner's perceptions, needs, and desires during this initial period of acquaintance or contact. I find that this can be the most useful time of the examination process. I can touch the pet, gently stroke it, feel the quality of the haircoat and skin, determine the hydration status, and generally get a good idea of the animal's physical well-being (e.g., debilitated or well conditioned, obese or thin, and so on) (Figures 1-1 and 1-2). This is also a convenient time to gently examine the pet without the animal being fearful, because a pet often seems more aware of its owner's voice than of the veterinarian going over its body. This also allows me to determine the animal's behavior and gives the client a feeling of assurance that I am getting to know or am reacquainting myself with the pet. Pets generally seem less fearful while I am at their eye level and when I refer to them by name. The physical examination begins while the history is still being taken.

It is not always possible to begin the examination process during this period, and I do not make a distinct effort to perform every examination this way. If the dog or cat is sitting anxiously (i.e., protectively or in a frightened manner) in the client's lap, I avoid this contact and dwell on the pet and the owner's story. Pets relax during this period and are less fearful of me as time goes by. A truly frightened or fractious animal presents a different situation, which may require use of a muzzle or, even better, an examination away from the owner in an environment that no longer requires the pet to feel it is protecting the owner. It is important to remember that owners should not be allowed to hold their pets during any examination process that entails a likelihood of injury to anyone in contact with a frightened or injured pet.

INITIATING THE PHYSICAL EXAMINATION

The physical examination commences when the veterinarian enters the examination room. The clinician should look at the general appearance of the pet, note odors, and observe irregularities. A severely sick or crisis presentation requires a different approach from that used for a dog or cat with a mild or chronic problem. Clients must also be observed and evaluated. They are prone to be particularly anxious in severe or acute life-threatening situations, and the veterinarian should assess the owner's state when first approaching the pet. Intense questioning may be inappropriate if the owner feels that the pet needs immediate medical attention.

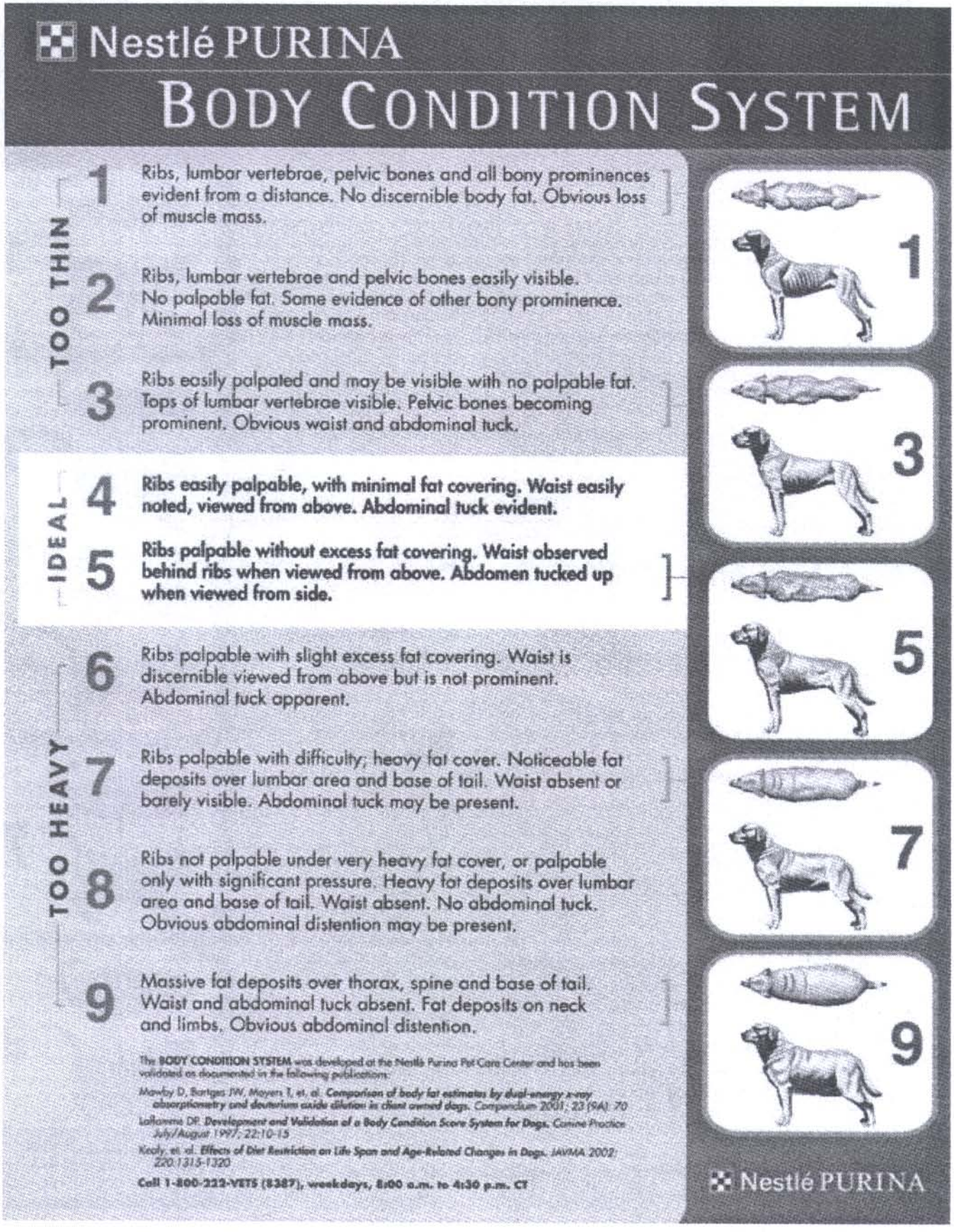


Figure 1-1 Body condition chart for the dog. (Used by permission from Nestle Purina Petcare.)

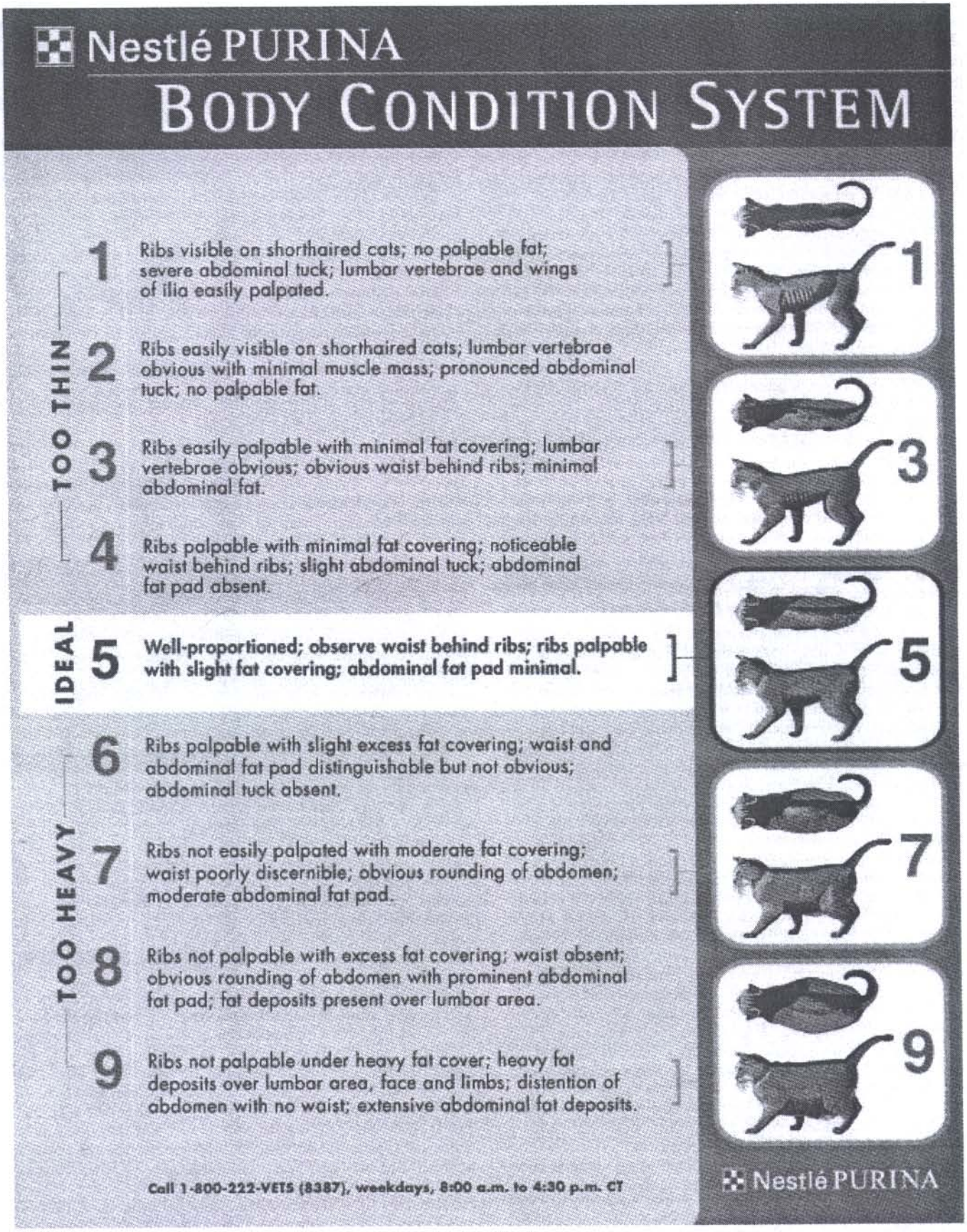


Figure 1-2 Body condition chart for the cat. (Used by permission from Nestle Purina Petcare.)

The veterinarian should listen for abnormal breathing sounds or grunting. The animal's body size and posture also should be observed: a plantigrade stance could suggest a neuropathy; head hanging in cats may indicate hypokalemia; fat pets may be overfed, hypothyroid, or inactive; thin pets may be hyperthyroid or cachectic. It is true that owners may point out these irregularities, but they may misinterpret such changes or may simply not be cognizant of their significance. In a desire to "wish well" for the pet, the owner also may fail to provide information for fear of its significance. The veterinarian has the responsibility to seek out this information.

Examples of signs and symptoms the veterinarian may observe upon entering the examination area are presented in this textbook under the section "Clinical Manifestations of Disease." The chapters in this section are not "complete," because the variety of maladies and the manifestations of disease are infinite. Suffice it to say that the examination process must not be so quick or superficial that an obvious underlying problem is overlooked.

If the animal is ambulatory and has a history of lameness, neurologic deficit, or weakness, it is essential that the veterinarian watch the animal move. This may be done before or after the hands-on physical examination process. At some point during this initial phase of the examination, the veterinarian must observe the pet's gait. This may require having the pet walk on a surface with traction, preferably with the owner as the handler. Lameness, signs of neurologic deficits, or irregularity in gait and appearance is noted. The physical examination is continued, and the clinician attempts to mechanically evaluate any specific lameness or suggestion of a localized abnormality (e.g., patella luxation, stifle cruciate drawer sign, elbow pain or mass).

A review of previous examination notes for prior irregularities can aid the clinical assessment. For example, comparing the size of a mass with previous findings is something clients appreciate, particularly if the records clearly identify prior size, appearance, and location. Measurement of lesions with calipers or a ruler is good for review and trend purposes.

Neurologic changes, such as diminished conscious proprioception, diminished muscle tone, limb dragging, or unusual pain during compression of the muscles or lumbosacral compression, are noted and may require further investigation to point to a diagnosis. Something can be said for performing at this time the "stand back" examination, which allows the veterinarian to observe breathing patterns or abdominal changes.

Every seasoned veterinarian has developed his or her own method of performing the physical examination, derived from a wealth of experience. For example, animals are frightened by a large figure looming overhead and are less anxious when approached at eye level. Therefore, as mentioned before, I prefer to kneel on the examination room floor to perform the physical examination (except for cats and small dogs). I find I am better able to perform auscultation completely and thoroughly in this way, and I also am able to palpate more thoroughly while having a good presence with the pet. Particularly with the neophyte examiner, there is something to be said for having most animals in the same position each time for the examination.

After the initial greeting, I prefer to stroke the pet to gain a more generalized knowledge of the overall body status. The body composition score is assessed (see Figures 1-1 and 1-2), as is hydration status, weight change, physical appearance, and the condition of the haircoat. Masses (size, shape, and appearance) are noted. I then examine the entire torso by touch, attempting to define the patient's status. Findings may include abdominal enlargement (fluid, fat, distention, pain), discomfort, and skin or musculoskeletal abnormalities (masses, changes in the haircoat, open wounds, fleas, dirt, ticks, or other abnormalities). Looking for bumps, lumps, or irregularities, I am able to distinguish lymph node changes, pain or swelling in the joints or limbs, physical deformities, and the nature of the femoral pulse. I evaluate the pulse, including its rate, quality, and character (see Chapter 56), and listen for any irregularities while auscultating the heart.

Swelling in the form of edema or fluid collections are correlated with other changes. Edema is identified as being generalized, localized to one limb or region, or associated with abdominal fluid and is noted to be pitting, cold, warm, or oozing in nature.

Specific lameness associated with trauma is identified and may provide an obvious cause; however, the veterinarian should not make that assumption without giving reasonable consideration to other possible causes (e.g., a pathologic fracture in a dog with osteosarcoma). I like to run both hands down the animal's body to check for asymmetry in body form.

Skin and coat changes must be evaluated in light of the animal's living arrangements, as established in conversation with the caretaker. Indoor pets should not have foreign body material in the coat; fleas, flea dirt, ticks, and other ectoparasites should not be present. Hair loss or thinning is a clue to clinical disease and should be noted. Hair loss should be assessed as unilateral or bilateral, and its full significance should be identified in the records. Coat changes must also be correlated with other body changes that may indicate a systemic illness, such as Cushing's disease. Areas of skin change should be evaluated and comments made with respect to the potential benefit of skin or hair culture, skin scraping, skin biopsy or allergy testing. Pets that live outdoors are more likely to have ectoparasites, weather-related haircoat changes, or bite wounds. As with the indoor pet, these conditions must be correlated with the clinical signs and recommendations made accordingly. Coats with a strong odor of perfume or smoke may indicate to the examiner possible problems with regard to allergic lung disease, highly reactive lungs, or an animal that has been in or around a fire.

My preference is to progress the physical examination from the head toward the tail. First, hydration status and mucous membrane color and moisture should be identified. Pain on dorsiflexion or ventroflexion or lateral movement of the head and neck is significant and may be noted when the head is first moved. The head first should be examined superficially for any changes or problems, such as hair loss or swelling. Areas of discomfort or irregularity are observed. The appearance of the mucous membranes (e.g., pallor gives reason to suspect anemia, hypoperfusion, or hypoxemia), oral cavity, pharynx, and teeth are recorded. Signs of drooling, discharge, or malodor from the oral region should be apparent at this time. It is important for the veterinarian to speak to the owner about the condition of the pet's teeth and gums; it also is important for the owner to see, if possible, any unexpected finding in the oral cavity.

A brief cranial nerve examination can be included during this portion of the examination process. The way the pet holds its jaw closed, the functions both of sensation and of motor ability of the maxillary muscles, and the appearance of the eyes may be relevant. Monitoring for superficial and deep changes within the eyeballs and the periorbital region extends this process. Ophthalmic sensitivity, squinting, or photophobia is recorded. Any discharge is noted and described as to color, composition, and volume and whether the discharge is unilateral or bilateral. Tear production is recorded (Schirmer tear testing), as is nasolacrimal duct patency (e.g., dry, cracked nasal tissue). If nystagmus, strabismus, or other deviations of one or both eyeballs are noted, the veterinarian continues the examination while looking for signs of conjunctival color changes or inflammation. Pupillary size and integrity are noted, as is the pupillary light response, both direct and consensual. Sensation in the eyelids and the surrounding tissue is observed.

The appearance of the skull, the muscles of mastication, and the muscles around the head are noted. Clients frequently suggest that a mass has developed in the occipital region associated with weight loss as the temporal muscles atrophy (occipital bone). Sinking of the eyes into the skull is a sign of periorbital fat loss and may relate to myositis, weight loss, cachexia, or another ophthalmic process. Pain, swelling, or heat in any region is observed. More detailed examination of the eyeballs, including direct and/or indirect ophthalmoscopy, may be completed at this time; or, if there are suggestions of change, the examiner first may complete the rest of the physical and then perform this part of the eye examination.

Airflow through the nostrils can be quickly assessed using a stethoscope and contralateral compression of the nares or by allowing the pet to breathe onto a metal surface (e.g., a counter top in the examination room).

Examination of the ears, pinnae, and ear canals is expected by the client and is an important part of every veterinary physical examination. This is particularly relevant in the new puppy or kitten examination as a check for ear mites, infection, or odor. An owner may report that a pet has difficulty eating or chewing, but the problem may in fact be caused by pain from one or both ear canals. Discharge, unusual odor, or discoloration of the canal tissue may be noted. Owners are more likely to notice abnormal conditions of the pinnae (e.g., aural hematoma), but even without such information, the pinnae must be examined. Superficial examination of the ear canal can usually be accomplished in the examination room without difficulty, allowing the veterinarian to discuss chronic ear disease with the owners while showing them the abnormality.

The integrity of the jaw bite must be determined, as well as the loss of teeth, or the presence of extra teeth. The color of the mucous membranes, capillary refill time, ulcers, color of the tongue, discolorations, and neurologic integrity are identified. The teeth are examined for calculus, caries, fractures, displacement, or discoloration. Abnormalities are recorded and mentioned to the owner. Signs of dental wear due to fence biting or rock chewing should be noted, as well as any resulting sensitivity. Gingival hyperplasia, masses, gingivitis, or ulcers may correlate with clinical signs. In first-time puppy or kitten examinations, evaluation for cleft palate or other congenital defects is required. With an uncooperative or fractious animal, examination of the oral cavity can be a daunting procedure. When the pet resists such an examination, removal to a treatment area away from the owner often allows further examination without difficulty.

Evaluation of the pharyngeal region is limited during the physical examination to external palpation. In some dogs, depressing the caudal tongue with the index finger allows visualization of the tonsils and oropharynx. However, this is not always the case, and if an indication of an abnormality exists in the pharyngeal or laryngeal region, a more thorough examination under sedation should be encouraged. The tongue should be elevated (using dorsally directed pressure with the thumb between the rami of the mandibles) to assess the sublingual region, such as for linear foreign bodies in cats. The laryngeal region should be checked for sensitivity, pain, or masses or institution of the gag reflex. Detection of visible or palpable deformities and monitoring of the laryngeal apparatus may yet be possible without sedation.

Moving to the ventral cervical region, the veterinarian evaluates for masses, tracheal sensitivity, and enlargement of the lymph nodes or thyroid gland. At the thoracic inlet, the clinician examines for lymph node enlargement, crepitus (subcutaneous air leakage), or other masses. Asymmetry of the thorax (scapula, muscles, rib cage, masses, or fat accumulation) should be correlated with signs, as should kyphosis or sternal deformities. Breathing difficulty can be associated with changes in the appearance of the rib cage. Fluid accumulation in the thoracic cavity, significant pleural or pulmonary disease, and some muscle disturbances cause the rib cage to feel or appear abnormal. Congenital thoracic deformities may cause respiratory signs. Peritoneal-pericardial diaphragmatic hernia (PPDH) may be associated with deformities of the xiphoid region of the sternum, such that the examiner can insert a finger into the thoracic cavity and sometimes actually touch the heart.

My preference is to complete the entire physical examination before auscultating lung and heart sounds. These portions of the physical examination are described in Chapters 54 and 55. When palpating the thorax, the examiner should notice the point of maximal intensity (PMI) of the heart. Normally this is over the left fourth to sixth intercostal space at the level of the costochondral junction. Deviations imply cardiac or thoracic cavity diseases. Similarly, palpation of a cardiac thrill is indicative of an extremely loud heart murmur (greater than grade 4/6). Cardiac thrills are usually found at the PMI but may be displaced; they should be identified and correlated with the heart sounds and clinical signs.

Progressing caudally to the abdomen, the examiner first should note whether the abdominal wall is pumping rapidly, a possible sign of anxiety, tachypnea, or dyspnea. Tachypnea and dyspnea are observed; they are not recognized through auscultation.

The general appearance of the abdomen is the first thing the clinician should assess. Distended, tucked up, muscular and firm, painful, tense, and soft and doughy are all terms used to describe the abdomen. Abdominal pain should be characterized as coming from the abdomen or from musculoskeletal dysfunction (e.g., disk disease) or just from plain annoyance with being examined. Not all pets are happy to be in the veterinarian's office, and some display their displeasure this way; it should not be mistaken for a pathologic process.

Examination of the abdomen, as with all other parts of the body, should be performed systematically. Examining the outside of the abdomen and spinal column first and then moving deeper with systematic palpation allows the clinician to review body systems in an organized manner.

During either the initial portion of the abdominal examination or at this time, the veterinarian has the opportunity to examine the mammary glands and surrounding tissue. Large lumps in the mammary tissue are usually easily recognized; however smaller, nondiscrete lesions may require more intensive evaluation and palpation. Carefully moving the finger tips up or down the chain on both sides permits the examiner to note discrepancies in the tissue. Likewise, enlargement of the sublumbar lymph nodes may be noted. In the male, changes in and around the prepuce are identified. Preputial discharge may not be readily seen unless the pet is placed in lateral recumbency. Extruding the penis to appreciate changes in the mucosa or sheath of the penis helps explain abnormal findings or a history of licking. In the male cat, evaluation of the penis and its surrounding area is important, particularly in cases of suspected feline urinary tract disease. Neutered tomcats have small to no spines present on the penis, in contrast to intact tomcats.

Palpation of the abdomen is an individually determined technique. I like to examine animals both from behind and from the side. When examining the abdomen from behind, I am able to palpate for bilateral changes, to assess the kidneys more accurately, and to identify midabdominal masses. Lateral palpation provides a clearer indication of hepatomegaly, splenomegaly, bladder stones, or an enlarged bladder. Occasionally it is helpful to pick up the pet and allow it to stand on the hind legs so that the abdominal viscera falls caudally, permitting a more comprehensive examination.

Distention of the abdominal cavity requires differentiation. In general, there are four major causes of abdominal

enlargement: fluid or fat accumulation, muscle laxity, and abdominal organ enlargement. The examination begins with gentle ballottement to determine whether the cause is obesity, pregnancy, fluid accumulation, one or more masses, internal obstruction, muscle weakness, or simply poor muscle condition. Correlating the findings of this examination with the weight and temperature allows the veterinarian to consider abnormal results.

It is generally easier to perform a complete abdominal palpation examination on the cat and many smaller dogs than it is on larger dogs. In cats, it is frequently possible to palpate the intestines, spleen, kidneys, and bladder carefully. In larger animals this may not be possible, but there is still much that can be appreciated, such as enlargement of abdominal organs, masses, and fluid collections. In cats, palpation of an enlarged spleen often is a sign suggesting mast cell disease, lymphoma, or another neoplastic process. In dogs, a large, irregular splenic margin strongly suggests hemangiosarcoma, although other causes of splenomegaly must be considered (see Chapters 184 and 276). Differentiation from other abdominal masses may be done initially through the physical examination and later by radiographic and/or ultrasonographic monitoring.

Pain upon palpation of the abdomen is a significant sign. Pain requires distinction between referred spinal pain, abdominal pain, generalized pain, and discomfort. The acute abdomen needs correlation with laboratory tests and clinical signs. Pain should be localized, if possible, as cranial, midabdominal, caudal, or generalized. Palpation for masses and the detection of enlarged viscera comprise an art that is not replaced by more sophisticated, expensive, and complicated tests. Pain in the abdomen is a clear indicator for further testing, including radiography, ultrasonography, and laboratory analyses. It also must be correlated with the clinical history. Malaise, failure to move or change position, fever, and nausea may be explained by abdominal pain, whereas a fractious cat, ears back and pupils dilated, that has a tense abdomen may simply be displeased with being examined.

Distention of the belly must be correlated with clinical signs (e.g., hair loss, polyuria/polydipsia, paper-thin, scaly skin), fluid collection, pregnancy, neurologic changes, and disease, most notably liver and splenic neoplasia. Urinary bladder distention should be palpable and defined. The kidneys often can be palpated bilaterally if enlarged in the dog and are usually palpable normally in the cat. In most dogs and cats, the left kidney normally can be palpated under all circumstances except when the animal is obese. The right kidney of the dog usually can be palpated only when it is enlarged or displaced. The presence of a large or painful prostate should be noted and correlated with clinical signs. Symmetric enlargement of the fat pads and muscles of the lumbar region (love handles) are commonly seen in an older pet, particularly if it is gaining weight.

Palpation of the abdomen is best completed with the dog or cat standing and with the examiner's fingers kept close together. If the thumb is allowed to rest on the spinal tissue and extreme pressure is exerted, the examiner may misinterpret pain as abdominal rather than spinal (induced by the thumb pressure).

The examination of the caudal abdomen is completed by rectal palpation, which is performed in older male dogs or when signs suggest lower bowel dysfunction, possible lower urinary tract problems, or hind end disorders of an orthopedic or neurologic nature. Prostatic abnormalities are likely to be palpated per rectum in all but the largest male dogs. Correct palpation of the prostate is done with the index finger of one hand and simultaneous cupping with the other hand (via dorsocaudal pressure on the caudal abdomen to elevate the prostate gland toward the palpating finger). This is especially useful for larger dogs and/or shorter index fingers. A normal rectal examination identifies a symmetric, bilobed, nonpainful, rubbery-textured prostate gland with a median raphe that clearly separates the two lobes. The peripheral tissue should evoke no pain or irregularity along the canal wall or the bony pelvic structure surrounding the gland.

Upon entering the rectum, the examiner palpates the anal sacs at the 4 and 8 o'clock positions to determine whether they are enlarged and if they can be readily expressed. The ease with which these glands can be expressed and the type of fluid released aids the evaluation for anal sac disease. Many clients worry considerably about "full" anal sacs, and it is important to identify problems if they exist. It also is necessary to establish adequate dietary measures in dogs with problems so that the anal sacs can be expressed regularly when the animal has a bowel movement. Serious anal sac disease does occur in the feline species, albeit uncommonly. The rectal tissue should be neither rough nor painful.

While examining the rectal region and tissue, the clinician should check the animal for evidence of constipation, obstipation, or generally dry, hard stools. Such problems lead to difficulty defecating. The perianal region should be examined for masses and, particularly when straining to defecate occurs, for perineal hernia, either unilateral or bilateral. Perineal hernias are detected by lateral deflection of the index finger immediately after entering the rectum (i.e., no farther than the first or second joint of the inserted finger). If the examiner probes too deeply past that point, this important lesion will be missed. Rectal prolapse must be differentiated from ileal-colic intussusception. Prolapse is associated with the inability to pass a blunt instrument only to the level of the pelvic inlet. During this portion of the examination, the tail is checked for skin lesions and for pain on motion. Animals experiencing tail pain, and occasionally urinary and/or anal sphincter problems, should be examined with injury to the tail region in mind. Tails that have been caught in doors or pulled aggressively (more common in the cat) may develop neurologic problems involving the urinary bladder, anal sphincter, and/or the ability to move the tail.

The testicles and scrotum should be examined in the intact male for pain, skin lesions, and variability in the size and shape of one or both testicles. The presence of one or no testicles in the intact male is an important diagnostic clue. Retention or neoplasia of one or both testicles may correlate with the presenting clinical signs. In the puppy examination, the presence or absence of testicles may indicate a congenital defect and must be identified to the pet owner because the purchase agreement may need to be reviewed. It is important to note the presence of an inguinal (flanker) testis because showing and breeding would be inappropriate, and the pet may be infertile.

In females, examination of the vulvar region is important in determining the presence of discharges, the state of estrus, or the presence of skin conditions that may be responsible for licking or irritability of the hind region. Asking questions that relate to the timing of the last or latest heat cycle may elicit insightful information relevant to pseudopregnancy or pyometra in the intact bitch. Vaginal swabs taken to evaluate the state of the vaginal mucosa are a quick, easy way to determine the presence of pus or red cells in the canal and the current hormonal status of the bitch.

Prior to examining the limbs, particularly in cases of lameness, the examining veterinarian must evaluate the mobility and flexibility of the head and neck. Particularly in larger breeds of dogs, cervical conditions cause neck guarding and failure to thrive, with nondescript signs of pain, lameness, and malaise. Intermittent or recurrent problems may not be immediately obvious on the physical examination. Dogs that are difficult to examine or animals with acutely painful conditions may be better evaluated under conscious sedation.

Rear leg pain, weakness, and wobbliness may be signs of a neurologic disorder, such as cervical disease, thoracolumbar disease, and/or lumbosacral disease. The physical examination

should include compression of the tissues along the spinal canal and the lumbosacral region. Sensitivity alone may be inadequate grounds for making a diagnosis and may only point to one of several conditions that must be considered in the differential diagnosis. Neurologic changes, including postural tone, conscious proprioception, or muscle atrophy, assist the process of evaluating disease states.

Evaluation and examination of the limbs, including the pulses, lymph nodes, joints, foot pads, and interdigital regions, can reveal important clues to the presence of internal medical problems. Joint disease, often silent or less than immediately obvious, is easily overlooked unless specific attention is paid to joint swelling or discomfort. It is important to observe symptomatic cats out of the carrier, on the floor in a safe, escape-proof room. Swelling, heat, and pain in one or more joints can explain many signs, including lameness, malaise, and fever. Swelling of the peripheral subcutaneous tissues provides reason for further evaluation. Claudication or painful or non-weight-bearing lameness directs the examiner to the affected limb. Thorough examination of the limbs for differentiation of warmth, pulses, or swellings may yield a direct clue to the cause of lameness.

Deep palpation of the bony tissue provides information relevant to both medical and orthopedic problems. Taking into account the age and health of the animal is relevant, because some diseases are specific to young, growing dogs (panosteitis), whereas others would be expected in older, overweight dogs (cruciate rupture, osteoarthritis, bone cancer). Although a general evaluation of the joints is required whenever lameness is present, it is always performed with the realization that only with the animal under conscious sedation or general anesthesia can it be determined with certainty whether a joint problem exists. Cats are usually easier to palpate than dogs, but larger breeds of dogs are often difficult to examine without sedation. With that as a given, it is often advantageous to discuss with the client the benefits of radiology and a joint tap under sedation so that a more complete examination can be done. Palpation of the hips and evaluation for coxofemoral disease must be distinguished from examination for lumbosacral problems and stifle disorders. The opportunity to evaluate these findings in greater detail may be left to a sedated state accomplished at another time. When radiographs of a limb are to be taken, the examiner should remember the benefit of radiographing both limbs to evaluate the significance of the changes noted. Other orthopedic problems, including patellar disease, may be more easily identified without sedation.

No lameness examination is complete without evaluation of the pads and interdigital regions. It is of paramount importance to examine these tissues carefully for infiltrating problems, particularly where foreign bodies are a possibility, and to distinguish interdigital cysts, digital tumors, and pad burns.

COMPLETING THE PHYSICAL EXAMINATION

Every hospital has its own set of paperwork. Smaller veterinary clinics may not require much in the way of paperwork, but this is the time to complete a well-written medical record. The traditional "SOAP" method provides the entire hospital and others with a record of the physical examination and history findings and of the plan for moving forward with the pet's care.

No physical examination is complete until the results are listed in the examination report and an assessment is made of the findings. This is the time for the veterinarian to identify in the records his or her recommendations for proceeding with the case. It is here that the client or caregiver can once again participate in the caregiving process. The veterinarian needs to summarize the findings, note the pertinent points, and identify how the case should proceed. Noting the findings alone without recommending a course of action does not complete the process. The owner must be informed of the possible courses of action and the estimated cost of such work. It is recommended that the veterinarian also note in the record, in addition to the subjective and objective findings, the likely rule-outs and tentative clinical assessment. A definitive diagnosis need not be made at this time, but identifying the rule-outs helps to portray a thought process in progress. If the prognosis is potentially poor or guarded, the examining veterinarian should discuss this with the owner at this point. Clients who fail to "hear" bad news may be very surprised to see that the veterinarian had written such news in the record one or more times in the course of record keeping. From a medical-legal point of view, keeping the client informed and up-to-date is very necessary. From the outset, discussing serious findings with the client ensures better practitioner-client communication.

CHAPTER 2

Hyperthermia and Fever of Unknown Origin

James B. Miller

Obtaining a body temperature is part of every physical examination. Too frequently the veterinarian associates any elevation in body temperature with true fever. The assumption is then made that an infectious agent causes the "fever," even if no obvious cause exists. If the animal's fever resolves after giving antibiotics, the assumption is made that it was a bacterial infection. A normal body temperature is often assumed to mean the absence of disease. This approach to hyperthermia, fevers of unknown origin, and normothermia can be misleading and lead to improper diagnosis or therapy (or the lack of therapy).

THERMOREGULATION

The thermoregulatory center for the body is located in the central nervous system (CNS) in the region of the anterior hypothalamus (AH). Changes in ambient and core body

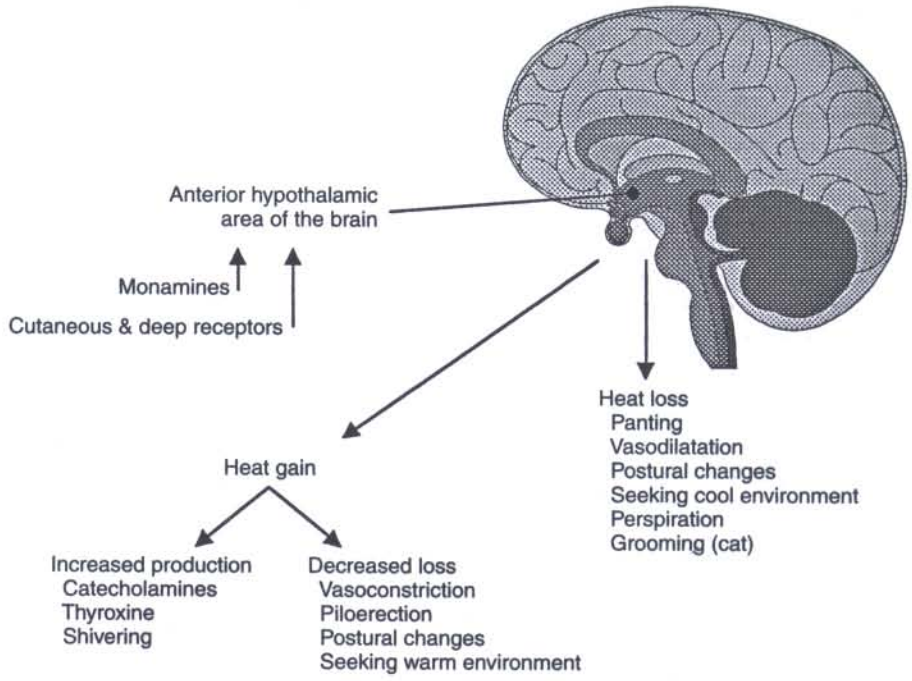


Figure 2-1 Schematic representation of normal thermal regulation.

temperatures are sensed by the peripheral and central thermoreceptors, and the information is conveyed to the AH via the nervous system. Thermoreceptors sensing that the body is below or above its normal temperature (normal "set point") will stimulate the AH to cause the body to increase heat production and reduce heat loss through conservation if the body is too cold or dissipate heat if the body is too warm (Figure 2-1). Through these mechanisms, dogs and cats can maintain a narrow core body temperature range in a wide variety of environmental conditions.

HYPERTHERMIA

Hyperthermia is the term used to describe any elevation in core body temperature above accepted normal for that species. Hyperthermia is a result of the loss of equilibrium in the heat balance equation such that heat is produced or stored in the body at a rate in excess of heat lost through radiation, convection, or evaporation. The term *fever* is reserved for those hyperthermic animals where the set point in the AH has been "reset" to a higher temperature. In hyperthermic states other than fever, the hyperthermia is not a result of the body attempting to raise its temperature but is due to the physiologic, pathologic, or pharmacologic intervention where heat gain exceeds heat loss. Box 2-1 outlines the various forms of hyperthermia.

True Fever

Exogenous Pyrogens

True fever may be initiated by a variety of substances, including infectious agents or their products, immune complexes, tissue inflammation or necrosis, and several pharmacologic agents including many antibiotics. Collectively, these substances are called *exogenous pyrogens*. Their ability to directly affect the thermoregulatory center is probably minimal, and their action is to cause the release of endogenous pyrogens by the host. Box 2-2 lists some of the more important known exogenous pyrogens.

Endogenous Pyrogens

In response to stimuli by an exogenous pyrogen, proteins (cytokines) released from cells of the immune system trigger the febrile response. Macrophages are the primary immune cell involved, although T and B lymphocytes and other leukocytes may play significant roles. The proteins produced are called *endogenous pyrogens* or *fever-producing cytokines*. Although interleukin-1 (IL-1) is considered the most important cytokine, at least 11 cytokines capable of initiating a febrile response have been identified (Table 2-1). Some neoplastic cells are also capable of producing cytokines that lead

Box • 2-1

Classification of Hyperthermia

True Fever
Production of endogenous pyrogens

Inadequate Heat Dissipation
Heat stroke
Hyperpyrexic syndromes

Exercise Hyperthermia
Normal exercise
Hypocalcemic tetany (eclampsia)
Seizure disorders

Pathologic or Pharmacologic Origin
Lesions in or around the anterior hypothalamus (AH)
Malignant hyperthermia
Hypermetabolic disorders
Monoamine metabolism disturbances

Box • 2-2

Exogenous Pyrogens

Infectious Agents
Bacteria (live and killed)
- Gram-positive
- Gram-negative

Bacterial products
- Lipopolysaccharides
- Streptococcal exotoxin
- Staphylococcal enterotoxin
- Staphylococcal proteins

Fungi (live and killed)
- Fungal products
- Cryptococcal polysaccharide
- Cryptococcal proteins

Virus
Rickettsia
Protozoa

Nonmicrobial agents
- Soluble antigen-antibody complexes
- Bile acids
- Pharmacologic agents
  - Bleomycin
  - Colchicine
  - Tetracycline (cats)
  - Levamisole (cats)
- Tissue inflammation/necrosis

Table • 2-1

Proteins with Pyrogenic Activity

ENDOGENOUS PYROGEN	PRINCIPAL SOURCE
Cachectin/tumor necrosis factor-α (TNF-α)	Macrophages
Lymphotoxin/tumor necrosis factor-β (TNF-β; LT)	Lymphocytes (T and B)
Interleukin-1α (IL-1α)	Macrophages and many other cell types
Interleukin-1β (IL-β)	
Interferon-α	Leukocytes (esp. monocyte-macrophages)
Interferon-β	Fibroblasts
Interferon-γ	T lymphocytes
Interleukin-6 (IL-6)	Many cell types
Macrophage inflammatory protein 1α	Macrophages
Macrophage inflammatory protein 1β	
Interleukin-8 (IL-8)	

Adapted from Beutler B, Beutler SM: The pathogenesis of fever. In Bennett JC, Plum F, editors: *Cecil textbook of medicine*, ed 20, Philadelphia, 1996, WB Saunders, p 1535.

to a febrile response. The cytokines travel via the blood stream to the AH, where they bind to the vascular endothelial cells within the AH and stimulate release of prostaglandins (PGs), primarily prostaglandin E_2 (PGE_2) and possibly prostaglandin $E_{2\alpha}$ ($PGE_{2\alpha}$). The set point is raised, and the core body temperature rises through increased heat production and conservation (Figure 2-2).

Inadequate Heat Dissipation

Heat Stroke

Heat stroke is a common form of inadequate heat dissipation. Exposure to high ambient temperatures may increase heat load at a faster rate than the body can dissipate the heat. This is especially true in larger breeds of dogs and brachycephalic breeds. Heat stroke may occur rapidly in the dog, especially in closed environments with poor ventilation (e.g., inside a car with windows closed), even on moderately hot days. Environmental temperatures inside a closed car exposed to the direct sun may exceed 120° F (48° C) in less than 20 minutes, even when the outside temperature is only 75° F (24° C). Death may occur in less than an hour, especially in the breed types mentioned. Heat stroke will not respond to antipyretics used in true fever. The animal must be treated with total body cooling immediately if a fatal outcome is to be avoided. Water baths and rinses using cool (but not cold) water best accomplish total body cooling. If the water is too cold, a tendency exists for peripheral vasoconstriction, which will inhibit heat loss and slow the cooling process. Cool water, gastric lavage, or enemas have also been suggested. Cooling should be discontinued when body temperature approaches normal to avoid potential hypothermia. In addition to total body cooling, treatment for vascular collapse and shock should be instituted with severe hyperthermia (greater than 107° F [41.6° C]) or when clinical judgement warrants its use. Intravenous crystalloid solutions given at shock doses and glucocorticoids are indicated in an attempt to prevent permanent organ damage and disseminated intravascular coagulopathy (DIC).

Hyperpyrexic Syndrome

Hyperpyrexic syndrome is associated with moderate-to-severe exercise in hot and humid climates. This syndrome may be more common in hunting dogs or dogs that "jog" with their owners. In humid environments, a tendency exists toward a zero thermal gradient for dry heat loss leading to a net heat gain. In addition, severe exercise may cause the cardiovascular system to supply skeletal muscles with adequate blood flow while compromising peripheral heat loss by not allowing proper vasodilation in the skin. Many hunting dogs and dogs that run with their owners will continue to work or run until they become weak, begin to stagger, and then collapse. In suspected cases, owners should obtain a rectal thermometer. If increased, in the future the clinician should evaluate the dogs' rectal temperature at the first sign of weakness or not wanting to continue. Owners should be instructed that rectal temperatures above 106° F (41° C) require immediate total body cooling, and temperatures above 107° F (41.6° C) are an immediate threat to permanent organ damage or death.

Exercise Hyperthermia

The body temperature will slowly rise with sustained exercise because of increased heat production associated with muscular activity. Even when extreme heat and humidity are not factors, dogs will occasionally reach temperatures that would require total body cooling. This is especially true in dogs not accustomed to exercise, overweight, or those with respiratory disease. Puppies seen for vaccinations have often been excited and active during the trip. Activity and probable release of catecholamines results in the increased body temperatures obtained on physical examination. These dogs will display

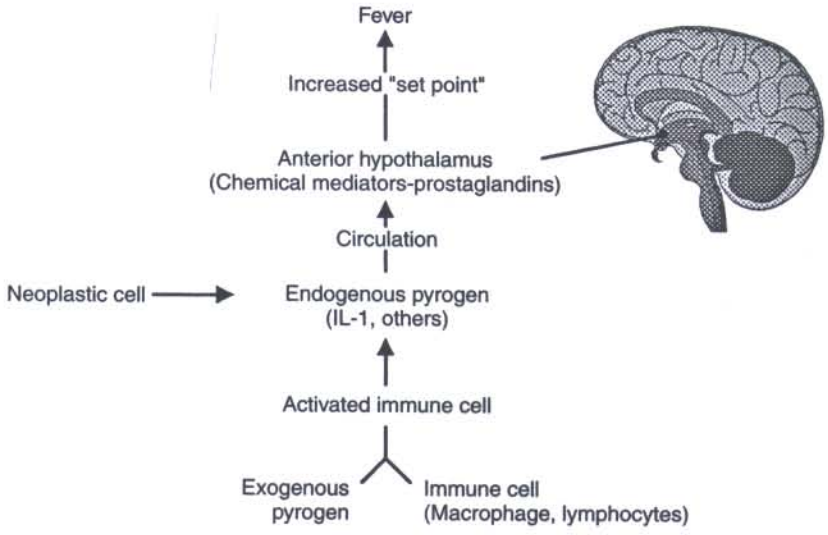


Figure 2-2 Schematic representation of the pathophysiology of fever.

features suggestive of attempting to dissipate excess body heat and are neither febrile nor ill.

Eclampsia results in extreme muscular activity that can lead to significant heat production resulting in severe hyperthermia. Total body cooling should be initiated in conjunction with specific eclampsia therapy if the dog or cat is hyperthermic. Be cautious of lowering body temperature too quickly and of decreases to subnormal levels.

Seizure disorders as the result of organic, metabolic, or idiopathic causes are encountered frequently. Hyperthermia associated with severe muscular activity can be a feature, especially if the seizures are prolonged or occur in clusters. The initial concern of the clinician should be to stop the seizures; however, when significant hyperthermia is present, total body cooling is recommended.

Pathologic and Pharmacologic Hyperthermia

These types of hyperthermia encompass several disorders that lead to impairment of the heat balance equation. Lesions in the hypothalamus may obliterate the thermoregulatory center leading to impaired response to both hot and cold environments. Malignant hyperthermia has been reported in the dog and cat. It leads to a pharmacologic myopathy that is initiated by pharmacologic agents, including inhalation anesthetics (especially Halothane) and muscle relaxants such as succinylcholine. Extreme muscle rigidity results with the production of excess body heat. Removal of the offending causative agent and total body cooling may prevent death. Hypermetabolic disorders may lead to hyperthermic states. Endocrine disorders such as hyperthyroidism and pheochromocytoma can lead to an increased metabolic rate, vasoconstriction, or both, resulting in excess heat production and decreased ability to dissipate heat. These conditions rarely lead to severe hyperthermia requiring total body cooling.

Clinical Approach to the Hyperthermic Patient

When a dog or cat has an increased body temperature, an effort should be made to approach the problem in a logical manner to avoid erroneous conclusions (Figure 2-3). A complete history and physical examination should be performed unless the problem is of extreme nature (temperature greater than 106°F [41°C]) and the animal is obviously attempting to dissipate heat (panting, postural changes) or comatose. In such cases, immediate total body cooling and supportive care should be initiated. In other cases, specific questions concerning previous injuries or infections, exposure to other animals, disease in other household pets, previous geographic environment, and previous or current drug therapy may be beneficial. Through this type of questioning and a complete physical examination, the clinician can frequently decide if the increased body temperature is true fever. Temperatures less than 106°F (41°C), unless prolonged, are usually not life threatening, and caution should be taken on using antipyretics before a proper clinical evaluation.

Fever of Unknown Origin

Fever of unknown origin (FUO) is defined in human medicine as a fever that has lasted 3 weeks and has a cause that has not been determined through laboratory evaluation and radiographs. In veterinary medicine, most clinicians consider any animal that does not have any historical or physical finding that would cause a FUO. Although research involving a large number of patients with FUO has been completed in humans, little veterinary information suggests the most common causes of FUO in dogs or cats. The information given in this chapter is based primarily on clinical experience. Most dogs and cats with FUO probably have an infection or suffer from products of those agents. The prevalence of the causative infectious agent varies depending on the area where the clinician practices and the previous travel history of the pet. Although bacterial infections are probably the most common cause of FUO in the dog, in some geographic locations, systemic fungal diseases or rickettsial infections might be more common. Endocarditis, pyelonephritis, prostatitis, closed pyometra, pyothorax, and other deep abscesses should be considered in a dog with FUO. In the cat, viral diseases such as feline leukemia virus (FeLV), feline infectious peritonitis (FIP) virus, and feline immunodeficiency virus (FIV) are common infectious causes of FUO and may exceed bacterial infections as the leading cause. The next most common cause of FUO in the dog and cat is immune-mediated disease. Most immune-mediated diseases occur in young adult dogs. Immune complexes are a potent stimulator for the release of fever producing cytokines and frequently lead to temperatures of 105°F (40.5°C) or 106°F (41°C). Neoplasia is not as common as immune-mediated disease in causing fevers but should always be considered, especially in the older animal. Another, often overlooked cause of fever, is tissue trauma. Trauma often causes mild fever (103°F to 104°F [39.6°C to 40°C]) 1 or 2 days postsurgery when there has been

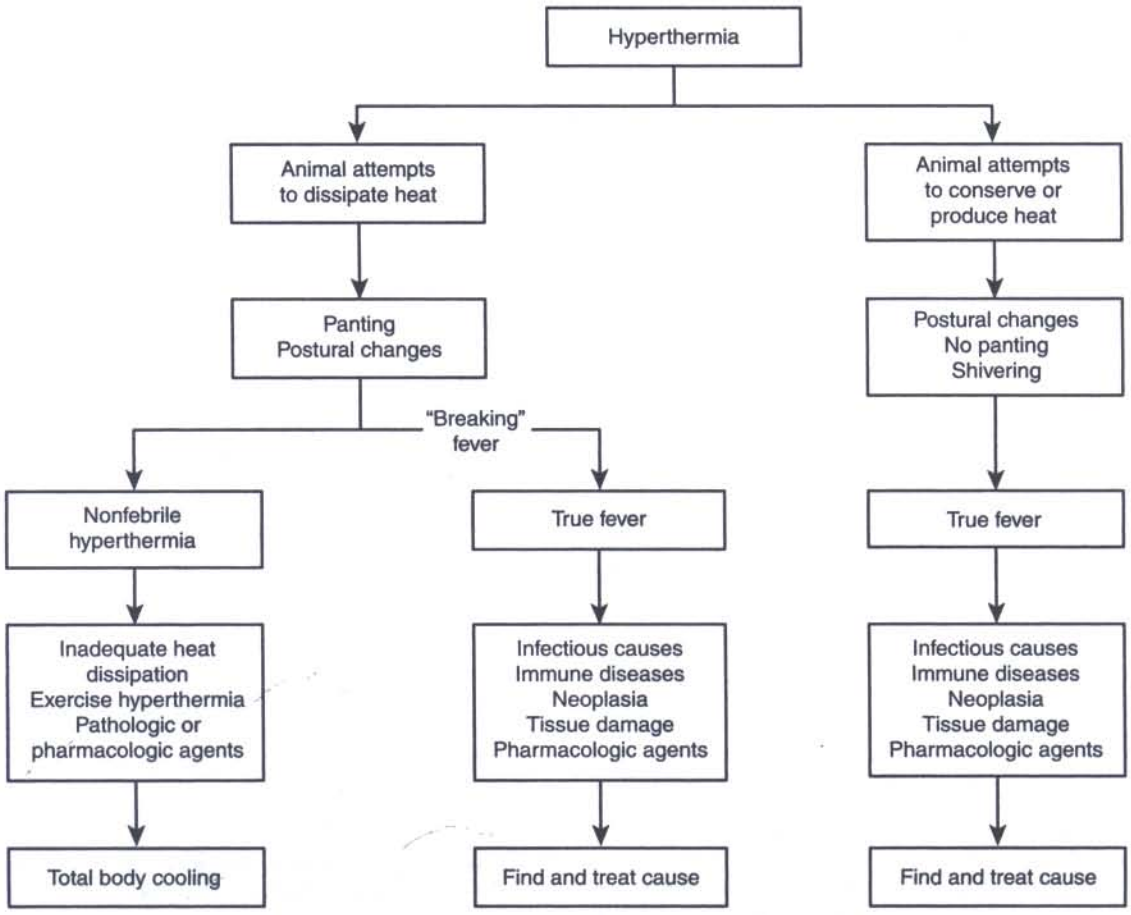


Figure 2-3 Algorithm for treatment of hyperthermia.

significant muscle involvement. Most of these animals do not have infections and probably should not be treated with antibiotics without additional evidence of infection.

Evaluating for infectious disease, immune-mediated disease, neoplasia, and causes of tissue trauma will usually lead to a final diagnosis, even when no obvious cause for the fever exists.

Nonspecific Therapy for Fever

Mild-to-moderate elevations in body temperature are rarely fatal and may be beneficial to the body. Hyperthermia may inhibit viral replication, increase leukocyte function, and decrease the uptake of iron by microbes, the latter being necessary for growth and replication of many microbes. If a fever exceeds 107° F, a significant risk of permanent organ damage and the initiation of DIC exist. The benefits of nonspecific therapy versus its potential negative effects should be considered before initiating such therapy.

Nonspecific therapy for true fever usually involves the use of inhibitors of prostaglandin synthesis. The compounds most commonly used are the salicylates (acetylsalicylic acid and sodium salicylate) and dipyrone. These products inhibit the chemical mediators of fever production and allow the normal thermoregulation. They do not block the production of endogenous pyrogens. These products are relatively safe, although acetylsalicylic acid is potentially toxic to cats and lower dose and frequency of administration relative to the dog is recommended. Dipyrone may lead to bone marrow suppression, especially when given over a prolonged period, and should be given only for a short period.

Phenothiazines can be effective in alleviating true fever and appear to act on the thermoregulatory center and cause peripheral vasodilation. The sedative qualities and potential for hypotension caused by the phenothiazines should be considered before use in the febrile patient.

CHAPTER 3

Hypothermia

Polly M. Taylor

MAINTENANCE OF NORMAL BODY TEMPERATURE

Mammalian body temperature is maintained closely around a constant set point at which cellular function is optimal. A number of complex mechanisms exist to maintain body temperature within tight control. The anterior hypothalamus maintains overall control of body temperature. It responds to local increases or decreases in temperature and also to neural input from warm and cold receptors in the skin, the abdominal viscera, and the spinal cord.

To maintain constant temperature, heat generated by muscular activity and metabolism is matched to heat loss. Temperature is regulated largely by control of heat lost from the body surface via the classic routes of heat exchange: conduction, convection, evaporation, and radiation (Figure 3-1). Heat is also lost from the respiratory tract through evaporation and in urine and feces. If the body becomes too cold, heat

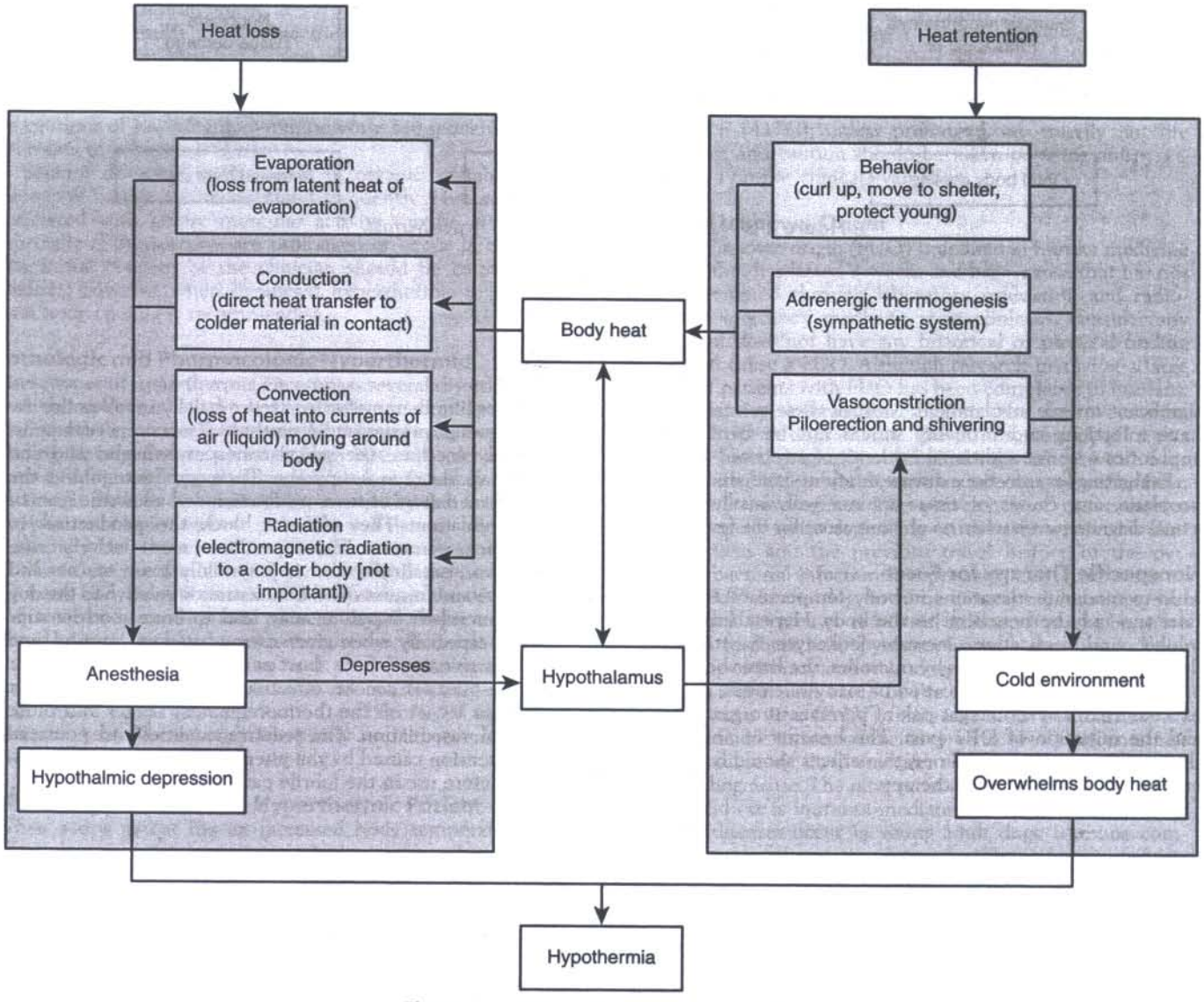


Figure 3-1 How heat is lost from the body.

is retained in the body core through peripheral vasoconstriction, which prevents warm blood reaching the body surface. Piloerection insulates the skin by trapping a layer of stationary air. Some additional heat is generated through muscle activity, such as shivering and voluntary movement. Chemical thermogenesis (adrenergic) may also play a part. Behavioral responses to cold are important in preventing heat loss; for example, moving into shelter and warmth, curling up, and dams protecting the young. Heat is lost by reversal of these processes, such that vasodilation of superficial blood vessels allows warm central blood to reach the skin. Panting increases evaporation from the respiratory tract. In some species, sweating is stimulated to provide the most effective heat loss through evaporation. Dogs and cats do not sweat from the skin, and loss via the respiratory tract through panting is the most significant form of active heat loss.

DEVELOPMENT OF HYPOTHERMIA

Hypothermia develops when either the methods of heat production and conservation are overwhelmed by a cold environment or when the mechanisms of heat retention are impaired. Smaller animals, in which the ratio between body surface area and volume are high, are more likely to develop hypothermia. Old, sick, or otherwise debilitated animals are also more likely to become hypothermic as heat generation and temperature control may be impaired. Neonates, with underdeveloped temperature-regulating mechanisms, are particularly susceptible. Hypothermia leads to a progressive failure of body function, ultimately leading to cardiac standstill and death. In man, a core body temperature of 35° C or below is regarded as hypothermia. Although animal temperatures are slightly higher than human temperatures, the definitions of degrees of hypothermia applied in human medicine serve well in other species as a guide to the expected degree of malfunction (Figure 3-2). Initially, as core body temperature falls below 36° C, respiratory rate, pulse rate, and arterial blood pressure fall. As temperature decreases below 34° C, muscular control and neural function begin to fail, consciousness is depressed, and metabolism is slowed. Acidosis and electrolyte imbalance may occur. Below 30° C, cardiac dysrhythmias are likely and temperature regulatory mechanisms fail even in the absence of any drugs. Hence, animals with a body temperature below 30° C are unlikely to regain normal temperature without treatment. Progressive metabolic and respiratory failure takes place when body temperature is below 28° C, with a high risk of ventricular fibrillation; cardiac standstill occurs at around 20° C.

Normal cats and, particularly, dogs withstand a cold environment very well. For instance, dogs immersed in water at 20° C can maintain heat regulation for 5 hours with less than a 1° C fall in body temperature. Hypothermia is most commonly seen when normal control mechanisms are disrupted by sedation and anesthesia, which impair hypothalamic function and behavioral responses. Many anesthetics and sedatives cause some degree of peripheral vasodilation, which itself allows more heat loss. As a consequence, most small animal patients are likely to lose body heat during anesthesia. Exposure to a cold environment or near drowning is a much less common cause of hypothermia in animals. In these circumstances the normal heat retention mechanisms are simply overwhelmed by the environmental conditions. The consequences of cold-exposure hypothermia and the treatment are essentially the same as in anesthesia-induced hypothermia. However, hypothermia is likely to be more severe after cold exposure but has the advantage of being uncomplicated by effects of surgery or drugs.

Anesthetic-associated heat loss and the resultant decrease in body temperature slows drug metabolism and leads to prolonged recovery from anesthesia. If severe, it is possible that cardiac function may be affected sufficiently to cause death. More commonly, postoperative hypothermia causes morbidity or death through the consequences of a slow recovery. A long period of unconsciousness increases the likelihood of unresolved, obstructed airway and prolonged hypoxia. Shivering will worsen this effect through increased oxygen and energy demands. Lack of movement while still under the influence of vasodilating anesthetics and sedatives leads to a vicious circle of further heat loss and reduced drug metabolism prolonging recovery and further increasing the chance of airway obstruction and hypoxia.

Prevention and Treatment

It is a great deal easier to prevent heat loss during anesthesia than to try to restore the temperature of a cold, anaesthetized patient at the end of a long surgical procedure. Effort should be made right from the start of anesthesia to maintain body temperature between 36° to 38° C. Much can be done by passive methods, largely insulation, although active methods using external heat are usually required where body cavities are exposed.

Passive Warming

Most heat is lost through conduction to colder surfaces in contact with the animal, such as the operating table, and through evaporation of body fluids and liquids used for surgical preparation. The animal should be insulated from colder surfaces and from the surrounding air, and it should be kept as dry as possible. A warm operating theatre may reduce heat loss into the surroundings, but working in an environment at body temperature is unpleasant; some heat loss by conduction into air circuits flowing around the animal will still occur unless it is insulated. Insulation between the operating table and the animal is easy to achieve with foam padding and other positioning aids. It is also easy to insulate the whole animal by

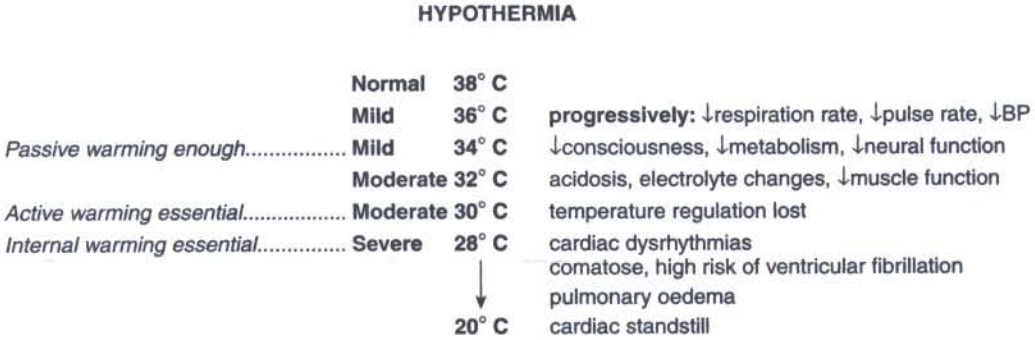


Figure 3-2 The effects of hypothermia (algorithm).

wrapping any exposed parts with bubble wrapping or aluminium foil. A compromise between the ultimate asepsis and the best heat retention must be made by clipping the minimal amount of hair and wetting the smallest area compatible with the proposed surgery. At all costs, excess scrub water must be dried up; the animal should not lie in a pool of scrub liquid during surgery.

It is impossible to prevent evaporation from the exposed surgical site. Intestinal surgery is the worst in this regard because large surface areas of serous membrane may be exposed. Regular flushing with warm (38° to 40° C) saline helps to reduce the amount of evaporation of body fluid and may help to prevent heat loss. Heat is also lost through the respiratory tract. Use of low-flow rebreathing circuits that retain both heat and moisture are advantageous in this respect. Heat and moisture exchangers placed between the endotracheal tube and the breathing circuit help to retain moisture and hence heat, as evaporation is reduced. These exchangers increase dead space and may be inappropriate for the very small patients that most need the heat retention.

Active Warming

Active methods to prevent heat loss are usually required during surgery of the body cavities. These include heated pads, infrared lights, heated gels, and hot-air circulators. Circulating water-heated pads are the safest because they do not become too hot; electrically heated pads may overheat, resulting in burns to the unconscious patient who cannot move off the heat source. Gel pads that are catalysed into an exothermic reaction when changing state to a stiff form are useful in very small patients. The heat generated is not excessive, lasts for 1 to 2 hours, and the stiffened gel bag can be used to position the animal. They are "regenerated" after use by placing in boiling water until the gel state returns. By far the most effective of the active-heating systems are the hot-air blankets, in which hot air is blown into a perforated blanket that is placed about the animal under the surgical drapes. A very wet animal will initially be cooled as the result of evaporation, but in all other circumstances this method has proved extremely effective.

Treatment of hypothermia depends on its severity and cause. After anesthesia, active warming is required as homeostatic mechanisms are impaired. Where the environment has caused hypothermia, normal heat-generating mechanisms will be more effective, and passive methods such as insulation with warm, dry blankets may be sufficient (see Figure 3-2). Very severe hypothermia (core temperature <30° C) requires internal active warming with intravenous fluids at 40° C and gastric, colonic, or peritoneal lavage with fluids at 40° to 42° C. This is to prevent further core cooling, which occurs when surface warming causes vasodilation, thereby allowing cold, peripheral blood to circulate into the body core.

CHAPTER 4

Pain Identification

Peter W. Hellyer

"Is this patient likely to be in pain, and if so, what is the best way to prevent and manage that pain?" This is an essential question that veterinarians should be asking themselves on a routine basis. When using this approach, the veterinarian has embraced a philosophy of providing the best care possible for the patient—this is practicing good medicine. The importance of measuring pain in patients is exemplified by what has been occurring in human medicine. The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) mandated in the year 2000 that human hospitals in the United States must measure pain in their patients and take steps to manage that pain. It is a sad commentary that the human medical community did not recognize that patient comfort is part of good medicine and all important to the patient, necessitating JCAHO to mandate that pain be considered the fifth vital sign (in addition to temperature, pulse, blood pressure, and respiration). In fact, the human medical community has known about the issues of unrelieved pain for almost 30 years, since the landmark study by Marks and Sacher (1973) exposed the practice of withholding effective analgesia from terminally ill patients. In establishing pain as the fifth vital sign, JCAHO acknowledged that treating pain results in quicker clinical recoveries, shorter hospital stays, fewer readmissions, and improved quality of life, leading to increased productivity. Thus pain relief should be considered part of good medicine. In veterinary medicine, pain may be considered as a vital sign, in addition to temperature, pulse rate, and respiratory rate. Pain is similar to other patient parameters in that it is more readily apparent once the clinician looks for it. Unlike the other vital signs, pain is difficult to measure and quantify. The tools to measure pain in veterinary patients will undoubtedly change as more clinical and research information becomes available. This chapter provides a brief summary of the current tools available to evaluate pain in dogs and cats.

IDEAL PAIN SCALES

Over the past decade, pain scales have been developed and used as part of research studies designed to evaluate specific therapeutic modalities in the treatment of acute or chronic pain in dogs and cats. Nevertheless, the science of accurately measuring pain in animals in general, and dogs and cats in particular, is still in the early stages of development. Because animals cannot tell clinicians that they are in pain, no "gold standard" exists to assess pain in animals. The situation in human medicine provides a useful comparison.

Identifying pain in neonates and young children has been extensively studied over the last 20 years. The results of those

Box • 4-1

Characteristics of an Ideal Pain Scale

Patient characteristics:

1. Species specific
2. Breed specific (there may be differences in genetic sensitivities to pain)
3. Environmental and rearing specific (e.g., individual animal versus group rearing, home versus clinic)
4. Developmental/age specific (e.g., neonates versus pediatrics versus adult versus geriatric)
5. Gender specific (the role of gender on pain perception is still unclear)
6. Cause of pain specific (e.g., pathology-induced pain, procedural pain, surgical pain)
7. Body region specific (e.g., facial pain, ocular pain, abdominal pain)
8. Character of pain state specific (i.e., acute, subacute, chronic, localized, diffuse)
9. Pain intensity specific (spectrum from none to severe)
10. Recognize individual variations

Pain scale indices and criteria should be:

1. Clearly defined
2. Consistently useable by different individuals
3. Have clearly understood strengths and weaknesses
4. Be able to differentiate differences in the intensity and degree of pain
5. Be straightforward and practical to use
6. Be validated according to carefully considered standards
7. Be a useful tool to guide clinical decision making

efforts have been a proliferation of scales that are used to assess pain in children of different developmental ages and in different settings. Refinement of the scales used in children continues to create tools that are sensitive and specific for pain. The same process needs to occur in veterinary medicine, with the additional challenge of creating scales that are species specific. Criteria for an ideal pain scale are presented in Box 4-1. Because ideal pain scales do not exist for every species and every medical condition, how should the information in Box 4-1 be used? When evaluating a patient for pain, it is essential to be aware of the normal behavior for that species, age, and individual. Deviations from normal behavior suggest pain, anxiety, or some combination of stressors that are inducing a state of distress. If a pain scale was developed to evaluate acute postoperative pain after orthopedic surgery, the scale may be of little help in assessing abdominal pain. Accordingly, pain scales should be used as a guide to identify behavioral changes from normal and as a way to track response to therapy. Pain scales should not be used to deny analgesia based on an arbitrary number.

Current State of Assessing Pain

Assessing pain in animals on either end of a spectrum from *no pain* to *severe pain* is relatively straightforward, provided the veterinarian and staff are aware of normal behavior for that species and individual. Realistically, many of the most challenging cases involve patients that have varying degrees of pain somewhere between the extremes of *none* and *severe*. Trying to determine the degree of pain and the ability of that animal to cope with its pain can be difficult. In a survey of Canadian veterinarians, Dohoo and Dohoo (1996) found that one of the main factors that determined if veterinarians routinely administered analgesic drugs postoperatively was the veterinarians' perception of the degree of pain felt by animals. The fact that 51.5% of those veterinarians surveyed never used analgesics highlights the clinical importance of being able to recognize pain in the species under a veterinarian's care. Even amongst veterinary personnel committed to treating pain, it can be frustrating at times trying to decide if the benefits (i.e., decreased pain intensity) of the analgesic protocol selected outweigh the side effects (e.g., sedation, nausea). Compounding the decision-making quandary is the fact that many veterinarians and their staff never received any formal training in the recognition of pain. As more studies focus on species-specific pain behaviors, the ability to recognize and treat pain in animals will improve; however, the assessment of pain in animals will remain a subjective and inaccurate undertaking for the near future. This brings up an interesting question: Is it appropriate to assume that if a procedure is painful in people it will also be painful in an animal? An ever-growing body of scientific literature describes new knowledge and understanding of the anatomy, physiology, and pharmacology of nociception (i.e., pain). The vast majority of those studies are carried out in animals with the information often extrapolated to people, leading to the development of new drugs and techniques and ultimately to clinical trials. From people, clinicians are able to evaluate the efficacy of these new techniques and drugs and often improve the way that pain is treated. In other words, clinicians can ask human patients if the treatment has improved their level of pain. However, if veterinarians apply this pain information gathered from humans to animals, they risk being accused of anthropomorphism. Recognizing that marked differences exist in species pain tolerance, in demonstration of overt signs of pain, and in responses to therapeutic interventions, it nevertheless defies logic and ethics for the scientific community to use animals to understand pain in people while simultaneously denying that pain exists or is important in animals. Thus it is appropriate at this time to assume that if a condition causes pain in people, it will also cause some degree of pain in animals. For animals, pain may be more or less than that experienced by a person; therefore it is incumbent on the veterinarian to determine how well the patient is coping with the pain.

The evaluation methods described in this chapter have been extrapolated from human medicine (i.e., visual analogue scale) or designed to assess acute postoperative pain in dogs. These methods can be adapted to cats and other species provided the veterinarian recognizes that pain behaviors are likely to be different between species. Importantly, all of the methods described are subjective and prone to the error of either underestimating or overestimating the degree of pain. All of the pain scales used in animals rely on the recognition or interpretation (or both) of some behavior. The most useful scales determine the presence or absence of specific behaviors while minimizing the interpretation of those behaviors. Even if the amount of pain is correctly estimated, determining how well the individual animal is coping with the pain may be difficult. In addition, all of the current pain scales are subject to interobserver variability to one degree or another. Finally, it should be recognized that all of these methods are used to assess the effects of physical pain and that none have been designed to evaluate mental or psychologic dimensions of pain that an animal may be experiencing.

Physiologic Assessment of Acute Pain

Physiologic data (e.g., changes in heart rate, respiratory rate, arterial blood pressure, pupil dilation) are useful in assessing responses to a noxious (painful) stimulus in a lightly anesthetized animal. Physiologic responses also occur in conscious

patients as a result of acute pain or other stressors but not with the same degree of reliability as in anesthetized patients. Central nervous system (CNS) and cardiopulmonary reflexes control cardiovascular and respiratory function to maintain a state of homeostasis; therefore reflex control mechanisms may dampen the physiologic responses to pain. In addition, physiologic parameters are not specific enough to differentiate pain from other stressors such as anxiety, fear, or physiologic responses to metabolic conditions (e.g., anemia). The reader should note that some pain scales use physiologic data and some do not. In the author's opinion, physiologic parameters are useful in assessing responses to noxious stimuli in patients under general anesthesia or for transient periods in conscious patients. The longer a conscious patient experiences pain, the less useful are physiologic parameters in assessing the degree of pain. When physiologic responses are used to assess pain, it is important to be aware of their limitations and to assess the selected parameter in light of baseline physiologic data. As such, changes in heart rate, respiratory rate, and other physiologic responses may be more useful in assessing the patient than any absolute value for each criterion.

Behavioral Assessment of Acute Pain

Evaluation of pain in animals relies on observation of animal behavior and interpretation of what the behaviors mean by an observer. Pain may be indicated by abnormal behavior that may appear as either an increase or a decrease in activity. In general, pain behaviors are easier to recognize in dogs as compared with cats. For example, dogs in pain may appear restless, agitated, or even delirious. This is particularly true during recovery from anesthesia after surgery. At the other end of the spectrum, dogs may be lethargic, withdrawn, dull, or obtunded. These dogs may not pay attention to environmental stimuli. The normal sleep-wake cycle may be disrupted, such that less sleep than normal is obtained. Normal activity such as grooming or eating may decrease or stop. Dogs may bite, lick, chew, or shake painful areas. Painful dogs may adopt abnormal body postures in an attempt to relieve or cope with pain in a given area. For example, dogs with abdominal pain (e.g., pancreatitis) may assume a posture with a rigid torso and arched back. Dogs with abdominal or thoracic pain may be reluctant to lie down in spite of obvious exhaustion. Although dogs do not have the same degree of motor control over their facial muscles as do primates, changes in facial expression can be used in some dogs to detect pain. The dog may hold its ears back or in a down position. The eyes may be wide open with dilated pupils, or partially closed with a dull appearance. Many dogs will display a "fixed stare" into space, apparently oblivious to their surroundings. Some dogs may display a type of grimace uncharacteristic of the dog when not painful. Disuse or guarding of a painful area is a fairly reliable indicator of pain. The dog's gait may be abnormal, or the dog may appear much more rigid than normal. Vocalization may indicate pain in the dog, however it is an insensitive and nonspecific indicator of pain. Vocalization may occur as a whimper, whine, yelp, groan, grunt, yowl, or any combination. Interactive behaviors are frequently changed in the painful animal. Dogs may become more aggressive and resist handling or palpation. In contrast, they may become more timid than usual and seek increased contact with caregivers. Behavioral changes indicative of pain may be too subtle or take too long to recognize under routine clinical situations. Similarly, sporadic observation of animal behavior may not reveal signs of pain. Except in the most severe circumstances, the signs of pain may be "masked" by behavior that is stereotypic of the species being observed. For instance, dogs may wag their tail and greet an observer at the cage door in spite of being in pain. Cats may simply hide in the back of their cage and demonstrate no behaviors that would suggest to a casual observer that they are in pain. Cats may continue to purr even when painful. Behavioral changes indicating pain may not be what we expect. A cat sitting quietly in the back of the cage after surgery may be in pain; however, pain would not be recognized if the caregiver expects to see more active signs of pain such as pacing, agitation, or vocalizing. Unfamiliarity with normal behaviors typical of a particular species or breed makes recognition of pain-induced behaviors difficult or impossible.

Types of Scoring Systems for Acute Pain

Preemptive Scoring System

The preemptive scoring system is a subjective scoring system based on the amount of pain an individual believes the animal will experience after a given procedure. Preemptive scoring systems assign a degree of pain (none, mild, moderate, severe) based on the procedure performed and the amount of tissue trauma involved. In essence, preemptive scoring systems follow the philosophy that if a procedure is likely to cause pain in a human, then it is likely to cause a similar degree of pain in animals. In general, the greater the amount of tissue trauma induced by a procedure the greater the assigned level of pain. Preemptive scoring systems are useful in planning perioperative analgesic strategies. Procedures inducing moderate to severe pain often require the use of multiple analgesic drugs and techniques to adequately manage pain. Preemptive scoring systems are not useful in actually determining the degree of pain felt by an individual patient or in assessing response to therapy. Therefore it is important to keep in mind that individual patients may experience more or less pain than predicted by the preemptive pain scale.

Visual Analog Scale

The visual analog scale (VAS) is typically a straight, horizontal line, 100 mm in length, bracketed with descriptors of pain intensity (e.g., no pain, worst pain possible) on either end of the line (Figure 4-1). The VAS is a semiobjective scoring system. The human patient draws a vertical line across the line in a position that best represents his or her degree of pain. The patient may be asked to assess pain at the current time or the worst pain that occurred since the last assessment. The VAS has been used extensively in people and is generally considered to be a useful tool to assess pain and the response to therapy. The scale avoids the use of imprecise descriptive terms and provides many points from which to choose. In people, bracketing the VAS with phrases such as "no relief of pain" and "complete relief of pain" may provide more clinically useful information because patients do not all start with the same degree of pain. The use of the VAS may result in greater variability of pain scores than a simple descriptive scale. The VAS may erroneously appear as a more sensitive scale compared with other scales resulting in overinterpretation or excessive confidence in the results. The advantages of the VAS are primarily ease of use and that it provides a general sense of whether pain is getting worse or improving. A disadvantage of a standard VAS used to rate pain intensity is that pain is a multidimensional experience, and pain intensity is only one aspect of that experience. Disadvantages of the VAS in veterinary medicine occur primarily because the scale relies on an observer to identify and interpret pain behaviors. Thus observer bias may play a key role in assessing pain, leading to the possibility of over- or underdiagnosing pain. Variability of visual acuity among observers may affect the accuracy of

Figure 4-1 Visual analogue scale (VAS).

Box • 4-2

Simple Descriptive Scale

No pain
Mild pain
Moderate pain
Severe pain

the VAS. Interobserver variability, when more than one observer evaluates an animal, affects the accuracy of the VAS. The sensitivity of the VAS has not been determined in animals; therefore changes in VAS score should be interpreted in light of overall patient appearance. If a VAS is to be used, it is important to have all individuals within the practice that will be assessing pain receive training on the use of the scale. It should not be assumed that an untrained individual would provide a similar assessment of animal pain as would someone with more training and familiarity with the species being observed.

Simple Descriptive Scale

The simple descriptive scale (SDS) is a semiobjective scoring system that usually consists of four or five categories or descriptions of pain intensity (Box 4-2). Each description is assigned a number, which becomes the patient's pain score. This differs from the preemptive scoring system, in that the SDS assigns a score based on observation of the animal and not the nature of the procedure performed. Advantages of the SDS are that it is simple to use and the results are not affected by visual acuity (no drawing of a line required). Disadvantages of the SDS are that it is not a sensitive scale to assess pain (it consists of only four or five categories); therefore it may overestimate or underestimate the degree of pain and the efficacy of analgesic therapy. As with other assessment tools, observer bias may play a key role in determining pain score.

Numerical Rating Scale

The numerical rating scale (NRS) is a semiobjective scoring system that consists of multiple categories in which to evaluate the patient, with descriptive definitions of pain for each category. The NRS generally uses categories that are assigned whole numbers, and the importance of each category is not weighted. The NRS prompts the observer to evaluate certain aspects of the patient that might otherwise go unnoticed (e.g., appearance of the eyes, interactive behaviors, physiologic parameters). Advantages of the NRS include a more thorough patient evaluation than what is prompted by the VAS or SDS, an easy method to tabulate the score, and numerous categories on which to base an assessment of patient comfort.

Disadvantages of the NRS include lack of accuracy and little improvement over the SDS. Categories are generally scored by whole numbers, suggesting that equal differences exist between categories when in fact that may not be true. Numeric rating scales have been used extensively in the evaluation of postoperative pain in dogs and cats. In spite of numerous categories, painful animals may go undiagnosed. For example, a dog with severe abdominal pain may not receive a high enough number to be considered painful when using a scale designed to assess surgical pain. In the postsurgical patient, NRS may be too insensitive to detect differences in some animals that receive analgesics and those that go untreated. Thus NRS may only be able to identify those animals with extreme pain that overtly demonstrate pain behaviors and would have been identified otherwise.

Behavioral and Physiologic Responses Scale

The University of Melbourne Pain Scale (UMPS) is a scale based on specific behavioral and physiologic responses. The UMPS includes multiple descriptors in six categories of parameters or behaviors related to pain. Advantages of the UMPS may include increased accuracy over the Preemptive Scoring System, VAS, SDS, or NRS and an ability to weigh the importance of certain behaviors or parameters. The evaluation of multiple factors increases the sensitivity and specificity of the UMPS. Most importantly the UMPS relies on behavioral observations and evaluates changes in behavior or demeanor, thereby limiting interpretation and observer bias. Disadvantages of the UMPS are limited validation to date; the specific types of patients and procedures in which the UMPS would be expected to be accurate have not been elucidated. As such, the UMPS may not be sensitive enough to detect small changes in pain behaviors, particularly if patient evaluations are performed only periodically. The UMPS was designed to evaluate dogs after surgery, therefore the accuracy of the scale for other uses or for use in cats has not been established. The UMPS requires some knowledge of the demeanor (mental status) of the dog before anesthesia and surgery. Although the veterinary staff usually knows this, the dog's actual mental status when truly comfortable at home will probably not be known. In other words, the mental status of the dog after surgery will be compared with an already altered mental status that exists simply because the dog is in a veterinary hospital and away from familiar surroundings.

Behavioral Response Scale

The Glasgow Composite Pain Tool is a scale based on specific behavioral signs believed to represent pain in the dog. The behaviors included in the scale were derived from a questionnaire of veterinarians. The expressions used to describe pain behaviors were reduced to specific words and expressions using a variety of statistical methods. The advantages of this scale include limited interpretation and bias by the observer providing increased accuracy over the Preemptive Scoring System, VAS, SDS, and NRS. An observer is asked to identify whether or not a behavior is present, rather than to interpret what various behaviors mean. Most importantly, the terms used to describe individual behaviors are specifically defined, thereby decreasing uncertainty in using the scale. Physiologic data are not included, making the scale easier to use than the UMPS and perhaps more accurate. Nevertheless, an evaluation of physiologic parameters can be added when evaluating any patient. Disadvantages of the scale are limited validation in actual animal studies and a lack of a numeric scoring system that would allow for comparison of scores over time.

Modified Pain Scale

A modified pain scale used by the Anesthesia Section at Colorado State University is presented in Figure 4-2. This is a composite scale derived from the UMPS and the Glasgow Composite Pain Tool and was developed as part of a study evaluating pain after ovariohysterectomy and castration in dogs (unpublished data). In accordance with the Glasgow Composite Pain Tool, behaviors are identified as either *present* or *absent*. Physiologic data are not included, with the exception of dilated pupils; although changes in heart rate, respiratory rate, and arterial blood pressure can be added. Salivation and vomiting are included as indicators of nausea and as occasional signs of pain. Regardless of the cause, frequent vomiting undoubtedly increases the discomfort of the patient. The modified scale provides a record to track the frequency of behaviors indicative of pain. The frequency of pain behaviors should be low or decreasing with effective analgesic therapy. If a numeric score is desired, behaviors can be assigned the number located in parenthesis. Advantages of this scale are

CSU Modified Pain Scale for Use in Dogs and Cats

Posture:		
Normal	(0)	_____
Rigid	(1)	_____
Hunched	(2)	_____
Tense	(2)	_____
Abnormal body posture	(3)	_____
Guarding affected area	(4)	_____
Does the dog or cat seem to be:		
At rest	(0)	_____
Comfortable	(0)	_____
Restless	(1)	_____
Uncomfortable	(2)	_____
Rolling, thrashing	(3)	_____
Dilated pupils? (Yes: 1; No: 0)		_____
Salivation? (Yes: 1; No: 0)		_____
Vomiting? (Yes: 1; No: 0)		_____
Vocalization:		
Not vocalizing	(0)	_____
Barking (If abnormal for this dog)	(1)	_____
Crying, whimpering, whining	(2)	_____
Groaning, hissing	(3)	_____
Screaming	(4)	_____
Mental Status:		
Aggressive, obtunded, disinterested, nervous/anxious/fearful, happy/content, happy, bouncy, submissive		
Change in mental status? (Yes: 1; No: 0)		_____
Movement/Walking:		
Assessment not carried out/too sedate (0)		_____
Will not walk/stand	(0)	
None of these	(0)	
Stiff	(0)	
Ataxic	(1)	
Slow or reluctant to rise or sit	(2)	
Lame	(2)	
Palpation:		
When touched, did the dog or cat...		
None of these	(0)	
Look toward wound	(1)	
Appear anxious	(1)	
Cry	(2)	
Flinch	(2)	
Snap/bite/hiss	(3)	
Growl or guard wound	(3)	

If indicated: include additional physiologic parameters:

Heart rate	0	0% to 15% above baseline value
	1	16% to 29% above baseline value
	2	30% to 45% above baseline value
	3	>45% above baseline value
Arterial blood pressure	0	0% to 15% above baseline value
	1	16% to 29% above baseline value
	2	30% to 45% above baseline value
	3	>45% above baseline value
Respiration rate	0	0% to 15% above baseline value
	1	16% to 29% above baseline value
	2	30% to 45% above baseline value
	3	>45% above baseline value

Modified from:
Firth AM, Haldane SL: Development of a scale to evaluate postoperative pain in dogs. *J Am Vet Med Assoc* 214:651-659, 1999.
Holton L et al: The development of a behavioural based pain scale to measure acute pain in dogs. *Vet Record* 148:525-531, 2001. See Holton L et al for complete definition of terms.

Figure 4-2 Modified pain scale.

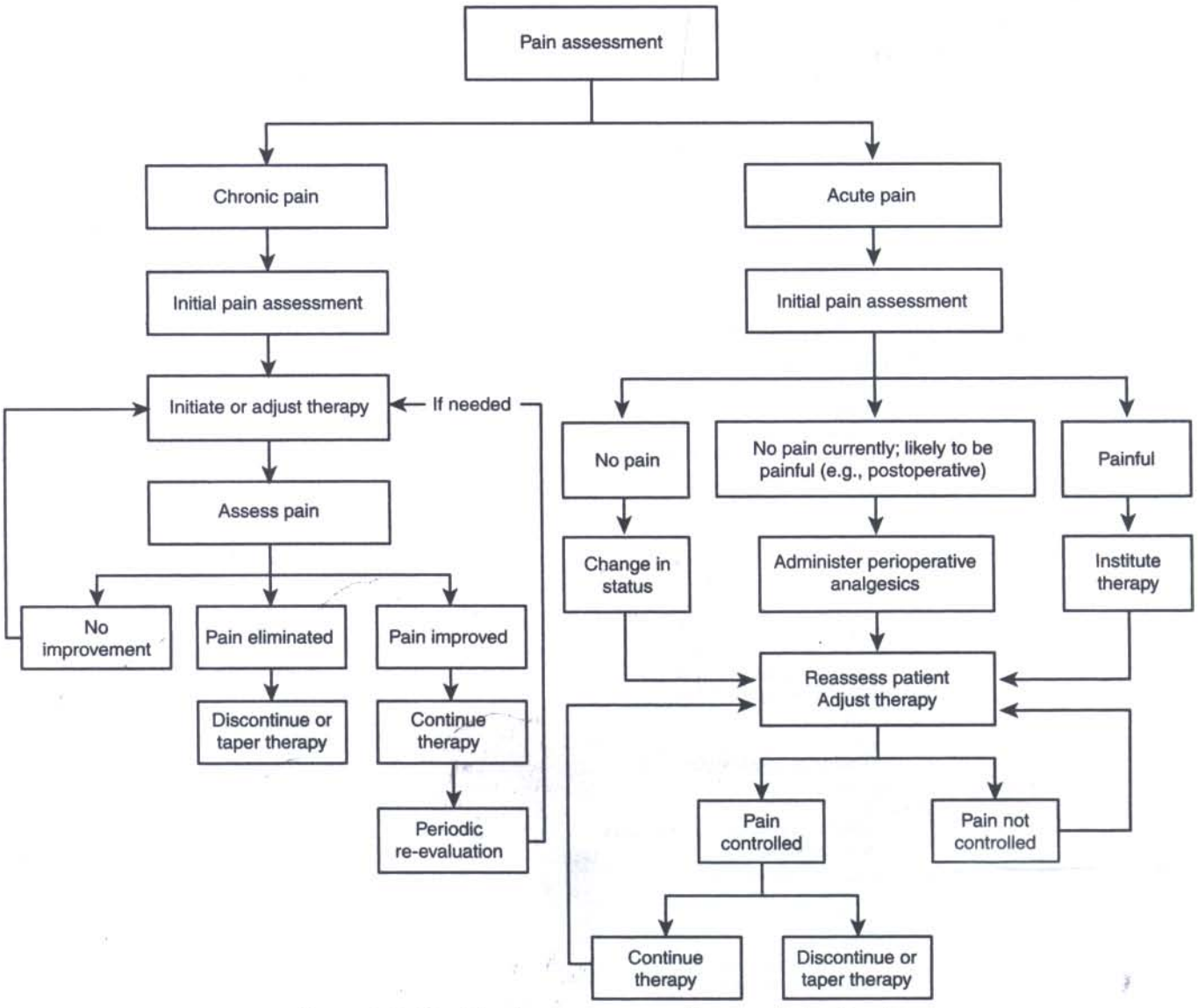


Figure 4-3 Algorithm for the assessment of acute and chronic pain.

ease of use and minimal interpretation required. Importantly, this scale uses the specific descriptors from the Glasgow scale for individual behaviors. Specific definitions of descriptors decrease interobserver variability and interpretation. Disadvantages of this scale include lack of validation by clinical studies comparing it to other scales and the use of an arbitrary numeric scale when a specific score is required. Another disadvantage is that modifications made in the scale for use in cats have not been validated to date.

Assessment of Chronic Pain

A number of pathologic states, such as osteoarthritis, cancer, and dental disease may cause chronic pain. The clinical signs of pain will depend on the underlying cause and may range from subtle to obvious. Chronically painful animals may experience acute flare-ups of pain that prompt an owner to seek veterinary assistance. For example, a dog with osteoarthritis may experience an episode of acute pain after excessive strenuous activity. In general, the clinical signs of chronic pain tend to be subtle and may be difficult to recognize during a brief examination in the veterinary clinic. Clinical signs suggestive of pain include decreases in activity, reluctance to get up or play, changes in sleeping patterns, changes in appetite, changes in social interactions and grooming habits, and other behavioral changes (e.g., aggression). Obviously, these clinical signs are also suggestive of numerous other medical conditions. Careful history taking, a thorough physical examination, appropriate laboratory tests, and the occasional response to analgesic therapy are used to diagnose the role that pain is playing in the patient's symptomology. A key aspect of treating the veterinary patient with chronic pain is the absolute requirement to have a close working relationship with the patient's caregiver. As noted in Figure 4-3, periodic reevaluations and possible adjustments in therapy are critical components in managing the chronically painful patient. As noted previously, species-specific pain scales need to be developed that are sensitive and specific for the type of chronic pain experienced. In the meantime, simply having the caregiver keep a log of daily behaviors may provide useful insight into the efficacy of therapy.

CHAPTER 5

Pain Management

Steven C. Budsberg

The sensation of pain, whether actual or anticipated, triggers a myriad of responses within the body. Pain is a complex experience involving not only the transduction of noxious stimuli from the periphery to the central nervous system (CNS) but also the processing of the stimuli by the higher centers in the CNS. Recent advances have been made in understanding the molecular mechanisms of pain yielding new, important information that is now being incorporated into clinical pain management at all levels. This molecular information coupled with the increasing data supporting the importance of pain modulation on normal systemic physiologic functions has led to increased use of analgesics. Yet despite all the new information, it is humbling to realize how little is known about pain; thus the ability of clinicians to intervene effectively and correctly in this treatment area is still in its infancy.

This chapter will focus on prompting proper use of analgesics in dogs and cats. It must be realized that despite an increased awareness of pain management, many animals are not currently receiving analgesics or are receiving inadequate amounts. The goal of this chapter is to guide the reader through a systematic approach to considering analgesic use in patients. However, the reader must remember that the current discussion is very limited. At least two recent publications have provided excellent compilations on pain and its management (see References). To that end, the present discussion heavily cites these two publications.

First, clinicians must acknowledge that their patients are in pain. In small animal practice, the diagnosis of pain is either observational or presumptive. Several studies have examined the attitudes of veterinarians, physicians, and associated health care providers about pain recognition and management. At best, results of these studies reveal significant knowledge deficits in all groups. These deficiencies contribute to the inconsistent recognition and treatment of pain. In the vast majority of cases the error is undermedication of patients. The paradigm that should be used is to assume the animal is in pain until proven otherwise. Thus the question is not whether analgesia is appropriate but rather what therapy can be instituted to maximize pain relief while minimizing potential side effects and costs. Two common false assumptions about managing pain are that (1) one drug at one dose will work for all patients, and (2) pain management is an "all or none" occurrence. First, each patient may require different drugs, doses, or even a combination of therapies to maximize pain relief. Secondly, a clinician should work toward the goal of pain reduction and subsequent improved patient comfort. Pain management should be individualized to the patient based on the mechanism of pain induction in that patient. Considerations with each patient must include whether the pain is acute or chronic, the type of pain, and the perceived intensity of the pain.

To begin to logically formulate a pain management plan, clinicians need to briefly review the peripheral and central mechanisms of pain. Peripheral sensitization is defined as enhanced sensitivity of nociceptive nerve endings. Nociceptive pain is evoked by activation of peripheral nociceptors. These sensory receptors are often classified by their size and degree of myelination and according to their responses to mechanical, thermal, and chemical stimuli. During inflammation, a high proportion of somatic and visceral peripheral nociceptors can be sensitized by various mediators, including bradykinin, prostaglandin (PG), various leukotrienes, serotonin, histamine, and perhaps free radicals. Tissue injury causes alterations in sodium- and calcium-mediated channels causing the C and A-δ fibers to send action potentials to the CNS. If the injury is persistent, additional recruitment of A-β fibers and silent nociceptors occurs along with alterations in ion activity. The action potentials are propagated to the CNS. Central sensitization is defined as enhanced sensitivity of nociceptive spinal dorsal horn neurons to sensory stimulation. Central sensitization is triggered by impulses in nociceptive C fibers. The neural mechanisms that underlie central sensitization are still being explored. Central sensitization is also evoked by several mediators in the dorsal horn of the spinal cord, including PG, nitric oxide (NO), glutamate and other excitatory amino acids, and substance P. Ascending pathways transmit pain to the brain. In the brain, complex modulation and processing occur at several sites. Finally, a short discussion of the concept of neuronal plasticity is needed before moving on to treatment. *Neuronal plasticity* refers to changes that occur in the established nervous system. More simply stated, it is the alteration of physiologic response based on previous stimuli. Pain perception by an individual for an identical stimuli may vary each time the stimuli is present. Injury, inflammation, and different diseases can cause neuronal plasticity. A subsequent increase in pain perception takes place by means of either increased excitatory or decreased inhibitory mechanisms. At a molecular level, pain hypersensitivity is the consequence of early posttranslational changes, including phosphorylation of membrane-bound proteins and later transcriptional dependent changes in genes at multiple levels along the nociceptive pathway. Neuronal plasticity can result in short-term changes that last minutes or hours, or it can result in permanent long-term changes.

The management of pain involves a myriad of events (Figure 5-1). Although the complexity of the process can seem overwhelming, it does offer several sites for potential intervention. The first concept to consider is the timing of analgesic initiation. Intuitively one should treat pain as soon as it occurs. The three basic periods to consider in pain management are (1) acute, (2) chronic, and (3) preemptive. Although the first two time periods are self-explanatory, the concept of preemptive analgesia is somewhat new but has already become a staple to the management of pain, especially perioperative pain. In essence, an injury causes central sensitization that leads to a prolonged and amplified hypersensitivity state in the patient. By giving drugs as a "preemptive analgesic," one attempts to prevent the induction of the aforementioned central sensitization, thus preempting the hypersensitivity state after the injury (which is usually surgically induced).

Anatomically, the sites of pain modulation are peripheral and central (both spinal and supraspinal). Attenuation at these

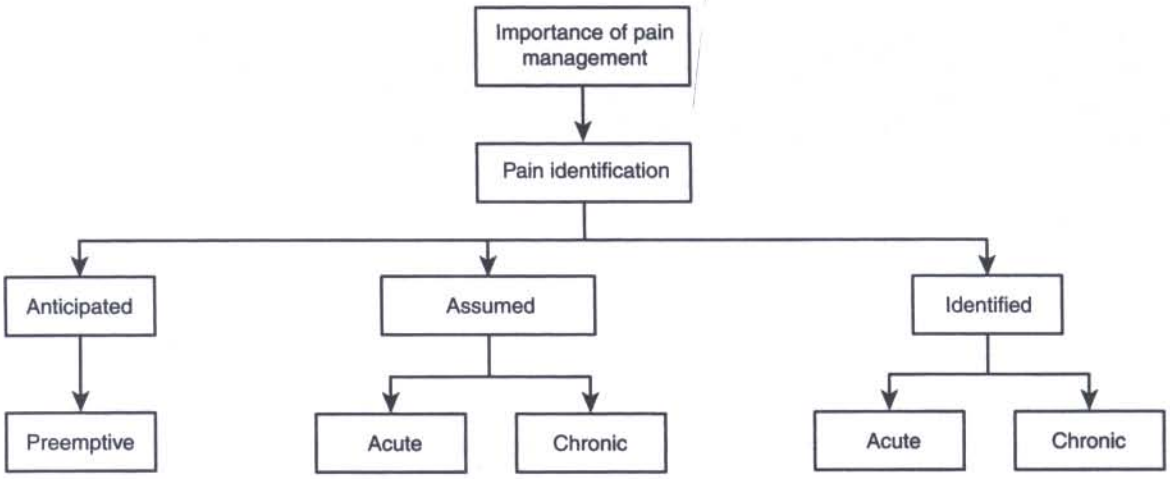


Figure 5-1 Algorithm for pain management.

sites can be done either by local infusion or systemic administration. As an example, nerve blocks (peripherally or epidurally) using lidocaine block sodium channel propagation of action potentials during painful stimuli. Another underused local administration is direct infusion into joints after arthrotomy. The instillation of local anesthetic agents have been shown to dramatically decrease surgically induced pain. Agents used in local infusions include local anesthetics, opioids, and nonsteroidal antiinflammatory drugs (NSAIDs). Systemic administration can alter both peripheral and central nociception. Interestingly, systemic NSAIDs act peripherally and spinally, whereas opioids can act peripherally, spinally, and supraspinally. Therefore clinicians must be familiar with the drugs to maximize their mechanistic effect and to administer the appropriate drugs according to their pharmacokinetic profiles. Finally, great benefit comes from combining drugs that act on different mechanisms of nociceptive modulation to enhance additive and synergistic effects; this is known as a *multimodal* or *balanced treatment* approach. Multimodal therapy is becoming more commonplace, and its use will continue to increase in small animal analgesia therapy.

The following is an overview of the major analgesic drugs that should be considered for use in the management of acute and chronic pain. Morphine and other pure μ-receptor agonists including fentanyl are often the first choice for severe pain (almost always acute pain) because their analgesic efficacy is very high. These drugs act at each target site (peripheral, spinal, and supraspinal). They show a sigmoidal dose and effect relationship that allows their dose to be adapted to the intensity of the acute pain perceived. The analgesic effects of opioids are related to their plasma concentration. Opioid drugs diffuse through the blood-brain barrier in proportion to their lipophilicity and the concentration gradient. Hepatic metabolism of opioids may produce pharmacologically active metabolites (morphine 6-glucuronide [M6G] is 20 to 40 times more potent than morphine). The phenylpiperidine analgesics, including fentanyl, are potent μ-receptor agonists with moderate to high lipid solubility. They diffuse rapidly through lipid membranes. The major pharmacodynamic differences between these drugs are potency and rate of equilibration between plasma and effect site. The next group of opioids to consider is the mixed agonist-antagonist agents. All opioids with mixed agonist-antagonist activity including butorphanol have limited flexibility in dosing in comparison with pure agonists, and they show ceiling effects for analgesia. Finally, partial agonist opioids (e.g., buprenorphine) exist. These compounds show high affinity for the μ-receptor but with low intrinsic activity. These drugs have a dose-response curve that exhibits a ceiling effect at less than the maximal effect produced by a full agonist. Therefore buprenorphine does not provide better analgesia than morphine but it may produce fewer side effects. However these side effects are often overemphasized and have been incorrectly used, more often than not, to justify avoiding the opioids in practice.

NSAIDs are another group of drugs that are rapidly becoming common as use for pain management. These agents are now available in both oral and parenteral formulations. Their analgesic effects result primarily from the inhibition of the cyclooxygenase (COX) isoenzymes (including COX-1, COX-2, and specific gene variants) that synthesize proinflammatory prostanoids. For this discussion, the primary prostanoid is prostaglandin E_2 (PGE_2) in the traumatized and inflamed areas. PGE_2 alters peripheral sensitization by binding to G protein–coupled receptors that increase levels of cyclic adenosine monophosphate (cAMP) within nociceptors, thereby increasing the threshold of activation of the nociceptors. Centrally, PGE_2 likely increases the excitability of dorsal root ganglion (DRG) cell bodies by reducing membrane depolarization needed to initiate action potentials and increase repetitive spiking. This is done by phosphorylation of the channel protein by cAMP-dependent proton kinase. The expression of COX-2 enzyme in the spinal neurons is believed to contribute to neuronal plasticity and central sensitization. NSAIDs are used today for the treatment of postoperative pain, with or without supplemental opioid agents. NSAIDs are useful for achieving multimodal or balanced analgesia given the multiplicity of mechanisms involved in pain. Clinically it must be remembered that NSAIDs are enzyme inhibitors, and their onset of effect is slower than that of opioids. Thus to be clinically relevant it has been recommended that clinicians administer NSAIDs before surgery to enhance their pain-relieving and opioid-sparing effects in the immediate postoperative period.

The α_2-agonists (medetomindine, xylazine) are also commonly used in clinical practice for both sedation and analgesia. These drugs act both peripherally and centrally by activation of α_2-receptor subtypes. The large variations in receptor structure, location, and specificity within and between species are important factors for the clinician to consider and may alter dose and expected effect within a particular patient. This group of drugs does have the potential for significant cardiovascular and respiratory side effects. They are, however, widely used very successfully in small animal practice.

The use of N-methyl-D-aspartate (NMDA)–receptor antagonists (most commonly ketamine) in pain management

has begun to rapidly increase in small animal practice. Studies suggest that the spinal dorsal horn NMDA–receptor has an important role in mechanisms underlying central sensitization. NMDA–receptor antagonists lessen the hyperactivity of dorsal horn neurons after prolonged activation of primary afferent neurons and inhibit nociceptive behavior induced by peripheral tissue or nerve injury. Ketamine is a noncompetitive NMDA–receptor antagonist. Analgesia obtained with ketamine occurs at serum concentrations one tenth to one fifth of an anesthetic dose, with a highly significant correlation between pain relief and serum concentrations of ketamine.

Finally, one should strongly consider local anesthetics in the management of pain. Local anesthetics reversibly block transmission of nerve fibers. Blockade of the sodium channels in the cell membranes causes an inhibition of the generation and conduction of the nerve impulses. The size and the presence of myelination drastically alter different nerve fiber susceptibility to local anesthetic blockade. Examples of local pain management include local tissue infiltrations, direct nerve blocks, or intraarticular administrations. The reader should remember that local blocks are easily combined with systemic analgesics to provide economic and effective mutimodal therapy.

Some key points should be remembered in reference to the management of pain. First, with pain management one must think in terms of mechanism-based, rather than symptomatic, treatment of pain. The clinician must focus on the reason the animal is in pain, not just on the fact that the animal is showing pain or discomfort (or the intensity of that reaction). To do this, one must understand the different types of inciting stimuli, neuronal pathways involved, and most importantly the systemic consequences of pain to the patient. These pathophysiologic considerations should lead the clinician to more multimodal therapy with improved clinical success without considerable increased costs. Finally, from a practical point of view the veterinarian needs to educate clients and staff about the importance of pain management. The use of analgesics should not be an option given to owners, it should be an integral part of each patient's therapy. Clinicians should establish protocols for assessing pain and what drugs to use when pain is encountered or anticipated. This is no different than the different anesthesia protocols each clinic has today. In addition, clinicians should routinely assess and record pain and provide a scoring system chart on each cage that is easy to use and read. This will begin to sensitize the staff to the course of pain in a particular disease or surgical procedure. The bottom line is that as one appreciates the negative side effects of pain and becomes more willing to treat it, everyone benefits—the patient, the client, and the clinician.

CHAPTER 6

Syncope

Sandra L. Minors

Sudden, transient and unpredictable loss of consciousness has both intrigued and frustrated physicians throughout the ages. Hippocrates is credited with having made the first description of syncope; the medical term for *fainting* is derived from the Greek term *syncoptein* (to cut short). Despite being one of the oldest recorded medical problems, syncope remains an alarming symptom. This is largely because the causes of syncope are diverse, ranging from benign to life threatening. As aptly stated by one observer, "The only difference between syncope and sudden death is you awake from one."

The definition of syncope is a sudden and brief loss of consciousness with a loss of postural tone, from which recovery is spontaneous. The pathophysiology of all forms of syncope consists of a sudden decrease in or brief cessation of cerebral blood flow and nutrient delivery to the parts of the brain subserving consciousness (i.e., the brain stem reticular activating system, and both cerebral hemispheres) (Figure 6-1). The brain has very limited storage of high-energy phosphates for oxidative phosphorylation and requires continuous delivery of both oxygen and glucose for normal function. Studies in humans have shown that after 5 to 15 seconds of cerebral anoxia, loss of consciousness, pallor, and muscle relaxation occur. More prolonged cerebral ischemia (>15 seconds) is associated with generalized tonic spasms and incontinence. Loss of vascular resistance and decreased cardiac output are responsible for the vast majority of syncopal events as a result of transient systemic hypotension. Episodic weakness or presyncope represent less severe grades of syncope without loss of consciousness, whereas more prolonged hypotension results in shock.

LOSS OF VASCULAR RESISTANCE

Changes in posture and physical exercise are among many activities that challenge cerebral perfusion. Baroreceptors located in the arterial and cardiopulmonary regions evolved to closely regulate blood pressure. Information from the baroreceptors is relayed to the central nervous system (CNS), where neuronal cell groups regulate reflex cardiovascular activity through changes in sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) outflow. Failure of these homeostatic mechanisms can result in hypotension and syncope. This type of syncope is referred to as *neurally mediated syncope* (NMS), reflex, vasovagal, or neurocardiogenic syncope. This is the most common cause of syncope in humans and is the most likely cause in healthy patients.

NMS is characterized by arterial vasodilation (SNS withdrawal) in the setting of relative or absolute bradycardia (PNS stimulation). Correction of the bradycardia does not necessarily alleviate symptoms of syncope because of the concurrent vasodepressor response. Neurally mediated syncope typically has specific triggers, such as strong emotion, pain, or strong vagal stimulation (e.g., cough, micturition, defecation, swallowing). Patients may experience prodromal signs of autonomic stimulation that include pallor, nausea, mydriasis, hyperventilation, and bradycardia. Complete recovery from NMS tends to be slower than with other causes of syncope. These episodes are believed to represent a hypersensitive autonomic system that overresponds to various stressors in predisposed individuals. The exact cause of NMS has not been elucidated

and is likely heterogenous. The risk of sudden death is thought to be very low in NMS. Markedly prolonged periods of asystole may rarely lead to sudden death.

NMS can be classified as postural (associated with the upright position), central (occurring in response to strong emotional stimulation or epileptic discharges), and situational (after specific stimulation of sensory or visceral afferents). In dogs, central and situational NMS is recognized. Examples include syncope induced by hyperexcitability or hyperventilation (or both), vomiting, excessive pulling on a lead, exertion, and cough. Long periods of ventricular asystole (>8 seconds) have been documented to precede cough-induced syncope. Boxers seem predisposed to NMS. Vigorous exercise, excitement, or both typically precede collapse, which is characterized by the classic pallor, absolute or relative bradycardia, and gradual recovery. In pugs, syncope associated with stimulation of afferent fibers from the laryngeal or nasal mucosa, leading to decreased blood pressure, cardiac standstill, and apnea has been demonstrated.

NMS represents only one aspect of a broad, heterogenous group of disturbances of the autonomic nervous system (ANS). In contrast to intermittent periods of hypotension seen in reflex syncope, other patients can develop failure of the ANS to function under normal circumstances. In contrast to patients with reflex syncope, patients suffering from ANS failure syndromes have many other complaints relating to ANS disturbances in other organ systems (e.g., disruptions in bladder and gastrointestinal function). Autonomic failure secondary to a wide variety of disorders, including diffuse systemic illnesses, such as renal failure, cancer, and diabetes mellitus may produce varying degrees of disruption in autonomic function, leading to hypotension and syncope.

REDUCED CARDIAC OUTPUT

In the evaluation of syncope, the presence of structural heart disease (such as cardiomyopathy, congenital and valvular

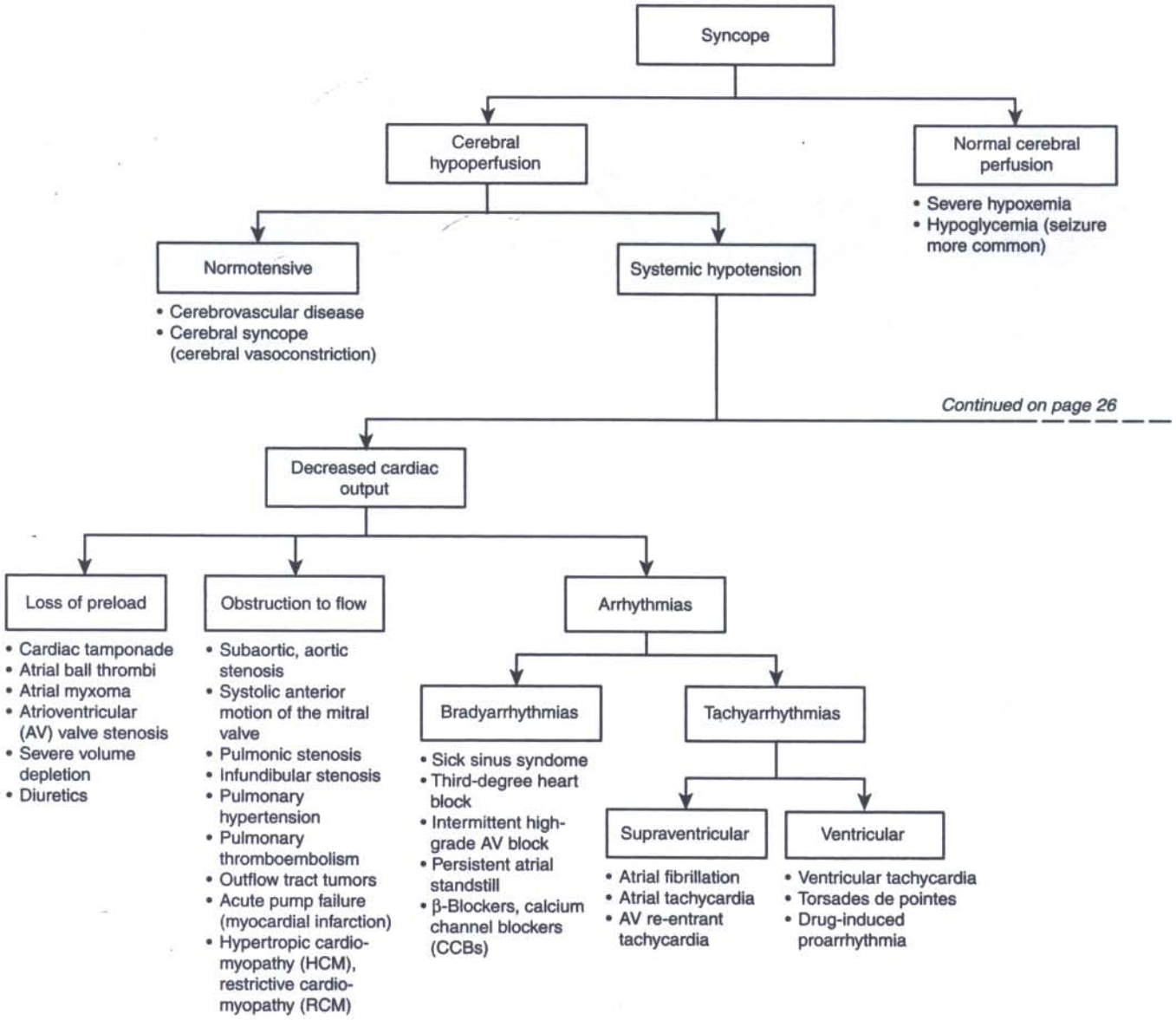


Figure 6-1 Pathophysiology and differential diagnosis for syncope. *A-V,* Atrioventricular; *RV,* right ventricular; *HCM,* hypertrophic cardiomyopathy; *RCM,* restrictive cardiomyopathy; *CCB,* calcium channel blocker; *ACEI,* angiotensin converting enzyme inhibitor.

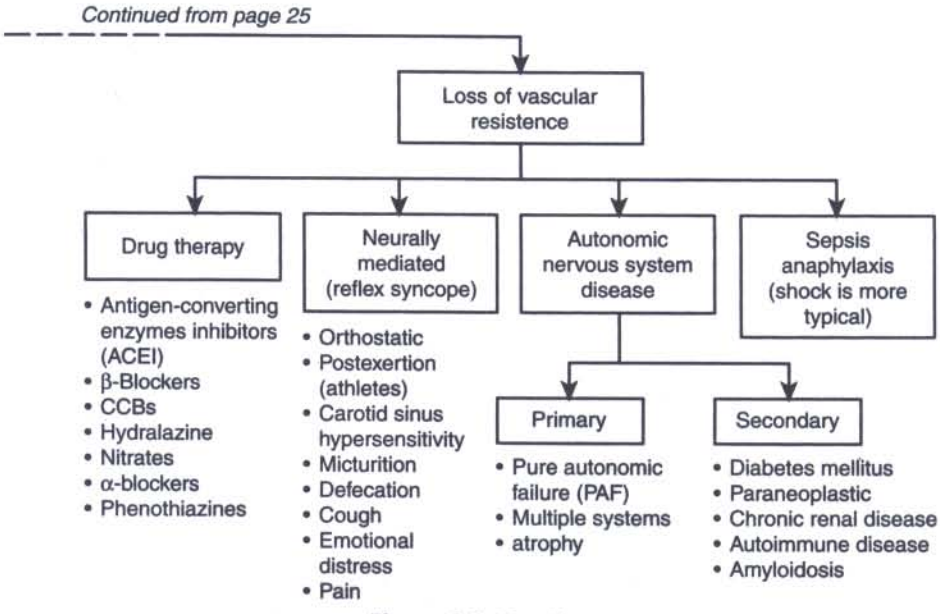


Figure 6-1 Cont'd.

heart disease) has emerged as the most important factor for predicting the risk of death and the likelihood of arrhythmias. Underlying heart disease, irrespective of the cause of syncope, is the factor associated with an increased risk of death.

Malignant causes are more likely if syncope is exertional. Exertional syncope is a common manifestation of all types of heart disease in which cardiac output is fixed and does not rise normally (or falls) with exercise. Systemic vascular resistance normally decreases with exercise because of arteriolar dilatation. This decline in peripheral vascular resistance normally is compensated for by an increase in cardiac output, thus maintaining arterial pressure and cerebral perfusion. In conditions that cause severe obstruction to flow, cardiac output may not increase, leading to hypotension and syncope. Exertion may also lead to neurally mediated syncope in patients with severe aortic or subaortic stenosis. Heightened SNS stimulation and high intraventricular pressures associated with exercise are thought to stimulate ventricular mechanoreceptors that normally respond to stretch. The resultant afferent neural traffic to the brain stem is thought to mimic conditions of hypertension, leading to a paradoxic sympathetic withdrawal and vagal simulation despite systemic hypotension. Abnormal vascular responses to exercise as a result of altered baroreceptor function have been shown to cause syncope in human patients with hypertrophic cardiomyopathy. Patients who demonstrated vascular instability were also at markedly increased risk of sudden cardiac death.

In patients with CHF, the combination of a low cardiac output, volume depletion caused by diuretic use, and vasodilator therapy likely all play a role in syncope. The propensity for arrhythmias is exacerbated in CHF. In addition, patients with overt pulmonary congestion may be prone to exertional collapse because of hypoxia-induced pulmonary vasoconstriction leading to pulmonary artery hypertension. Many animals with congestive symptoms that collapse will not experience syncope once their heart failure is controlled.

Arrhythmic causes for syncope include tachyarrhythmias and bradyarrhythmias. Tachyarrhythmias lead to collapse as the result of the abrupt reduction in cardiac output related to the marked reduction in diastolic filling. Supraventricular tachyarrhythmias in young dogs without structural heart disease should raise one's suspicion of atrioventricular (A-V) reentrant tachycardias caused by accessory pathways. In the presence of substantial heart disease and concomitant atrial enlargement, atrial tachycardias and atrial fibrillation (sustained or paroxysmal) are common. Supraventricular arrhythmias are less likely to lead to sudden death than ventricular tachyarrhythmias.

Life-threatening ventricular tachyarrhythmias occur most commonly in patients with advanced heart disease of any cause. Boxer and Doberman cardiomyopathies are considered particularly high risk for sudden death, which may be the first manifestation of malignant ventricular arrhythmias in these breeds. Advanced mitral valve disease can result in ventricular arrhythmias and sudden cardiac death. Because exercise can exacerbate subendocardial myocardial ischemia, ventricular tachyarrhythmias may be provoked by exertion in all types of severe heart disease. Exertional sudden death is common in severe subaortic stenosis.

Bradyarrhythmias can lead to very subtle symptoms, such as occasional stumbling, to very dramatic symptoms, such as multiple transient collapses on a daily basis. Seizure activity caused by cerebral hypoperfusion (termed *convulsive syncope*) is most likely to occur in the setting of bradyarrhythmias, as a result of prolonged periods of asystole. Convulsive syncope in patients with intermittent conduction disease is commonly mistaken for neurologic disease. Sick sinus syndrome (SSS) is most commonly associated with the miniature schnauzer but may occur in other breeds. By the time these dogs are syncopal, easily detected abnormalities exist in the rhythm during auscultation and a routine electrocardiogram (EKG). Multiple periods of asystole typically occur, sometimes oscillating with runs of supraventricular tachycardia. Dogs with third-degree heart block may be syncopal with the initiation of their disease, but in some the arrhythmia is an incidental finding. Many dogs with chronic third-degree heart block are not syncopal, presumably as a result of compensatory changes of the cardiovascular system (volume retention) and a stable escape rhythm. Sudden death is surprisingly rare in both SSS and third-degree heart block. Some dogs and cats are syncopal because of intermittent high-grade A-V block characterized by long periods of ventricular asystole. These animals may have extended periods of sinus rhythm, although signs of conduction disease (first-degree heart block, bundle branch block, and intermittent second-degree heart block) should raise one's suspicion of more severe intermittent heart block. It is also worth

noting that the symptoms of asystole (opisthotonus, syncope, seizure) are delayed, usually occurring at the termination of the pause, once the rescue rhythm has resumed. Therefore a bradycardic arrhythmia should not be dismissed based on finding a relatively normal heart rate in a recently collapsed patient.

APPROACH TO THE SYNCOPAL PATIENT

The evaluation of a patient with syncope involves excluding other disorders of consciousness (e.g., presyncope, dizziness, vertigo, sleep disorders, seizure), then determining the cause for the syncopal episode. Causes for episodic weakness should be considered when collapse occurs without loss of consciousness. Dizziness and vertigo do not result in a loss of consciousness or postural tone. Narcolepsy and cataplexy are rare disorders in animals that may mimic syncope. These disorders are characterized by "sleep attacks" in the former and rapid onset and termination of partial to complete flaccid paralysis in the latter. These are heritable disorders in Doberman pinschers, Labrador retrievers, daschunds, and miniature poodles. Seizure is the primary differential for syncope. Distinguishing syncope from seizure can be difficult. Based on the classical features of each, the differentiation seems straightforward; however, in reality the boundaries can be indistinct (Table 6-1).

The generalized epileptic or motor seizure is the classic manifestation of a primary neurologic event; however, complex partial seizure activity is now recognized in veterinary medicine. The primary abnormality of the complex partial seizure is a decrease in consciousness. Motor activity may occur along with autonomic signs such as salivating, urinating, and defecating. In humans, *temporal lobe syncope* is the term used for complex partial seizure in which a loss of consciousness resembles a syncopal episode.

In approximately 40% of patients with syncope, the cause is undetermined. The cause of syncope is difficult to diagnose in many cases because of the transient and often infrequent nature of the events and the fact that syncope rarely occurs in settings where vital functions such as the heart rate, rhythm, and blood pressure can be monitored while symptoms are being displayed. From the foregoing discussion it should be clear that the cornerstone of evaluation of a syncopal patient is thorough history and physical examination. When carefully performed these will have a greater diagnostic yield (45%) than a battery of laboratory tests. This begins with a detailed history, for which veterinarians must rely on witnesses. Because of the distressing nature of these events, owners are often unable to provide an accurate account of the events. For example, their estimation of time is often exaggerated. The frantic struggling to rise after collapse may be interpreted as the tonic clonic limb motions characteristic of generalized seizure. The key questions that should be part of every history taking should extract information about the event (see Table 6-1), age at first episode, frequency of episodes, interepisode duration, symptoms of underlying disease, medications, relation to meals and administration of medications, and relation to exercise. Breed predisposition for cardiac disease or epileptic seizures can also be important.

A thorough physical examination should then be performed. Because cardiac disorders are most likely to result in a risk of sudden death, it is important to search for any evidence of cardiovascular disease. A neurologic examination is also very important to look for evidence for underlying neurologic disease. Interepisode abnormalities may point to the causes for a subacute or chronically reduced cardiac output (e.g., cardiac tamponade, pulmonary thromboembolism), severe systemic disorders (e.g., hemorrhage, severe anemia), or neurologic disease (e.g., abnormal gait or mentation). Once cardiac disease and other malignant causes for syncope (e.g., pulmonary thromboembolism) are excluded, then more benign causes such as NMS and complex partial seizure must be considered. Thus even in the absence of a definitive diagnosis, an owner's mind can be put at ease in most cases.

Table 6-1

General Features Differentiating Syncope versus Seizure

	SYNCOPE	SEIZURE
Precipitating event	Exertion, pain, micturition, defecation, cough, stressful event	
Prodrome	Seconds Acute weakness, staggering, vocalization, autonomic stimulation	Minutes to days Atypical behavior (e.g., anxious, more withdrawn, attention seeking) (+/–) Vomit
Aura	None	None (epileptic seizure) Marks onset of partial seizure, often with secondary generation
Event characteristics	Opisthotonus Motionless Flaccid or rigid extension of limbs *Exception:* convulsive syncope Duration often transient (<1 minute)	Chomping, hypersalivation Tonic/clonic limb motion Motor activity *Exception:* complex partial seizure or akinetic or temporal lobe seizure Duration often 1 to 2 minutes (>5 minutes suggests seizure versus syncope)
Recovery	Rapid recovery of normal mentation Often able to walk within minutes *Exception:* neurally mediated syncope (NMS) may be a more prolonged recovery	Slowness returning to consciousness Disorientation (commonly 10 minutes or longer) *Exception:* recovery can be rapid

CHAPTER 7

Weakness

Rhonda L. Schulman

Weakness is a common presenting complaint in small animal medicine. In veterinary medicine, the terms *fatigue* and *lethargy* are often used synonymously with weakness. A multitude of diseases can result in weakness, often making this presenting complaint a diagnostic challenge (Figure 7-1).

The patient's history can provide many important clues as to the cause of the weakness. In addition to routine questions regarding time course, concurrent illness, medications, and familial history, the owners should be asked about any associations with either exercise or time of day. For example, patients with disorders of glucose homeostasis may typically display symptoms either after eating or fasting. Classically, myasthenic dogs exhibit profound weakness after short bursts of normal activity.

The patient's signalment will assist in ordering the differential list. Purebred animals are susceptible to breed-specific conditions that can result in weakness. The age of the patient may be more in accordance with some differentials. Puppies and kittens will be more likely to suffer from congenital diseases, portosystemic shunts, hypoglycemia, toxin exposure, and infectious diseases, whereas geriatric patients may present secondary to neoplastic conditions or major organ dysfunction. Immune-mediated diseases are more prevalent in female dogs.

A thorough physical examination is mandatory. Pain on manipulation of joints or long bones may suggest an underlying orthopedic problem, manifesting as weakness. Dermatologic signs such as symmetrical alopecia might indicate an endocrine disorder. Primary cardiovascular disease may be apparent during examination of mucous membranes, capillary

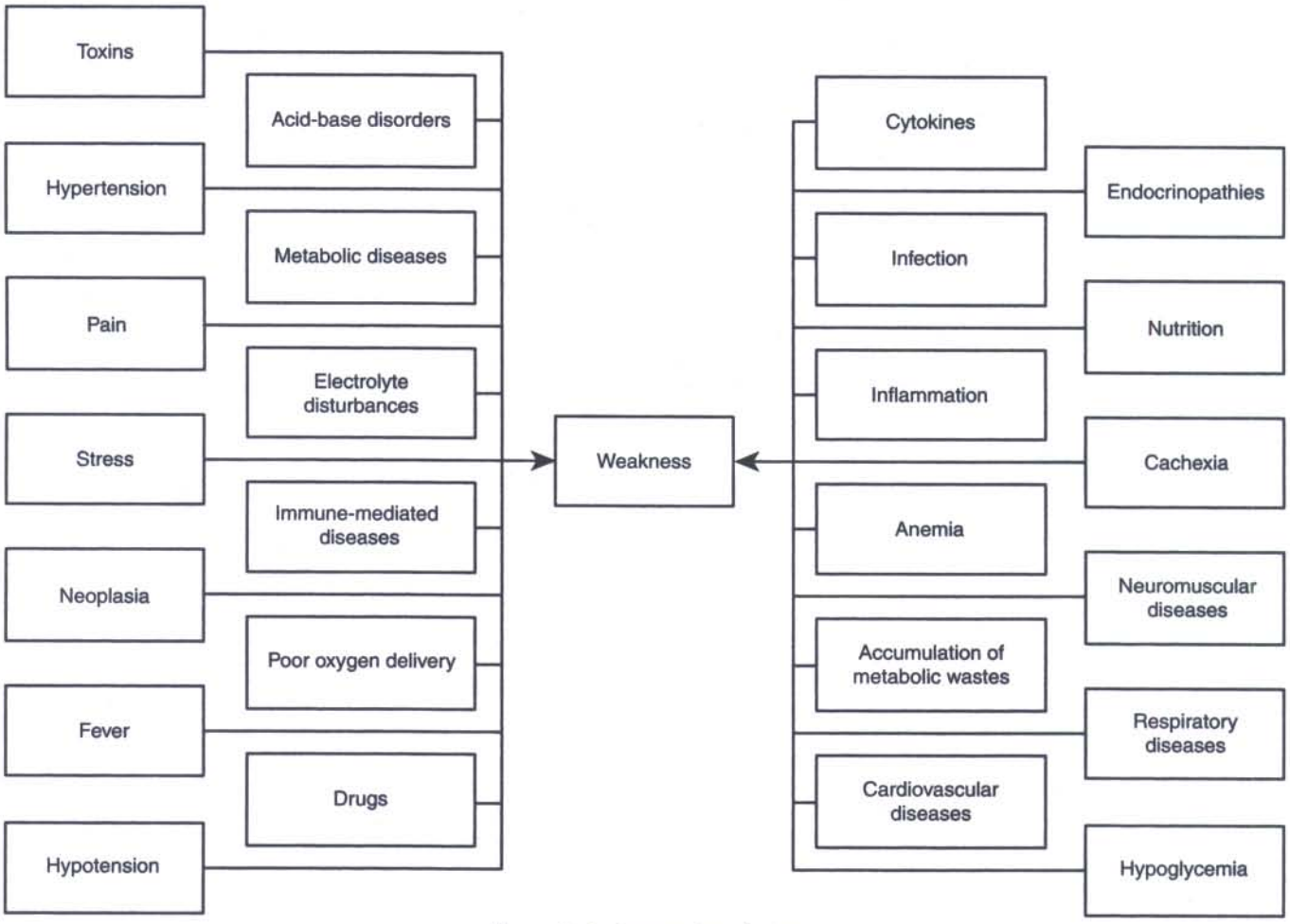


Figure 7-1 Causes of weakness.

refill time, thoracic auscultation, and peripheral pulses. Because many neurologic disorders can also result in weakness, a complete neurologic examination is indicated in the weak patient.

In some cases a specific finding during the initial physical examination and laboratory analysis results in a definitive diagnosis; unfortunately, many of the conditions resulting in weakness have nonspecific clinical signs and laboratory findings. As a result the initial diagnostic evaluation is used to prioritize differential diagnoses and identify additional diagnostic tests. This chapter discusses the different mechanisms and diseases that result in weakness.

SPECIFIC MECHANISMS AND DISEASES

Metabolic Diseases

Metabolic diseases are among the most common causes of weakness. Major organ dysfunction can result in weakness through many pathways, such as accumulation of metabolic products, cytokine production, electrolyte imbalances, acid-base disorders, anemia of chronic disease, and nutritional disturbances. Renal and hepatic failure are two examples of metabolic diseases that cause weakness by multiple mechanisms. Biochemical evaluation is essential in the diagnosis of metabolic disorders.

Electrolyte Disorders

Electrolyte imbalances accompany a multitude of conditions and are often the component of the disease that leads to the clinical sign of weakness. Mild changes in electrolyte levels rarely cause weakness. Significant hypokalemia may result from excessive loss (gastrointestinal, urinary) or be iatrogenic in nature (fluid diuresis, diuretics). Hyperkalemia, as is seen with hypoadrenocorticism and urinary tract obstruction or rupture, also results in weakness. Sodium imbalances, both increases and decreases, can result in weakness. Hyponatremia is seen in hypoadrenocorticism, congestive heart failure, liver diseases, and losses through the gastrointestinal system and third space. Hypernatremia may be seen with hyperaldosteronism, salt poisoning, and free-water loss. Perturbations in calcium homeostasis are an important cause of weakness. Hypocalcemia produces excessive excitability of the nervous system, manifested as tetany and possibly seizures. Between bouts of tetany, patients may exhibit weakness. Common causes of hypocalcemia include hypoparathyroidism, renal disease, ethylene glycol toxicity, and eclampsia. Hypomagnesemia may also result in weakness. Hypomagnesemia is prevalent in critically ill patients because of renal and gastrointestinal losses coupled with decreased intake.

Acid-Base Disorders

Disturbances in blood pH can accompany many metabolic conditions and can be seen with pulmonary disease. Drugs and toxins may also lead to acidosis or alkalosis. Weakness can be seen with either disorder.

Inflammatory Conditions

Inflammation accompanies many disease processes such as pancreatitis, hepatitis, neoplasia, infectious disease, and immune-mediated conditions. Systemic inflammation can result in pyrexia, negative energy balance, cytokine production, anemia, and acid-base disorders, all exacerbating signs of weakness. Many of these changes are mediated by increased cytokine production in response to the inflammatory stimuli. Certain cytokines, such as interleukin (IL)-1, IL-6, and interferon (IFN)-α, directly cause fatigue via central pathways. Cachexins, such as IL-1, IL-6, IFN-γ, and tumor necrosis factor (TNF)-α suppress hunger and promote muscle wasting. Cytokine inhibition of erythropoiesis, resulting in anemia, indirectly contributes to weakness.

Infectious Diseases

Bacterial, viral, fungal, rickettsial, protozoal, or parasitic agents can infect any organ or body system. The presenting signs typically indicate the involved organ, such as coughing with respiratory disease or dysuria with prostatitis, as well as nonspecific signs of infection, such as weakness and inappetance. The infecting agent may produce toxins that cause weakness in addition to this being related to the resultant inflammation and organ dysfunction secondary to the infection.

Immune-Mediated Diseases

Generalized weakness or exercise intolerance is a common component of many immune-mediated disorders. Immune-mediated diseases may lead to anemia, joint or muscle disease with resultant pain, hepatic or renal dysfunction, and inflammation and chronic wasting. Through any or all of these mechanisms, patients suffering from a variety of immune-mediated diseases will display weakness.

Anemia

Anemia, with the resultant decrease in oxygen delivery to the tissues, can cause weakness. The presence of weakness or exercise intolerance does not specify the pathophysiologic mechanism resulting in the anemic state. Often more severe signs will be seen with acute blood loss than will be noted with more chronic cases, even if the magnitude of the anemia is greater in the chronic case. With chronic diseases, the patient has more time to adapt to the anemia, and clinical signs may be subtle.

Endocrine Diseases

Weakness can be seen with almost every endocrine disease including diabetes mellitus, hypothyroidism, hypoadrenocorticism, hyperadrenocorticism, hypoglycemia, hyperparathyroidism, hypoparathyroidism, and pheochromocytoma. Hyperthyroidism uncommonly manifests as weakness. Until a severe crisis occurs, owners and veterinarians miss early, nonspecific episodes of weakness caused by hypoadrenocorticism. Endocrine disturbances can result in weakness via various mechanisms. Many endocrinopathies, such as hypoadrenocorticism, hypo- and hyperparathyroidism, and diabetes mellitus can produce weakness as the result of electrolyte abnormalities. Neuropathies and myopathies may be seen with diabetes mellitus and hypoglycemia, as well as hyperadrenocorticism and hypothyroidism.

Cardiovascular Disease

The physical examination will often be strongly suggestive of cardiovascular disease if the dysfunction is of sufficient severity to induce exercise intolerance. Heart murmurs will frequently be ausculted in these patients. Crackles may be heard if the patient is suffering from left heart failure. Right heart failure can produce a variety of abnormalities that may be detected on physical exam, including jugular pulses, ascites, and decreased heart and lung sounds secondary to pleural effusion. Often, the biggest diagnostic challenge is establishing that a heart murmur does not signify heart disease of a nature sufficient to induce exercise intolerance. Cardiovascular disease results in the clinical sign of weakness caused by poor cardiac output leading to diminished oxygen delivery to the tissues or by cardiac cachexia. Valvular disease tends to cause exercise intolerance only when it has progressed to congestive failure. Because of the associated septicemia, bacterial endocarditis usually results in extreme lethargy. Arrhythmias may manifest as intermittent weakness. Diseases resulting in pericardial effusion often produce profound weakness and potentially sudden collapse.

Blood Pressure

Alterations in blood pressure can produce weakness, often episodically. Hypotension can result from cardiac dysfunction,

hypovolemia, or decreased vascular tone. Hypotension creates poor perfusion and oxygen delivery. Systemic hypertension damages many organs, including the heart, brain, kidneys, and eyes. Systemic hypertension is usually a secondary problem in veterinary patients, with underlying diseases including heart disease, renal disease, hyperthyroidism, hyperadrenocorticism, and diabetes mellitus. Caution must be exercised when treating hypertension to not create hypotension.

Respiratory Diseases

Similar to heart disease, respiratory disease may be obvious during the initial physical examination. Historical complaints frequently include coughing, alterations in respiration, or nasal discharge. Changes in lung sounds and respiratory rate or effort will be detected when examining the patient. Respiratory diseases that result in exercise intolerance are commonly infectious or inflammatory in nature. Thoracic radiographs, arterial blood gases, and bronchoalveolar lavage or tracheal wash are often necessary diagnostics. Pulmonary hypertension can also lead to weakness. Pulmonary hypertension may occur secondary to heartworm disease or chronic pulmonary disease and carries a guarded prognosis.

Neuromuscular Diseases

Brain

Any disorder affecting the brain can cause weakness. The neurologic exam will localize the problem as being central in origin. Encephalitis caused by infectious agents, inflammatory conditions, or immune-mediated disease; cerebral vascular accidents (embolism or hemorrhage); space-occupying lesions (neoplasia, granulomas, or hydrocephalus); vestibular disease (central or peripheral); and idiopathic epilepsy can present as chronic or intermittent weakness. Additionally, many medications act on the central nervous system (CNS) result in lethargy or exercise intolerance. The minimum data base may help further define the cause. Often more advanced diagnostics such as imaging of the brain or analysis of the cerebrospinal fluid (CSF) will be necessary to fully diagnose the underlying condition.

Spinal Cord Disease

Lesions affecting the spinal cord between C1 to T2 can result in quadriparesis. More caudal lesions may cause paraparesis. Causes of spinal cord disease include trauma, degenerative disc disease, vascular accidents, neoplasia, infectious diseases, and inflammatory conditions. Chronic, progressive conditions are more likely to result in the vague presentation of weakness compared with the more recognizable problem of acute paraparesis. In addition to the minimum data base, imaging and CSF analysis may be required to determine the underlying cause of spinal cord disease.

Neuropathies

Disorders affecting peripheral nerves can result in generalized weakness. The neurologic examination of these patients will typically reflect lower motor neuron dysfunction with reduced or absent reflexes. Causes of polyneuropathy include polyradiculoneuritis; paraneoplastic disorders; endocrine diseases including diabetes mellitus, hyperadrenocorticism, and hypothyroidism; drugs and toxins (vincristine, lead); infectious agents *(Toxoplasma, Neospora)*; and developmental disorders. Weakness may also result from disruption of neuromuscular transmission. Myasthenia gravis can be either acquired or congenital. Severe exercise intolerance is often a hallmark of this disorder. Other neuromuscular disorders include tick paralysis and botulism. Specialized testing such as electromyography, nerve and muscle biopsy, and serology for antibodies to the acetylcholine receptor are often necessary to establish the diagnosis.

Neoplasia

Neoplasia can lead to weakness through many different pathways. Associated inflammation will result in the release of a variety of cytokines that can cause fatigue, cachexia, and anemia. Tumors may specifically release substances such as insulin, corticosteroids, thyroid and parathyroid hormones, catecholamines, and estrogen that cause or exacerbate weakness. Some tumors such as hemangiosarcoma can cause severe, acute blood loss. Cancers can also result in anemia via disseminated intravascular coagulopathy (DIC). Neoplastic invasion or embolization can instigate organ failure. Finally, cancer can produce weakness in patients from pain.

Physical and Psychologic Stress

Stress is the major cause of fatigue in humans. Psychologic causes of lethargy are much harder to evaluate in veterinary patients but should not be completely discounted. Events that can cause clinically significant anxiety (thunderstorms, fireworks, boarding) or chronic stress (social status, deprivation, illness, pain) may result in generalized weakness. Stress of any nature can activate the hypothalamic-pituitary-adrenal axis, with resultant increased levels of corticotropin-releasing hormone (CRH) and cortisol. Hyperactivity of this axis can lead to depression and weakness. CRH may play a specific role in the development of fatigue. It has also been suggested that primary hypothalamic dysfunction may be important in the cause of generalized weakness.

Exercise intolerance may be seen in an animal pushed beyond its physical capabilities. This can occur both in animals that are not used to exercise and in fit animals that overexert themselves during activities such as hunting and racing.

Nutritional Derangements

Nutritional derangements may be the patient's primary problem or may be a reflection of chronic disease. Changes or reduction in protein synthesis, altered glucose homeostasis, or dyslipoproteinemias may all result in weakness. Specific vitamin and mineral deficiencies may also cause weakness. Nutritional disorders may arise from an inadequate diet, either in content or calories. The patient may not be able to use or synthesize nutrients appropriately or may lose them excessively. Liver, pancreatic, kidney, and gastrointestinal disease may all cause weakness via nutritional deficits. Lipid disorders can arise from endocrinopathies such as diabetes mellitus, hypothyroidism, and hyperadrenocorticism; renal disease; liver disease; pancreatitis; diet; or familial causes. Any chronic condition can lead to cachexia. The clinical signs of cachexia are anorexia, weight loss, and muscle wasting. Cachectic patients suffer from a negative energy balance and metabolic derangements. These changes are often mediated by the same cytokines that cause fatigue.

Drugs

A complete history is essential for the patient with lethargy or weakness. Many medications including anticonvulsants, antihistamines, glucocorticoids, tranquilizers, narcotics, antibiotics, chemotherapeutics, diuretics, and cardiovascular agents can result in side effects, including weakness. If the onset of exercise intolerance coincides with the administration of a new medication, it may be prudent to discontinue that medication or lower the dose.

Pain

Patients may appear exercise intolerant if they are in extreme pain. Animals with spinal, bone, or joint pain are often quite reluctant to move. The physical examination should elucidate musculoskeletal or neurologic pain. Abdominal pain can result from distention, inflammation, or ischemia of organs. These patients may display a hunched appearance and resent abdominal palpation. Visceral pain is less localized and may be harder to pinpoint.

Skin and Subcutaneous

CHAPTER 8

The Skin as a Sensor of Internal Medical Disorders

Sandra R. Merchant

Cutaneous manifestations of internal disease are uncommon. As expertise is strengthened in the field of veterinary dermatology, clinicians continue to discover subtle clues of the skin that alert them to further investigate internal organ systems. In certain diseases the skin may provide the first clinical signs noted. In some conditions, cutaneous and systemic signs occur simultaneously, whereas in others, the skin may reflect a general catabolic and cachectic stage brought about by the primary disease process.

FUNGAL DISEASES

Deep mycoses are fungal infections of internal organs that can spread hematogenously to the skin. Primary inoculation of the skin is rare. Infections that can cause nodules, plaques, and draining tracts include *Blastomyces dermatitidis, Histoplasma capsulatum, Cryptococcus neoformans,* and *Coccidiodes immitis*. Because of the accessibility of the skin, nodules and draining tracts of the skin can be easily biopsied for culture and histopathology to aid in diagnosis and choice of therapy for treatment of systemic mycotic diseases.

Pithium insidiosum, an aquatic oomycete, primarily affects the gastrointestinal tract but can also cause an ulcerative, draining dermatitis of the skin. With *Pithium*, each organ system is inoculated separately by contact with fresh water containing the infective zoospores.

Lagenidium spp. is a recently recognized oomycete pathogen also causing cutaneous or subcutaneous nodules or ulcerated, thickened edematous draining lesions. In contrast to *Pithium*, most dogs with lagenidiosis have lesions in sites other than the gastrointestinal tract.

VIRAL DISEASES

Canine distemper can cause hyperkeratosis of the nasal planum and foot pad, "hard pad disease." Young puppies may develop widespread impetigo.

Feline rhinotracheitis is an infection with an alpha herpes virus. Occasionally, cats will develop oral and cutaneous ulcers that are usually multiple and can occur anywhere on the body. An ulcerative and necrotizing facial dermatitis has been recognized in cats that involves the periocular skin, nasal planum, and bridge of the nose. Exfoliative erythema multiforme has been seen after upper respiratory infections in the cat, and ulceration of the foot pads and perineal skin has been seen with cats infected with *Calicivirus*.

Feline leukemia virus (FeLV) most commonly affects the skin by its cytosuppressive actions. Clinical signs include chronic or recurrent gingivitis or pyoderma, seborrhea, exfoliative dermatitis, pruritus, and cutaneous horns. A facially distributed pruritic crusting dermatosis has been seen secondary to FeLV infection.

Feline immunodeficiency virus (FIV)–infected cats may have chronic or recurrent abscesses, chronic bacterial infection of the skin and ears; and increased incidence of fungal, ringworm, and *Demodex* infections. Generalized papules with crusts, alopecia, and scaling more severely affecting the head and limbs have been associated with FIV-positive cats.

BACTERIAL DISEASES

Lyme disease is a tickborne disorder of dogs caused by the spirochete *Borrelia burgdorferi*. Arthritis and fever are prominent signs. An expanding annular lesion called *erythema chronicum migrans* can characterize early disease in humans. This clinical sign has been documented in affected dogs in Europe.

Dogs infected with *Rickettsia rickettsii* may have erythema, petechia, edema, and occasional necrosis of the oral, ocular, and genital mucous membranes, as well as the skin of the pinna, nose, ventrum, and scrotum.

Dogs infected with *Ehrlichia* spp., may have crusting of the nasal bridge, pustular and purpuric lesions secondary to vasculitis, and an intensely pruritic papular and crusting dermatitis.

IMMUNE-MEDIATED DISEASES

Erythema multiforme usually has an acute onset of erythematous macules and papules that spread peripherally and clear centrally. The lesions are most commonly seen at the mucocutaneous junctions, nasal mucosa, pinnae, axilla, and inguinal regions. Erythema multiforme can be associated with infectious diseases and neoplasia and less likely as a manifestation of a drug eruption.

Toxic epidermal necrolysis (TEN) is an acute condition believed to be caused by a lymphocyte- and macrophage-mediated mechanism of immunologic injury. Drugs are the most common known inciting cause, but neoplasia and infection have also been documented. The first signs of TEN are widespread erythema of the skin that may be painful on palpation. Rapid and widespread full-thickness necrosis of the epidermis occurs. The most common areas affected are oral mucosa, footpad, face, and skin of the trunk.

Systemic lupus erythematosus (SLE) produces skin lesions that can be highly variable. They may be nonspecific cutaneous lesions or take the form of cutaneous lupus erythematosus lesions that are specific skin syndromes characterized by certain clinical and histopathologic findings. Cutaneous manifestations

of SLE include seborrheic disease, alopecia, diffuse or regional erythema, cutaneous or mucocutaneous vesicles and bullae, footpad ulcers and hyperkeratosis, panniculitis, refractory secondary bacterial infection, and nasal dermatitis. Skin lesions commonly affect nonhaired areas.

Vasculitis is most commonly believed to be immunologically mediated and the result of a drug reaction. It may be initiated by a hypersensitivity reaction, food allergy, insect sting or arthropod bite reaction, canine mast cell tumor, feline collagenolytic granuloma, rabies vaccine reaction and dermatomyositis in the dog, coexisting disease (e.g., infections, malignancies, lupus), precipitating factors (e.g., drugs, vaccines), or idiopathic in origin. Cutaneous lesions include poorly healing ulcers typically located in the center of the footpads, erosions, ulcerations, and crusting that either affect the pinnal margin or form a linear lesion extending down the center of the concave aspect of the pinna. Some animals experience an urticarial form of vasculitis.

Hemolytic uremia syndrome, a cutaneous and renal glomerular vasculopathy has been described in greyhounds. Greyhounds can have this syndrome (with skin disease alone), systemic signs coincident with typical skin lesions, cutaneous disease before systemic signs, or manifestations of azotemia before cutaneous ulcerations. Cutaneous signs include multiple palpable purpura primarily on the limbs varying from pinpoint to 10 cm in diameter that subsequently ulcerate and discharge a serosanguineous fluid. The ulceration may extend into the subcutaneous tissues.

This syndrome is presumed to be a vasculopathy secondary to a verotoxin elaborated by *E. coli* obtained from eating raw beef products. A genetic predisposition or a propensity for feeding raw beef products to greyhounds may explain the breed susceptibility.

Dermatomyositis is a familial, idiopathic (vascular?) condition of the skin and muscle of collies and Shetland sheepdogs and has been recognized in other breeds of dogs. Skin lesions occur in areas of mechanical trauma and are commonly seen on the face, especially around the eyes, on the tips of the ears, on carpal and tarsal regions, on the digits, and on the tip of the tail. Early lesions include pustules, vesicles, papules, or small nodules progressing to crusting or alopecia. Ulceration can be seen in severely affected dogs. Many of these dogs are left scarred.

NEOPLASIA

Nodular dermatofibrosis is a disease seen primarily in German shepherd dogs but has also been reported in golden retrievers, boxers, German shepherd crosses, and mix-breed dogs. Clinical signs include numerous firm dermal to subcutaneous nodules that vary in size from a few millimeters up to 5 cm that can coalesce. The epidermis overlying the nodules may be intact but can sometimes be ulcerated and inflamed. Alopecia and hyperpigmentation can be seen over the nodules.

Systemic disease seen in association with these multiple skin tumors include renal lesions varying from polycystic kidneys to cystadenomas to cystadenocarcinomas and uterine leiomyomas in intact females. Most kidney involvement is bilateral. Many dogs have multiple small intestinal polyps that are asymptomatic.

Testicular Tumors

Dermatologic manifestations of testicular tumors are uncommon. Dermatologic manifestation occurs most commonly in the male feminization syndrome associated with Sertoli cell tumors. Dogs with male feminization display dermatologic signs of bilaterally symmetric alopecia that is nonpruritic, usually beginning in the perineal and genital regions and spreading to the ventral abdomen, thorax, flank, and neck. In some cases, the alopecia is restricted to the flanks. Other dermatologic manifestations of testicular tumors include seborrhea, ceruminous otitis externa, macular melanosis of the inguinal and perianal skin, and a linear erythematous or melanotic macular change that is present along the ventral aspect of the prepuce extending to the scrotum. Occasionally a dog will have a papular, pruritic eruption.

Pheochromocytoma

Pheochromocytomas are endocrine tumors arising from the adrenal medulla. The clinical signs associated with pheochromocytomas are quite variable and often subtle. Episodic panting or dyspnea and increased bronchovesicular sounds, weight loss, anorexia, depression, weakness, and collapse are some of the systemic abnormalities noted. The dermatologic manifestation is intermittent flushing, especially of the pinna.

Paraneoplastic Syndromes

Paraneoplastic syndromes consist of clinical signs that are associated with malignancies but not directly related to tumor invasion. In the dog these paraneoplastic syndromes include the crusting and fissuring dermatosis associated with necrolytic migratory erythema, nodular skin disease seen with nodular dermatofibrosis, paraneoplastic pemphigus vulgaris associated with a thymic lymphoma, suspect paraneoplastic pemphigus foliaceus from a Sertoli cell tumor or mammary carcinoma, and necrotizing panniculitis associated with pancreatic carcinoma or severe pancreatitis. In the cat these paraneoplastic dermatoses include the skin fragility syndrome seen with feline hyperadrenocorticism; exfoliative dermatosis associated with feline thymoma; and a unique bilaterally symmetrical, ventral glistening paraneoplastic alopecia associated with pancreatic carcinoma, bile duct carcinoma, and thymoma.

Paraneoplastic pruritus has been seen associated with lymphosarcoma in the dog, squamous cell carcinoma in a cat, and liver disease or cholangiohepatitis in the cat.

ENDOCRINOPATHIES

Hypothyroidism

Dermatologic manifestations of hypothyroidism consist of a dry scaly coat, bilaterally symmetrical nonpruritic truncal alopecia, rat tail, variable degrees of hyperpigmentation seen on the ventral neck, abdomen, or in a diffuse truncal distribution; lichenification; myxedema; vesicular mucinosis; haircoat color change; comedones; hypertrichosis; seborrhea oleosa; seborrhea sicca; seborrheic dermatitis; and *Malassezia* dermatitis. Pruritus may be seen with the occurrence of secondary dermatologic diseases of seborrhea, *Malassezia* dermatitis, and staphylococcal pyoderma. Many dogs (with the exception of working and breeding dogs) may be examined when dermatologic abnormalities become evident.

Hyperadrenocorticism

Hyperadrenocorticism or *Cushing's syndrome* refers to the constellation of clinical and chemical abnormalities resulting from chronic exposure to excess glucocorticoids. Dermatologic abnormalities may be quite striking. Classic changes include hair loss that is usually bilaterally symmetrical, but focal hair loss may also be seen. Comedones, especially on the ventral abdomen and thin, inelastic skin, are also usually seen. Other changes include hyperpigmentation, seborrhea sicca, telangiectasia, increased prominence of surgical scars, lack of hair regrowth after shaving, and adult-onset generalized demodicosis. One dramatic manifestation seen in 5% of dogs is calcinosis cutis. Adult dogs that have never had bacterial skin disease may show a marked predisposition to recurrent staphylococcal skin infections.

Hyperthyroidism

The most common endocrine disorder of middle-aged to old cats is hyperthyroidism. Many of these cats have an unkempt haircoat, with excessive shedding and matting of the hair. Changes in hair texture, partial hair loss, and increased nail growth also are features of feline hyperthyroidism. In cats with areas of complete alopecia, behavioral changes associated with excessive grooming have been documented.

Diabetes Mellitus

Cutaneous lesions associated with diabetes mellitus are uncommon. The most common dermatologic manifestations are otitis externa, pyoderma, seborrheic skin disease, demodicosis, thin skin, alopecia, and xanthomatosis.

PARASITIC DISEASES

Leishmaniasis is a protozoal infection caused by a variety of *Leishmania* spp. endemic in many areas of the world, including the United States. It has been reported in foxhound kennels in 20 states in the United States. Skin lesions occur in over 80% of the dogs with visceral involvement. The most common sign is an exfoliative dermatitis primarily on the head, pinnae, and extremities. Nasodigital hyperkeratosis can been seen. Periocular alopecia is also common. An ulcerative dermatitis, onychogryposis, paronychia, sterile pustular dermatitis, nasal depigmentation with erosion, ulceration, and nodular dermatitis may be seen.

Demodicosis of the dog is most often caused by *Demodex canis*. Demodectic mange of the cat is caused by *Demodex cati* and *Demodex gatoi*. Adult-onset canine generalized demodicosis is most likely caused by suppression of the immune system. Several factors have been suggested or documented as initiating canine generalized demodicosis, including administration of immunosuppressive drugs, serious systemic disease to include hyperadrenocorticism, hypothyroidism, diabetes mellitus, blastomycosis and other deep mycoses, lymphosarcoma, hemangiosarcoma, and mammary adenocarcinoma. In addition, estrus, whelping, heartworm disease, and intestinal parasite infestation have all been associated with the onset of generalized demodicosis.

Because most cases of demodectic mange in the cat have occurred in the adult, immunosuppression as a result of an underlying disease has been proposed as the initiating factor. Generalized demodicosis has been seen in cats with diabetes mellitus, respiratory infection, FeLV infection, SLE, toxoplasmosis, feline endocrine alopecia, FIV infection, hyperadrenocorticism, feline infections peritonitis (FIP), and neoplasia. Immunosuppressive drugs (glucocorticoids and progestational compounds) should also be considered potential initiating factors.

Generalized patchy or diffuse alopecia with erythema, scaling, crusting, and follicular plugging may be seen in the dog. Some animals will have prominent hyperpigmentation in affected areas. In some cases the *Demodex* infection is confined to the feet only.

In the cat, signs of generalized demodicosis secondary to *Demodex cati* include multifocal to generalized patches of alopecia with variable scaling, macules, papules, erythema, hyperpigmentation, crusting, and symmetrical alopecia of the head, neck, legs, and trunk. Pruritus, when present, is either intermittent or mild. Clinical signs associated with *Demodex gatoi* include more severe pruritus, mild erythema, broken hairs, and alopecia of the hind limbs, flank, and ventral abdomen.

NUTRITIONAL DISEASE

Pansteatitis is caused by a deficiency of vitamin E. It has been reported in cats, usually eating diets containing red fish or excess cod liver oil. Affected cats are usually depressed, febrile, anorectic, and sore or painful on palpation of the skin or abdomen. Subcutaneous and abdominal fat may feel firm or lumpy. Draining tracts may be present.

NECROLYTIC MIGRATORY ERYTHEMA

Necrolytic migratory erythema (diabetic dermatopathy, hepatocutaneous syndrome, superficial necrolytic dermatitis, metabolic necrolytic dermatopathy, metabolic epidermal necrosis) has been seen in older dogs with glucagon-producing pancreatic endocrine tumor, Cushing's disease, hyperglucagonemia from a glucagon-secreting liver metastasis (primary tumor not found), hepatopathy secondary to ingestion of mycotoxins, hepatopathy secondary to phenobarbital or phenytoin administration, and hepatopathy of unknown origin. The disease has also been reported in the cat.

In the dog, necrolytic migratory erythema is an ulcerative dermatosis, displaying, erythema, crusts, and alopecia. It occurs most frequently periorally, periocularly, on the legs, feet, and external genitalia, and often in the groin region. The foot pads are usually hyperkeratotic and may be fissured and ulcerated. Cutaneous signs may precede evidence of internal disease by weeks or months.

CHAPTER 9

Alopecia

Dominique Heripret

Alopecia is defined as a loss of hair, varying from partial to complete. Alopecia can be focal or generalized, diffuse or complete. The causes of alopecia are numerous. However, the major cause of alopecia in the dog, and especially in the cat, is self-trauma associated with pruritus. The hair is damaged from licking and scratching or may be easily removed because of inflammation within the hair follicle, such as in pyoderma and demodicosis. Noninflammatory alopecias are also frequent in dogs (e.g., endocrine alopecia, alopecia X) but are rare in cats.

The diagnostic approach to alopecia should be methodical and involve certain fundamental steps; history and clinical examination should allow formation of a differential diagnosis leading to appropriate diagnostic procedures.

HISTORY

1. Breed: Congenital hypotrichosis (Burmese, Devon rex, miniature poodles, American cocker spaniel, and other breeds); color mutant alopecia (Doberman pinschers, dachshunds, whippets, Chihuahuas, and other breeds); dermatophytosis (Persian cats, Yorkshire terriers); hyperadrenocorticism (Poodles, Boston terriers, dachshunds, and other breeds); alopecia X (Nordic breeds, poodles, and other breeds); sebaceous adenitis (Akita, Vizla, poodles, Samoyeds, and other breeds).
2. Age of onset of signs: Young animal (congenital or hereditary problems, demodicosis, pyoderma), older animals (neoplasia, endocrinopathy, internal disease).
3. Life-style: Outdoor cats and dogs more likely to have parasitic or fungal dermatoses.
4. Transmission to "in-contact" animals or owners: Dermatophytosis, parasitic dermatoses.
5. General symptoms: Polyuria-polydipsia, asthenia.
6. Initial distribution and aspect of the dermatoses.
7. Pruritus present at the beginning or not: If pruritus began after alopecia, one must carefully look for secondary infections.
8. Evolution: Slow progression of alopecia more indicative of a systemic problem (endocrinopathy); seasonality more indicative of recurrent flank alopecia or flea allergy dermatitis (FAD).
9. Previous treatments: Mainly steroids and megestrol acetate (iatrogenic Cushing's disease, interference with thyroid measurements) and their efficacy.
10. General examination: Pendulous abdomen and hepatomegaly (hyperadrenocorticism), enlarged lymph nodes (Leishmaniasis), abnormal testis, feminization of male dogs.
11. Dermatologic examination: Localized or generalized alopecia that is symmetrical (or not), only on the trunk (or not), aspect of hair shafts (broken or not), epilation, follicular casts (demodicosis, sebaceous adenitis), primary or secondary lesions (papules, pustules, scaling, crusts), skin thickness.

DIFFERENTIAL DIAGNOSIS

The list of differential diagnoses should be organized so that the most likely diagnoses comprise the top two or three differentials (Tables 9-1 and 9-2).

DIAGNOSTIC PROCEDURES

In practice the approach should include consideration of costs and owner's willingness to perform diagnostic tests. Diagnostic procedures (or therapeutic recommendations) will be determined from the differential diagnosis list.

1. Routine examinations: Microscopic examination of skin scrapings, direct examination of hair shafts (trichogram), Wood lamp examination (+/– fungal culture), cytologic evaluation of impression smears.
2. Second-intention examinations: Skin biopsies, hematology, biochemistry (FeLV, FIV for cats), endocrine measurements, ultrasonography.

See Figures 9-1 and 9-2.

OUTCOME

The prognosis of complete return of the haircoat to the normal state is dependent on the presence or lack of hair follicles. In some cases if alopecia is present without abnormal systemic condition (e.g., color dilution alopecia, alopecia X), it is important for the veterinarian to explain to the owner that lack of hair is only a cosmetic problem, and that it may be harmful to prescribe drugs (i.e., hormones) to try to have a normal haircoat.

Table • 9-1

Main Causes of Alopecia in the Dog, Classified as Noninflammatory versus Inflammatory Alopecia

NONINFLAMMATORY ALOPECIA	INFLAMMATORY ALOPECIA
Congenital/Hereditary Alopecia	**Infectious Alopecia**
Ectodermal dysplasia	— Dermatophytosis
Follicular dysplasia	— Demodicosis
— *Tricorrhexis nodosa*	— Bacterial folliculitis
— Pili torti	— Viral infection
— Color mutant alopecia	— Leishmaniasis
— Black hair follicular dysplasia	
	Traumatic Alopecia
Acquired Alopecia	— Hypersensitivity
— Telogen effluvium	— Pruritic parasitic dermatoses
— Endocrine alopecia	— Scares
— Hyperadrenocorticism	Traction alopecia
— Iatrogenic Cushing's syndrome	
— Hypothyroidism	**Noninfectious/Immune-Mediated Alopecia**
— Sexual imbalance	— Sebaceous adenitis
— Alopecia X	— Superficial pemphigus
— Recurrent flank alopecia	— Alopecia areata
— Anagen effluvium	— Erythema multiforme
— Metabolic imbalance (prot, FA*)	— Lupus
	— Epitheliotropic lymphoma
	Atrophic Alopecia
	— Dermatomyositis
	— Cutaneous vasculitis
	— Postrabies vaccination alopecia

*FA, Fatty acids.

Table • 9-2

Main Causes of Alopecia in the Cat, Classified as Noninflammatory versus Inflammatory Alopecia

NONINFLAMMATORY ALOPECIA	INFLAMMATORY ALOPECIA
Congenital/Hereditary Alopecia	**Infectious Alopecia**
— Alopecia universalis (sphinx)	— Dermatophytosis
— Congenital hypotrichosis	— Demodicosis
— Hair shaft dysplasia (Abyssinian)	— Viral infection (FIP*, poxvirus)
— Follicular dysplasia (Cornish rex)	
— Pili torti	**Traumatic Alopecia**
	— Self-induced alopecia
Acquired Alopecia	— Anxiety
— Paraneoplastic alopecia	— Allergy (FAD†)
— Hyperadrenocorticism	— Dermatophytosis
— Iatrogenic Cushing's syndrome	— Pruritic parasitic dermatoses
— Hypothyroidism (rare)	— Hypersensitivities
— Hyperthyroidism	— Scares
— Effluvium	
	Noninfectious Alopecia
	— Lymphocytic mural folliculitis
	— Paraneoplastic exfoliative derm.
	— Pseudopelade
	— Epitheliotropic lymphoma

*FIP, Feline infectious peritonitis.
†FAD, Flea allergy dermatitis.

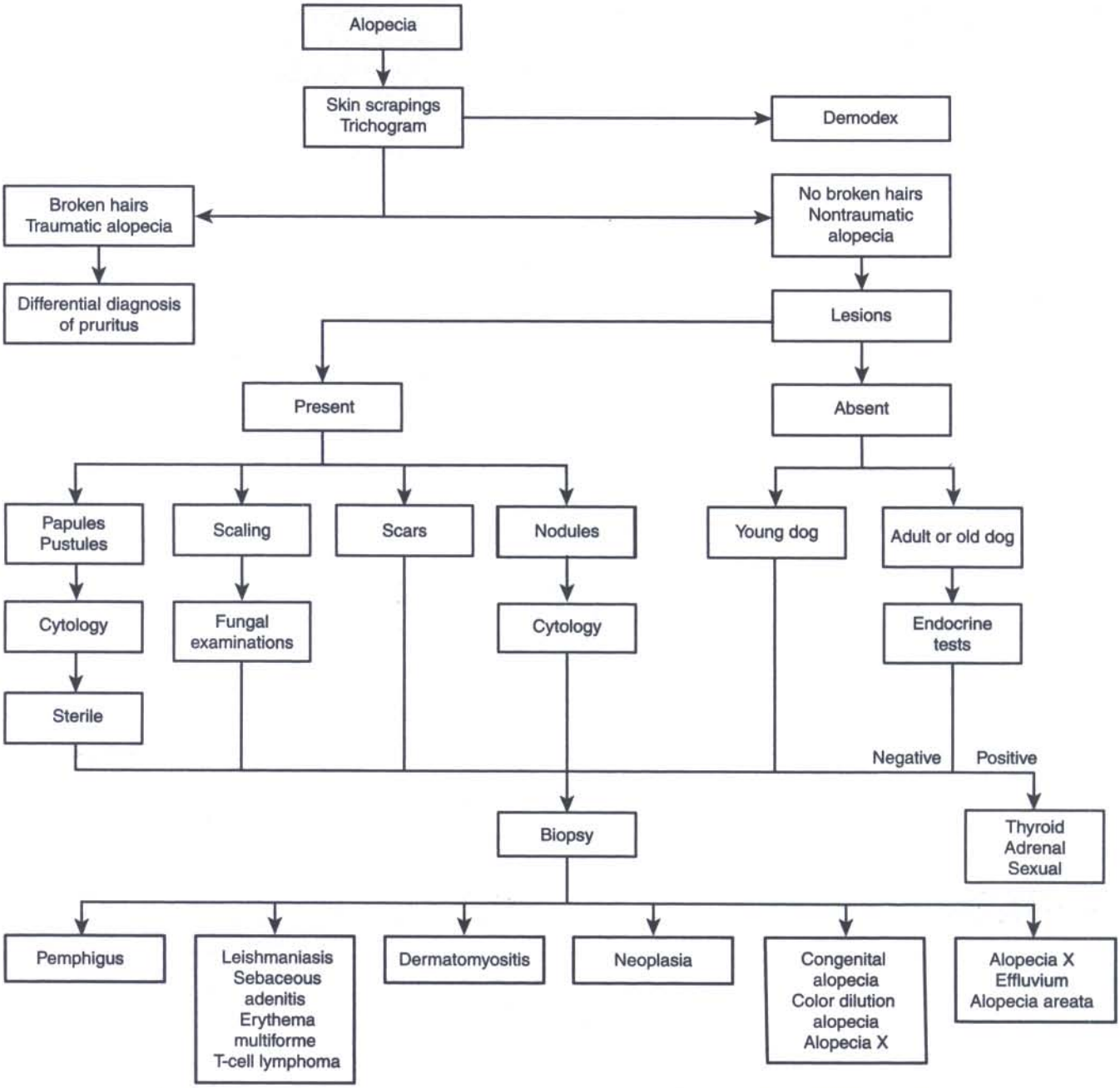


Figure 9-1 Diagnostic approach to alopecia in the dog. (Adapted from Alhaidari Z: *Prof Med Chir Anim Comp* 26(4): 290–300, 1991.)

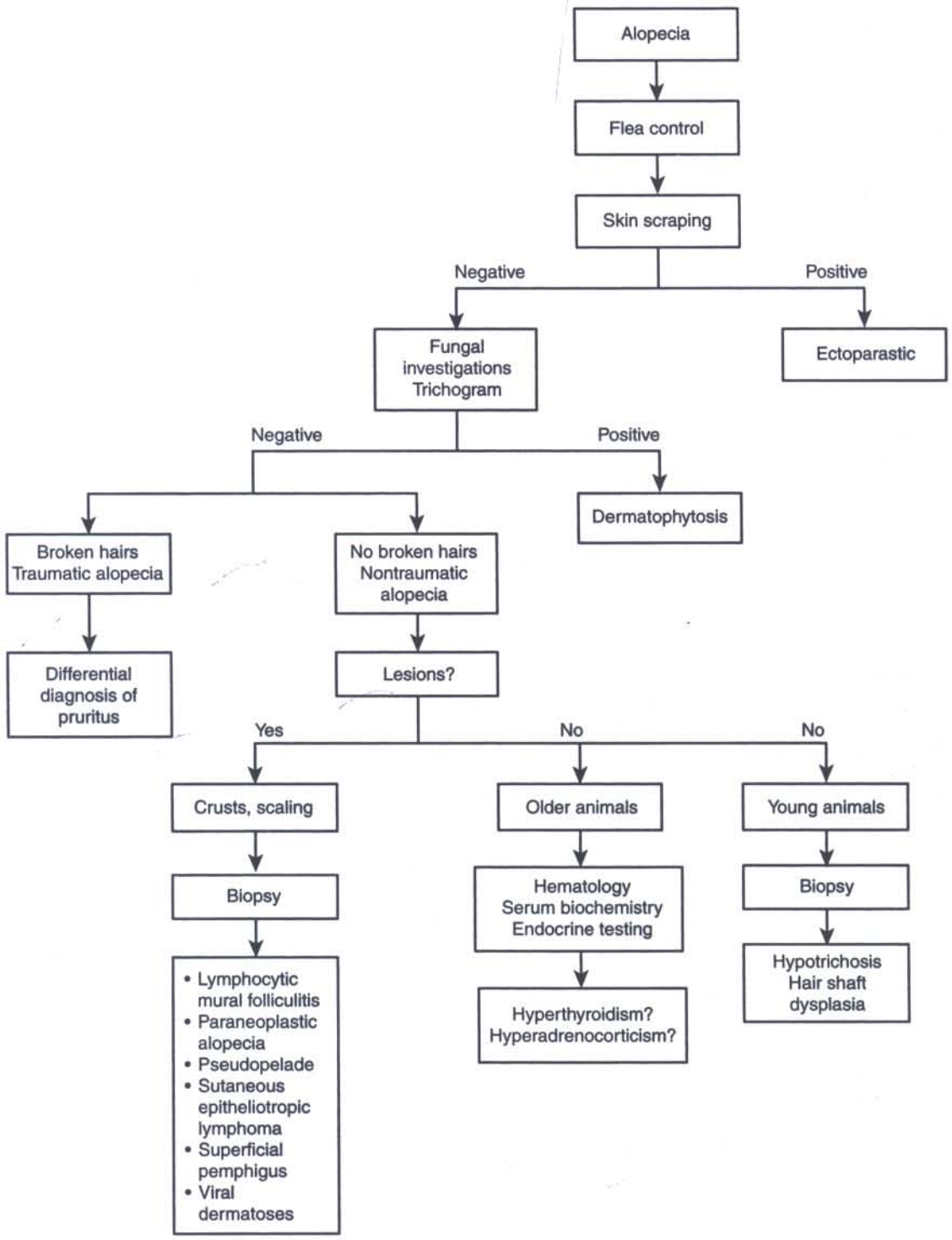


Figure 9-2 Diagnostic approach to feline alopecia. (Adapted from Alhaidari Z: In Guaguere E, Prelaud V, eds: *Feline dermatology*, 2000.)

CHAPTER • 10

Pruritus

Peter J. Ihrke

Pruritus can be defined as the sensation that elicits the desire to scratch, chew, or initiate other self-trauma. Pruritus is assumed to occur in animals that have self-trauma or erythema, excoriations, alopecia, lichenification, or hyperpigmentation that results from inflammation and self-mutilation. Licking, chewing, rubbing, hair removal, irritability, and even personality change (lack of tolerance, aggressive behavior) can result from pruritus; it is the most common clinical manifestation of disease that causes owners to bring their pets in for treatment. Because skin changes from self-trauma of any cause are similar clinically, pruritic skin diseases often are diagnostically challenging and frustrating.

PATHOPHYSIOLOGY

The skin functions as an "external nervous system," providing continuous sensory input to the central nervous system (CNS) through a finely arborized network of free nerve endings responsible for transmitting the sensations of touch, temperature, pain, and pruritus. In humans, "sensory spots" or "itch points" coincide with areas of increased density of free nerve endings. This may be true of domestic animals as well because the face, distal extremities, and groin are common sites of self-trauma in many species. The sensations of pruritus and pain are carried centrally by nonmyelinated slow conducting C fibers and, to a lesser extent, along myelinated A delta fibers. Myelinated ganglion cell axons carry the message of itch from free nerve endings to neurons located in the posterior horn of the spinal cord. Axons of second-order neurons transmit the message across the midline to the lateral spinothalamic tract and upward to the thalamus. Thalamic neurons then carry the signal to the postcentral gyrus of the cerebral cortex, where the message is interpreted as the sensation of pruritus.

Pruritus commonly stimulates self-trauma. The mechanisms by which self-trauma relieves itching are unclear. Self-trauma may disturb the amplified, reverberating spinal pathways that perpetuate the sensation of itch. More severe self-trauma probably substitutes pain for pruritus. Severe self-trauma characterized by deep excoriations is more common in cats than in dogs.

Diffusible chemical mediators induce the sensation of itch. Implicated endogenous mediators include histamine, peptides (endopeptidases, bradykinin, substance P, vasoactive intestinal peptide, neurotensin, secretin, enkephalins, endorphins), proteases (trypsin, chymotrypsin, mast cell chymase, fibrinolysin, kallikrein, cathepsins, plasmin), prostaglandins, leukotrienes (especially LTB_4), monohydroxy fatty acids, and opioid peptides. Proteolytic enzymes are thought to be the most important mediators of pruritus in dogs, cats, and humans. Leukotrienes also play an important role. The hypothesized magnitude of the role of histamine has diminished as the importance of other mediators is recognized. Bacterial and fungal endopeptidases also can initiate pruritus. Chemical mediators present in arthropod saliva, venom, body fluids, and on poisonous hairs or spines include proteolytic enzymes, histamine, cantharidin, apamin, mellitin, histidine decarboxylase, kinins, serotonin, endopeptidases, and proteinases.

A "gate control theory" has been hypothesized to explain how the CNS can amplify or reduce the sensation of pruritus. Stress or anxiety may amplify pruritus in humans by releasing opioid peptides. Boredom or other cutaneous sensations such as pain, heat, cold, or touch also can alter the perception of pruritus. Factors such as increased skin temperature, diminished skin hydration, and low humidity can heighten the sensitivity of the skin to pruritic stimuli.

The concepts of *threshold phenomenon* and *summation of effect* are paramount in understanding and managing pruritus. A certain pruritic load may be tolerated without initiating clinical signs, but a small increase in that load can provoke clinical signs. The itch threshold often is reduced at night in humans and animals when other sensory inputs are diminished. *Summation of effect* occurs when additive pruritic stimuli from coexistent skin diseases raise an animal above threshold. As an example, pruritus from mild flea allergy is additive to pruritus from other skin diseases during flea season, thus exacerbating and perpetuating itch-scratch cycles.

DIAGNOSIS OF PRURITUS

Signalment, history, physical examination, diagnostic testing, and, occasionally, response to therapy are the cornerstones of diagnosis. Because many pruritic skin diseases are visually similar, clinical history coupled with signalment predilections may offer more direct clues to diagnosis than physical examination. Canine and feline scabies and cheyletiellosis may have increased in frequency during the past 5 years because of the popularity of newer, more narrow-spectrum flea control products that do not kill acarids. The effect of newer flea control products on the incidence of pruritic skin diseases is controversial. Although the frequency of flea allergy dermatitis may have declined in regions where newer products are used, flea allergy dermatitis is still common globally. Effective flea control also may have unmasked formerly undiagnosed cases of canine atopic dermatitis where the pruritus was assumed to be due only to flea allergy dermatitis rather than combined flea allergy and atopic dermatitis. The importance of pyoderma and *Malassezia* dermatitis as frequent causes of pruritus cannot be overemphasized.

Signalment

Age

Age provides critical information for prioritizing differential diagnoses. Some skin diseases occur more commonly in young animals, whereas other dermatoses are seen more frequently in middle-aged or older animals. As examples, scabies and demodicosis are pruritic skin diseases seen more commonly in young dogs. Similarly, atopic dermatitis, food allergy, and pyoderma occur more commonly in adult animals.

Breed
Breed predilections for skin diseases are becoming increasingly available (see appendices). Further, some skin diseases are breed specific. As examples, golden retrievers, Dalmatians, and many small terrier breeds are at increased risk for the development of atopic dermatitis. The West Highland white terrier is at increased risk for secondary *Malassezia* dermatitis and the Chinese Shar Pei seems predisposed to atopic dermatitis, food allergy, pyoderma, and demodicosis.

Sex
Sex predilections are not common in pruritic skin diseases. However, pruritus may be seen with Sertoli cell tumors, male-feminizing syndromes, and canine female hyperestrogenism.

Historical Findings
General History
General history should be sought referable to diet, environment, use, home skin care, recent exposures, other household pets, and the presence or absence of pruritus in other animals or people in the environment. These data are helpful in prioritizing differential diagnoses.

Diet. Food allergy or intolerance can cause pruritus in both dogs and cats. However, adverse reactions to food frequently coexist with other allergic skin diseases such as atopic dermatitis and flea allergy dermatitis. In addition, lipid-deficient diets may exacerbate cornification abnormalities (seborrhea).

Environment and exposure. The likelihood of contagious pruritic ectoparasitic skin diseases is affected by environmental exposure. Flea allergy, canine and feline scabies, and less common ectoparasitic skin diseases are all seen more frequently in animals permitted to roam free. Feline scabies is endemic to certain geographic urban areas. Recent exposures such as acquisition of a new pet or sheltering a stray animal increase the likelihood of contagious disease. Grooming establishments, kennels, and veterinary practices offer additional opportunities for contagion.

Other household pets. Pruritus or lack of pruritus in other animals may offer clues to contagion. However, even though dogs and cats share the cat flea as a common ectoparasite, flea allergy is much more common in dogs. A seemingly unaffected indoor or outdoor cat is often the source of flea acquisition in indoor dogs with flea allergy dermatitis. Although uncommon, asymptomatic carriers of canine scabies do exist because clinical disease requires hypersensitivity.

Human contacts. A pruritic papular rash in an owner with a pruritic pet may suggest zoonotic infestation with canine or feline scabies mites or cheyletiellosis. Annular, erythematous lesions may suggest dermatophytosis.

Specific History
Specific history relates to the current pruritic skin disease. The initial site of skin lesion development, onset and progression, intensity of pruritus, seasonality or other pattern (predictability), and response or lack of response to previous therapy may aid in establishing a diagnosis.

Site, onset, and progression. Knowledge of the initial sites of skin lesions may be useful, if the disease has generalized before veterinary care is sought. For example, canine scabies often begins on the margins of the pinnae before generalizing. Rapid-onset pruritus should increase suspicion for ectoparasitic diseases and, less commonly, adverse drug reactions. Pruritus of insidious onset is more suggestive of slowly progressive, chronic skin diseases such as atopic dermatitis, food allergy, pyoderma, cornification abnormalities, and *Malassezia* dermatitis.

Intensity. Most animals do not exhibit pruritus in examination rooms. Canine and feline scabies, canine flea allergy dermatitis, and feline food allergy are notable exceptions. Frequency and intensity of pruritus may be inferred from asking the owner how many times the animal will scratch (or chew or lick) if it is ignored while the owner observes the animal at home.

Seasonality or pattern (predictability). Atopic dermatitis and flea allergy dermatitis are seasonal in many regions of the world. *Malassezia* dermatitis may occur more frequently during months of higher humidity. Cyclical pruritus without seasonality can sometimes signify contact dermatitis associated with change of environment. Psychogenic pruritus may began as a predictable, attention-getting device. Pruritus seen with food allergy should be continuous unless the diet is changed.

Response to previous therapy. Response or lack of response to previous medications, particularly corticosteroids, antibiotics, or parasiticides, may offer additional clues. Although allergic diseases all respond to corticosteroids to some degree, food allergy may be less responsive to corticosteroids than atopic dermatitis or flea allergy dermatitis. Prior diminished pruritus in response to antibiotics in dogs is often overlooked and indicates the likelihood of pyoderma. Pruritus as the result of pyoderma may also diminish in response to corticosteroids.

Physical Findings
A complete physical examination is extremely important when evaluating any animal with skin disease. Skin disease may be seen secondary to internal medical disorders (see Chapter 8). Proper lighting is of paramount importance. The clinician should observe the animal for general demeanor and signs of pruritus while taking the history. Examination of the skin, mucocutaneous junctions, oral cavity, ears, genitals, and lymph nodes should be emphasized. Objective signs of pruritus include excoriations and broken or barbered hairs with a dry lusterless haircoat. In the dog, worn incisors (buccal surface) and canine teeth (mesial surface) most frequently indicate chronic flea allergy dermatitis.

Pruritus may occur with or without primary skin lesions. If present, primary skin lesions such as papules or pustules may be helpful in establishing a diagnosis. Coexistent alopecia may offer additional clues (see Chapter 9). Unfortunately, self-trauma often leads to the obliteration of initial, more diagnostic primary skin lesions substituting excoriations, lichenification, and alopecia. The concept of "a rash that itches" indicates primary skin lesions that are itchy, and "an itch that rashes" indicates that pruritic patients without primary lesions traumatize themselves. Ectoparasitic skin diseases, pyoderma, and cornification abnormalities are among the more common pruritic skin diseases where primary skin lesions are identified. Conversely, primary lesions are much less common in atopic dermatitis and food allergy. The distribution of lesions, presence or absence of bilateral symmetry, and major foci of pruritus can be valuable aids to diagnosis. Primary or secondary lesions, if present in a particular site, may be highly suggestive of specific diseases (Tables 10-1 and 10-2).

Diagnostic Plan
Diagnostic plans should be formulated based on prioritization of differential diagnoses using signalment, history, and physical findings. Diagnostic procedures are selected based on the most likely differential diagnoses. The algorithm in Figure 10-1 offers an overview of possible diagnostic plans.

Table • 10-1

Pruritic Canine Dermatoses

DISEASE	SITE	LESIONS
Flea allergy dermatitis A, E, F	Bilaterally symmetric, dorsal lumbosacral, caudal thighs, groin, axilla, caudal half of body	Papules, macules, alopecia, erythema, lichenification, hyperpigmentation, excoriations, fibropruritic nodules
Canine scabies A	Ventrum, pinnae margins, face, elbows, partially bilaterally symmetric	Macules, papules, erythema, alopecia, crusts, excoriations
Demodicosis A	Periorbital, commissures of mouth, forelegs, generalized	Alopecia, erythema, crusts, follicular plugging, hyperpigmentation, secondary pyoderma
Pyoderma A	Groin, axilla, ventrum, interdigital webs, generalized, pressure points	Pustules, crusted papules, erythema, alopecia, target lesions, coalescing collarettes, hyperpigmentation
Atopic dermatitis A, F	Face, periorbital, ears, caudal carpi and tarsi, feet (dorsum), otitis externa, axilla, generalized	Erythema, alopecia, excoriations, lack of primary lesions, lichenification, hyperpigmentation
Malassezia dermatitis A, E, F	Ventral neck, groin, skin folds, face, feet, ventrum	Erythema, exudative or dry, alopecia, hyperpigmentation, lichenification
Cornification defects A, E, F	Generalized, ears, preen body	Scales, crusts, alopecia, erythematous plaques
Acral lick dermatitis A	Anterior carpal, metacarpal, radial, metatarsal, tibial regions	Firm, alopecic plaque, central irregular ulcer, hyperpigmented halo
Food allergy B	Face, feet, ears, generalized	Erythema, alopecia, excoriations, lack of primary lesions
Contact dermatitis C	Hairless areas, feet (ventrum), genitals, groin, axilla, generalized	Erythema, exudation, lichenification, hyperpigmentation, papules
Drug eruptions C	Anywhere, localized or generalized, face, ears, scrotum	Pleomorphic, erythema, papules, coalescing target lesions
Endoparasitic migration in puppies C	Face, feet, generalized	Erythema, alopecia, excoriations, lack of primary lesions
Cheyletiellosis B, E	Dorsum of thorax, generalized	Large scales, crusts, alopecia, erythema
Chiggers B, E, F	Ventrum, legs, anywhere	Erythema, scales, crusts, papules, alopecia
Superficial necrolytic dermatitis C	Footpads, face, mucocutaneous junctions, genitals, groin	Adherent crusts, ulcers, excoriations, erythema, fissured pads
Psychogenic pruritus C	Carpi, tarsi, feet (especially forelegs), perianal, generalized	Erythema, alopecia, excoriations, lack of primary lesions
Pediculosis C, E, F	Dorsum, generalized	Scales, crusts, alopecia, papules
Tail-dock neuroma C	Previously docked tail	Erythema, excoriations, alopecia
Rhabditic dermatitis D, E, F	Ventrum, legs, groin	Erythema, papules, alopecia, crusts, scales

A, Common; *B,* less common; C, uncommon; *D,* rare or controversial; *E,* regional; *F,* seasonal.

Skin Scrapings

Multiple skin scrapings should be performed on all pruritic dogs and cats. Affected areas should be gently clipped, and then a no. 10 scalpel blade or spatula, dipped in mineral oil, should be scraped perpendicular to the skin surface in the direction of hair growth. The acquired debris should then be dispersed on a slide, a cover slip applied, and the specimen examined microscopically using low light.

Demodectic mites usually are readily demonstrable (except in chronic pododemodicosis and in the Chinese Shar Pei). Scabies mites are documented in less than half of affected dogs, underscoring the need for trial therapy in suspected cases. Dry scrapings may be stained as smears to look for *Malassezia pachydermatis*.

Exfoliate Cytology

Affected skin, intact pustules, or exudates should be smeared, stained with a rapid stain such as Diff Quik®, and examined microscopically for the presence of bacteria, *Malassezia* organisms, and inflammatory cells. Clear tape preparations

Table • 10-2

Pruritic Feline Dermatoses

DISEASE	SITE	LESIONS
Flea allergy dermatitis A, E, F	Neck, dorsum, lumbosacral, caudal and medial thighs, groin, ears	"Miliary dermatitis," erythema, alopecia, eosinophilic plaques
Eosinophilic plaque A, E, F	Ventral abdomen, medial thighs, anywhere	Raised, ulcerated, erythematous alopecic plaques, secondary to allergy (primarily flea allergy dermatitis)
Otodectic acariasis A	Ears, head, neck, rarely generalized	Otitis externa, excoriations, "miliary dermatitis"
Food allergy A	Head, neck, ears, generalized	Erythema, excoriations, alopecia, lack of primary lesions, "miliary dermatitis"
Self-induced pruritic hair loss (atopic dermatitis, food allergy, flea allergy) B	Bilaterally symmetric, caudal and lateral thighs, ventral abdomen, perineum	Alopecia, hair stubble, erythema, papules, underlying skin may be normal
Self-induced psychogenic hair loss B	Bilaterally symmetric, stripe(s) on dorsal thorax, caudal and lateral thighs, ventral abdomen, perineum, forelegs	Alopecia, hair stubble, normal underlying skin
Cheyletiellosis B, E	Dorsum of thorax, generalized	Large scales, crusts, seborrhea, "miliary dermatitis"
Demodicosis B, E	Trunk, ventral, generalized	Alopecia, scaling
Mosquito-bite hypersensitivity C, E, F	Bilaterally symmetric, dorsal muzzle, planum nasale, periorbital, pinnae, paw pad margins	Papules, crusts, alopecia, erosion, exudation, fistulation
Pediculosis C, E, F	Dorsum, generalized	Scales, crusts, alopecia
Feline scabies C, E	Head, ears, neck, generalized, partially bilaterally symmetric	Erythema, papules, crusts, excoriations, alopecia
Pruritic dermatophytosis C	Head, neck, ears, generalized	Erythema, alopecia, hair stubble, "miliary dermatitis," hyperpigmentation
Atopic dermatitis B, F	Head, neck, ears, generalized	"Miliary dermatitis," erythema, excoriations, alopecia
Drug eruptions C	Anywhere, localized or generalized, pinnae, face	Pleomorphic, erythema, papules, coalescing target lesions
Pemphigus foliaceus D, E?, F?	Bilaterally symmetric, face, planum nasale, ears, interdigital webs, nipples, generalized	Crusts, vesicopustules, alopecia

A, Common; *B,* less common; *C,* uncommon; *D,* rare or controversial; *E,* regional; *F,* seasonal.

may demonstrate *Cheyletiella* mites, and stained tape preparations may demonstrate bacteria or *M. pachydermatis*.

Fecal Examination

Fecal examination may document endoparasite infestation in pruritic puppies and may reveal mites or other ectoparasites in any animal.

Skin Biopsy

Skin biopsy is especially valuable if primary skin lesions free of self-traumatic excoriations are present. If only self-traumatic lesions are present, definitive diagnosis is less likely, but results may aid in prioritizing or ruling out various differential diagnoses.

Fungal Culture

Most dogs and cats with dermatophytosis are not pruritic. However, fungal culture may be warranted because many cases of dermatophytosis are not visually distinctive.

Elimination Diets

Animals suspected of having food allergy or food intolerance as a cause of pruritus should be fed a home-cooked diet consisting of one protein and one carbohydrate source for 8 to 12 weeks. Alternatively, newer "limited antigen" or "hydrolyzed" diets are available. Commercial restricted diets are recommended for long-term maintenance. Nothing is specifically "hypoallergenic" about any food source. Foods are selected based simply on lack of previous exposure. Whitefish, rabbit,

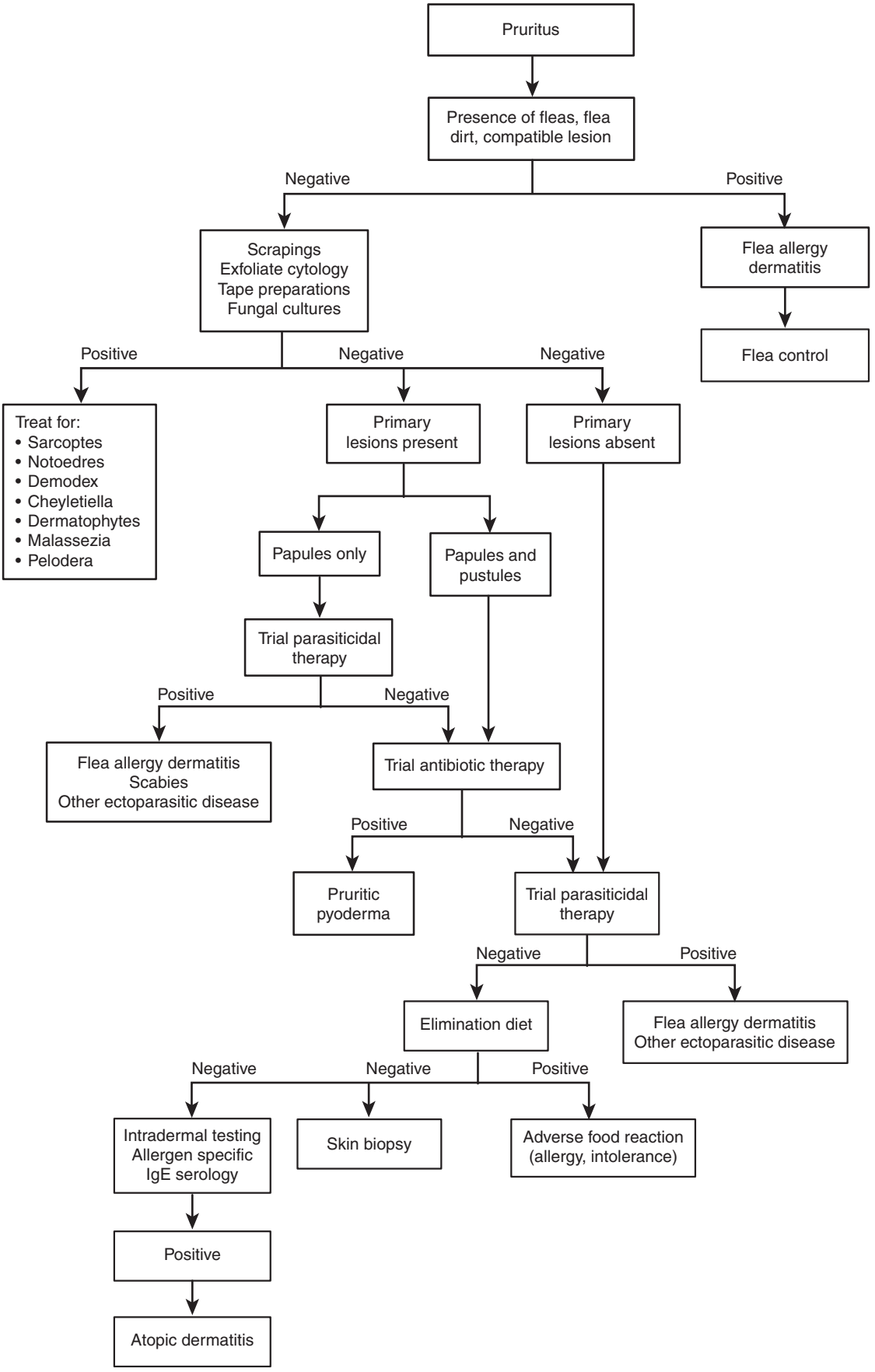


Figure 10-1 Algorithm for diagnosis and management of pruritus.

venison, pork, cottage cheese, or tofu mixed with either potatoes or other novel carbohydrate sources are commonly used in the dog. Mutton, lamb, and chicken are no longer as useful because they are frequently used in commercial dry dog foods. Cats may be fed rabbit, venison, pork, or mutton without an added carbohydrate source, or they may be fed commercial restricted or hydrolyzed diets.

Intradermal Testing
Substantial training is required to select appropriate candidates suspected of having atopic dermatitis, to choose antigens, to develop and maintain a reproducible technique, and to interpret results. Consequently, skin testing is most effective when practiced by dermatologists or other clinicians with a strong interest in dermatology.

Allergen-Specific IgE Serology (enzyme-linked immunosorbent assay [ELISA] or radioallergosorbent test [RAST])
In vitro testing for atopic dermatitis offers convenience and accessibility. Reproducibility of test results has increased dramatically over the past decade. However, problems still remain with antigen selection, grouped testing, and standardization of results.

Environmental Restriction
If allergic contact dermatitis is suspected, an animal may be housed in a markedly different environment (water-rinsed kennel) for 10 days.

Response to Trial Therapy
Trial therapy with parasiticidal agents is used routinely in suspected cases of scabies or flea allergy dermatitis. Flea allergy dermatitis remains the most common cause of canine and feline pruritus despite effective modern products. Because the lesions seen with canine superficial pyoderma may be pleomorphic, trial use of antibiotics may be indicated in undiagnosed pruritic crusted papular dermatoses. Although response to corticosteroids is suggestive of underlying allergic disease, superficial pyoderma will frequently respond partially to corticosteroid therapy.

Cost Containment
Skin scrapings, fungal culture, exfoliate cytology, trial therapy for ectoparasites, and, surprisingly, skin biopsy, are the most cost-effective diagnostic procedures for the pruritic animal.

GOALS OF THERAPY

Successful long-term management of a pruritic dog or cat usually requires definitive diagnosis. Repetitive parasiticidal therapy on a weekly basis for 3 or 4 weeks will rule out most contagious ectoparasitic diseases such as canine or feline scabies. However, management of flea allergy dermatitis is a lifelong endeavor encompassing control of fleas on the affected animal and all in-contact dogs and cats, as well as environmental control. Atopic dermatitis responds best to allergen-specific immunotherapy. Secondary pyoderma and *Malassezia* dermatitis are common sequelae to most pruritic skin diseases and must be assessed for and managed long-term. If corticosteroids are used adjunctively for the long-term management of allergic skin disease, short-acting oral corticosteroids such as prednisone, prednisolone, or methylprednisolone are recommended on an alternate-day basis. Corticosteroids are contraindicated in the treatment of canine demodicosis and pyoderma. Many pruritic animals require long-term adjunctive topical management with shampoos and emollients or antipruritic rinses.

CHAPTER • 11

Cutaneous and Subcutaneous Lumps, Bumps, and Masses

Didier N. Carlotti

Cutaneous and subcutaneous lumps, bumps, and masses include hematomas, abscesses, urticaria and angioedema, neoplasms and pseudoneoplasms.

CLINICAL AND HISTOPATHOLOGIC DEFINITIONS

A hematoma is a focal extravasation of blood with purpura (bruising) and pain, whereas an abscess is a localized collection of pus with pain, heat, and sometimes purpura. Urticaria is referred to as a group of wheals (sharply circumscribed, raised, edematous lesions) that appear and disappear rapidly. Angioedema is a large swelling in a distensible region such as the face and limbs.

Clinically, pseudoneoplasms and neoplasms appear as nodules, plaques, and tumors. Ulceration always indicates a severe pathologic process. Pseudoneoplasms include cysts, nevi, keratoses, granulomas, and pyogranulomas and other lesions. *Pseudoneoplasm* is a better term than *pseudotumor* because the term *tumor* is clinical and should refer to a localized hypertrophy of a tissue or an organ, neoplastic or not. Cysts are epithelial lesions containing grayish keratinous material or serous material, such as apocrine cysts, which appear fluctuant, bluish, and well circumscribed. A hamartoma is a malformation formed by components of a normal organ arranged erroneously. A nevus is a cutaneous hamartoma that may arise from any skin component. Collagenous nevi are single or multiple nodules characterized histopathologically by large areas of collagen hyperplasia. In German shepherds, multiple collagenous nevi may appear, particularly on the limbs, in association with renal adenocarcinomas and uterine leiomyomas (nodular dermatofibrosis syndrome). Organoid (i.e., pilosebaceous) and epidermal nevi are variable in shape and may be linear. Vascular nevi are seen on the

Organoid (i.e., pilosebaceous) and epidermal nevi are variable in shape and may be linear. Vascular nevi are seen on the scrotum in dogs. Keratoses are solid, elevated, and circumscribed lesions characterized by a hyperproduction of keratin. They show up as greasy nodules and plaques (seborrheic keratoses), squamocrustous plaques (actinic keratoses, lichenoid keratoses on the ear pinnae), or cutaneous horns.

A granuloma is a circumscribed tissue reaction characterized by an organized infiltration of mononucleated phagocytes (histiocytes and macrophages) that may occur when foreign bodies, bacteria, fungi, parasites, or any material penetrates or deposits into the skin. If an acute inflammatory process does not destroy the "invader," macrophages become epithelioid. A granuloma may persist until the cause has been eliminated. "Pyogranuloma" means granulomatous reaction with many neutrophils.

Lesions of calcinosis circumscripta are pink-colored plaques located on pressure points or in the tongue that contain grayish material. Hard erythematous plaques containing whitish material characterize calcinosis cutis, as seen in canine Cushing's disease. Eosinophilic lesions in the cat are indolent ulcer, eosinophilic plaque, and collagenolytic granuloma (the latter often appearing linear). Nodular sterile panniculitis is characterized by deep nodules that fistulize, expressing an oily material. Canine juvenile cellulitis is characterized by facial swelling. Nodular lesions, particularly on the face, with a "clown nose" appearance, may characterize canine histiocytosis.

Other various pseudoneoplasms include acral lick dermatitis, idiopathic lichenoid dermatitis (coalescent plaques), feline plasma cell pododermatitis or stomatitis, and idiopathic focal mucinosis seen in Doberman pinschers.

CAUSE AND PATHOPHYSIOLOGY

Hematomas are the result of trauma causing the rupture of blood vessels. They appear frequently after minor trauma in dogs with coagulopathies. Abscesses are the result of the collection of degenerated neutrophils and necrotic tissue cells when an infectious agent has penetrated into and under the skin. Usually a peripheral membrane forms from necrotic tissue and fibrin. Urticaria and angioedema are caused by immediate hypersensitivity reactions generated by insect bites (e.g., hymenoptera); food; drugs; airborne allergens (atopy), and nonimmunologic stimuli such as contact with irritant material (e.g., weeds, such as *Urtica dioica*; insects, such as *Thaumetopoea pityocampa* [caterpillar]; physical stimuli, such as cold, heat, and sunlight; and even psychogenic factors). Cysts may be traumatic (epidermoid), hereditary (dermoid), follicular, or pilar (i.e., trichilemmal) caused by retention of material (i.e., keratin, glandular products) as a result of congenital or acquired loss of follicular orifices. Apocrine cysts are idiopathic. Nevi may be congenital, and the mechanism of their formation is unknown. However, nodular dermatofibrosis is due to an autosomal dominant gene. Keratoses are idiopathic except actinic keratoses and some cutaneous horns, which are associated with various skin neoplasms or feline leukemia virus (FeLV) infection in the cat.

Bacterial granulomas and pyogranulomas include canine furunculosis caused by cocci such as *Staphylococcus intermedius*, botryomycosis (bacterial pseudomycetoma) caused by various bacteria that may cause a granulomatous reaction, and nocardiosis and mycobacterioses (atypical mycobacterial infection, feline leprosy, tuberculosis, which is very rare). Fungal granulomas and pyogranulomas include kerions (inflammatory reaction to a dermatophyte) and pseudomycetomas caused by the subcutaneous development of a dermatophyte (*Microsporum canis* in cats, mainly), subcutaneous (intermediate) mycoses (sporotrichosis, pythiosis, mycetomas, phaeohyphomycosis, zygomycosis), and deep (systemic) mycoses (blastomycosis, coccidioidomycosis, histoplasmosis, aspergillosis, cryptococcosis, protothecosis, paecilomycosis, trichosporonosis).

Endogenous or exogenous foreign bodies can cause granulomas. Endogenous foreign bodies are usually hair and keratin (leading to bacterial furunculosis), calcium (calcinosis circumscripta, idiopathic, Cushing's disease), and lipids (xanthomas in case of hyperlipidemia in cats, associated with diabetes mellitus or hereditary). Exogenous foreign bodies include sutures and weed material. Parasitic granulomas include tick bites, canine dracunculosis, canine filariasis, canine leishmaniasis (the nodular form is seen more frequently in short-haired dogs such as the boxer), feline toxoplasmosis, and canine cysticercosis. Arthropod bites (e.g., mosquitoes, spiders) lead to eosinophilic furunculosis (particularly on the face in dogs and cats) with a granulomatous reaction. Some granulomas are idiopathic: lesions of the feline eosinophilic granuloma complex (although most of the cases are caused by flea allergy dermatitis, feline atopic dermatitis, or food allergy or intolerance), canine eosinophilic granuloma, sterile pyogranulomatous dermatosis, nodular sterile panniculitis (the result of an inflammatory process of subcutaneous fat), canine juvenile cellulitis (perhaps viral), canine cutaneous histiocytosis (caused by a proliferation of normal histiocytes), canine erythema nodosum-like granuloma, canine sterile sarcoidal granulomatous skin disease, and amyloidosis. Acral lick dermatitis is often a deep bacterial folliculitis and furunculosis caused by constant licking attributed to an allergic pruritus or behavioral disorder. Lichenoid dermatitis may be idiopathic or an immune-mediated disease such as feline plasma cell pododermatitis and stomatitis sometimes associated with FeLV, feline immunodeficiency virus (FIV)-infection, or both.

Cutaneous and subcutaneous neoplasms include epithelial (epidermal and follicular), glandular (sebaceous, sweat, and hepatoid gland), mesenchymal (fibrocytic, histiocytic, vascular), and melanocytic and round cell tumors (mast cell, histiocytic, lymphoma).

Mammary neoplasms can be considered as subcutaneous. Most of the neoplasms have an unknown cause. Viruses can cause specific tumors such as papillomas in dogs and fibrosarcomas and carcinomas in situ (Bowen's disease) in cats. Other causes include irritation, trauma, and actinic exposure. The latter is likely to be the cause of squamous cell carcinoma of the face and ears in the cat (particularly of white color). It is not clear whether repeated vaccinations can lead to fibrosarcomas in cats. Benign neoplasms can be harmful if they reach a large size, are located in particular areas (face, eyelids, external ear canal, mouth, feet, genitals, anus), or both. Malignant neoplasms are invasive and will cause the necrosis of surrounding cells, leading to ulceration.

DIAGNOSIS

Diagnosis of cutaneous and subcutaneous lumps, bumps, and masses is based upon history, physical examination, and complementary aids (Figure 11-1). Signalment of the animal may be of some importance. Neoplastic lesions occur mostly in adults and old dogs. However, viral papilloma and histiocytoma (Langerhans' cell tumor) will be seen mainly in young animals. Intact male cats are prone to develop abscesses as the result of fighting. Mammary tumors and their cutaneous metastases occur in female dogs, whereas perianal gland tumors occur most frequently in intact males. Most neoplasms, however, have no sex predilection. Breed predispositions are

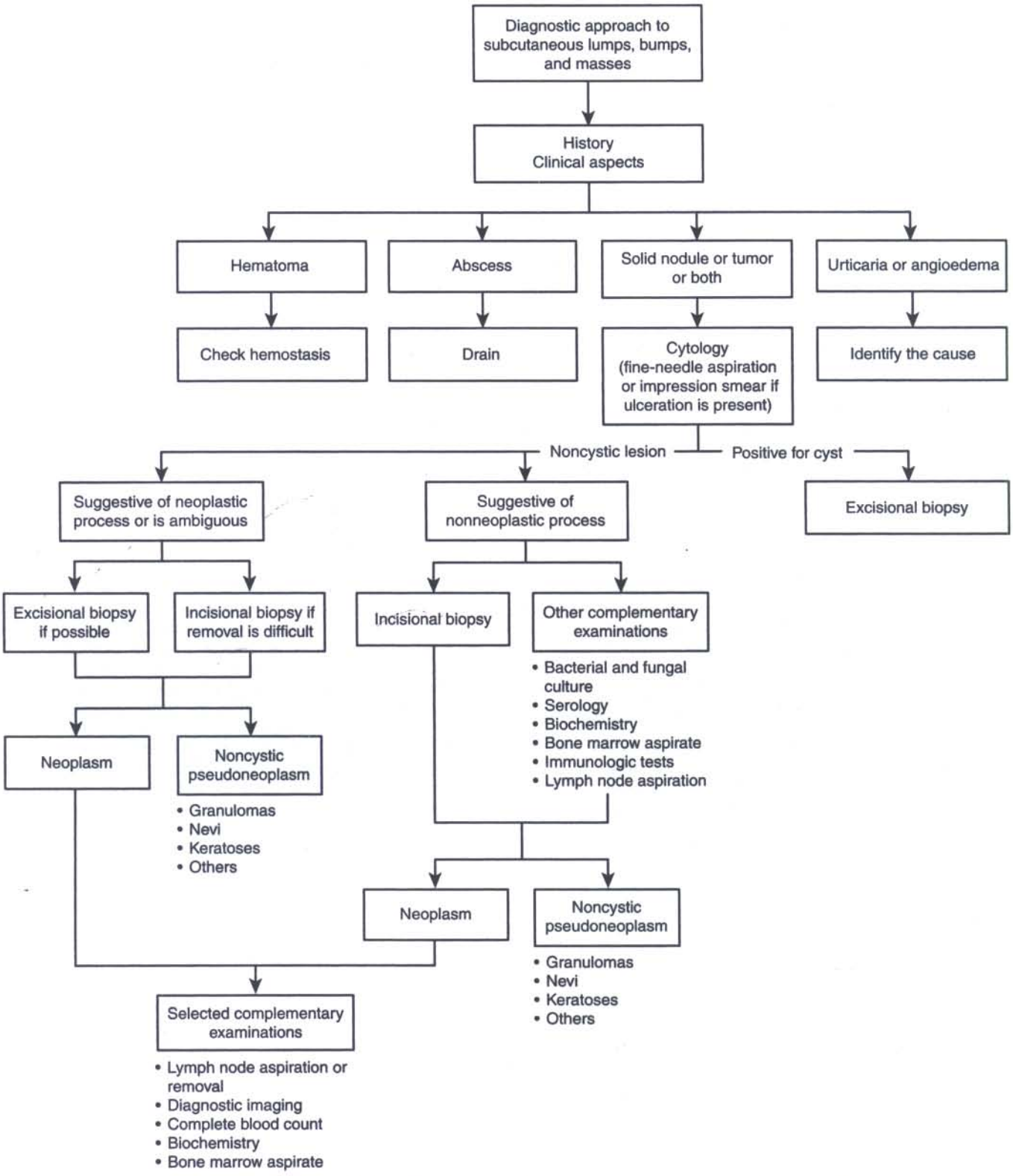


Figure 11-1 Algorithm for diagnostic approach to subcutaneous lumps, bumps, and masses.

recognized for many superficial neoplasms. The boxer is known to be predisposed to many of them, as it is for nodular leishmaniasis. The German shepherd is predisposed to keratinous cysts and nodular dermatofibrosis. Persian cats are predisposed to dermatophytic pseudomycetoma.

History of the lesions should be taken into account. Important points are the existence of previous similar lesions, association to general disease, known trauma, and rapidity of onset. Obviously, hematomas, abscesses, urticaria, and angioedema appear rapidly. Some lymphomas can develop

rapidly. Feline eosinophilic plaques, urticaria and angioedema, some cases of calcinosis cutis, and mast cell tumors are pruritic. Hematomas, abscesses, and some tumors may be painful.

Physical examination should include evaluation of the lesions, local lymph nodes, and distant sites such as lungs. This strategy applies to most lumps, bumps, and masses, using the TNM approach (tumor, node, metastasis). The lesions should be characterized by localization, size, shape, pedunculated appearance, consistency, depth, and whether or not they are freely movable, ulcerated, or both. For instance, feline collagenolytic granuloma and canine epidermal nerves can be linear; hematomas and most benign neoplasms are not attached to underlying tissues, whereas most of abscesses and malignant neoplasms are attached. Abscesses evolve from firm to fluctuant stages, whereas most pseudoneoplasms and neoplasms are firm (except apocrine cysts and some angiomas and angiosarcomas). Benign neoplasms can be pedunculated. Feline indolent ulcer, eosinophilic plaques, some malignant neoplasms, and canine acral lick dermatitis ulcerate. Enlargement of local lymph nodes can be caused by inflammation (even in case of a neoplastic process) or metastasis. General lymph node enlargement can result from severe infections and lymphosarcoma. Metastasis can rarely be suspected clinically, except for cutaneous metastasis of mammary neoplasms and when an abnormal abdominal mass is palpated.

Cytologic techniques usable for lumps, bumps, and masses are impression, scrape, swab, and fine-needle aspiration smears. No contraindications exist. Cytology allows rapid identification of cell types. High cellularity and a homogeneous cell population characterize neoplasms. Cytologic criteria of malignancy include pleomorphism, high nucleocytoplasmic ratios, large nucleoli, and atypical mitoses. In many nonneoplastic lesions, the cytologic examination is highly suggestive of the diagnosis (e.g., pyoderma, fungal diseases, eosinophilic plaques). Fine-needle aspiration cytology of a local lymph node can help to differentiate an inflammatory reaction from malignancy.

Histopathology has a fundamental role in establishing specimens' diagnoses. Incisional biopsy specimens can be obtained with a scalpel or a punch, particularly when cytology is ambiguous. Results aid in selecting appropriate medical therapy, surgery, or both. The sample should be biopsied at the margin of the lesion to incorporate some normal-looking tissue, should not be larger than 1 cm, and should be put in 10 times its volume of 10% formalin. No contraindication exists for incisional biopsy because it does not increase risk of metastasis. The wound should be repaired, and the biopsy site should be removed by further surgery. General anesthesia may be required, and wound repair can be difficult. Excisional biopsy can also be performed, particularly when cytology is ambiguous, when the surgical removal of the lesion is easy, and when physical examination suggests a nonneoplastic or benign neoplastic lesion. If lesions are multiple, excisional biopsy of a typical mass should be considered. The removal of a lymph node for histopathologic analysis can be helpful and has no harmful consequence. Radiology, ultrasonography, or both are useful in many instances (e.g., a lesion appearing to be attached to an underlying bone or suspicion of lung or abdominal metastasis).

PROGNOSIS

The prognosis of cutaneous or subcutaneous (or both) lumps, bumps, and masses is obviously linked to diagnosis, location of the lesion or lesions, and continuing evaluation (TNM). Establishing a prognosis based on physical examination only and clinical neglect (waiting for a possible enlargement of the lesion or lesions), are unacceptable errors.

TREATMENT

Treatment should be based upon diagnosis and prognosis. Medical treatment of urticaria and angioedema, hematomas, and abscesses is almost always successful. The result of treatment of granulomatous pseudoneoplasms can lead to complete cure, particularly when a bacterial or superficial fungal agent has been identified. Surgical excision of cysts, nevi, keratoses, feline plasma cell podal lesions, and benign neoplasms is usually successful. Treatment for malignancies is rarely curative, but long remissions can be obtained, particularly if the owners wish to cooperate.

CHAPTER 12

Erosions and Ulcerations

Ian S. Mason

Erosions and ulcers are skin defects with a wide range of causes. Erosions are superficial breaks in the continuity of epithelia that fail to breach the intact basement membrane and usually heal without scarring. Ulcers are deeper and extend through the basement membrane into the underlying dermis. They heal slowly and residual scarring is common. It may be impossible to distinguish between ulcers and erosions without histology. In some diseases, ulcers and erosions occur concurrently, whereas in other conditions only one type of lesion may be present.

Ulcers and erosions may result from a variety of conditions (Box 12-1). Trauma, including self-trauma associated with pruritus, may lead to eroded and ulcerated lesions. Infectious diseases can lead to defects in the epithelial surface. In canine skin, bullae and vesicles are thin walled and rupture promptly after formation, leading to erosions and ulcers. Chemical and

Box • 12-1

Differential Diagnosis of Ulcers and Erosions Affecting Skin and Mucous Membranes

Canine Diseases

Infectious:

Bacterial pyoderma:
- Surface:
  - Acute moist dermatitis (pyotraumatic dermatitis)
  - Intertrigo
- Deep:
  - Folliculitis/furunculosis (including pyotraumatic folliculitis)
  - Oral bacterial infections (aerobic/anaerobic)

Fungal:
- Yeast infections (*Malassezia pachydermatis, Candida* spp.)
- Systemic/subcutaneous

Parasitic:
- Demodicosis

Metabolic:
- Calcinosis cutis (hyperadrenocorticism)
- Uremia/renal failure
- Necrolytic migratory erythema/metabolic epidermal necrosis

Neoplastic:
- Epitheliotropic lymphoma
- Squamous cell carcinoma

Physical, chemical:
- Drug reactions
- Solar injury
- Thermal injury (freeze or burn)
- Urine scald

Immune-mediated/autoimmune:
- Discoid lupus erythematosus
- Pemphigus group
- Uveodermatologic syndrome
- Miscellaneous autoimmune subepidermal vesiculobullous diseases:
  - Bullous pemphigoid
  - Epidermolysis bullosa acquisita
  - Linear IgA bullous disease
  - Mucocutaneous pemphigoid
  - Bullous systemic lupus-type 1

Miscellaneous:
- Arthropod bites
- Dermatomyositis
- Dystrophic epidermolysis bullosa
- Idiopathic ulceration of collies
- Junctional epidermolysis bullosa
- Toxic epidermal necrolysis/erythema multiforme

Feline Diseases

Infectious:

Viral:
- Calicivirus and herpesvirus

Bacterial:
- Atypical mycobacteriosis

Fungal:
- Subcutaneous and systemic mycoses
- Cryptococcosis
- Sporotrichosis

Metabolic:
- Uremia/renal disease

Neoplastic:
- Fibrosarcoma
- Lymphoma
- Squamous cell carcinoma

Physical/chemical:
- Drug reactions
- Thermal

Immune-mediated/autoimmune:
- Bullous pemphigoid
- Pemphigus foliaceus
- Toxic epidermal necrolysis/erythema multiforme

Miscellaneous/idiopathic:
- Arthropod bites
- Dystrophic epidermolysis bullosa
- Eosinophilic plaque
- Idiopathic ulceration of dorsal neck
- Indolent ulcer
- Junctional epidermolysis bullosa

physical factors such as urine scalding, irritant contact dermatitis and thermal injury may also be responsible for defects in cutaneous continuity.

Erosive and ulcerative diseases in dogs and cats may affect the mucous membranes with or without concurrent cutaneous involvement. Animals with oral lesions usually have halitosis, dysphagia, or both. Clinicians often suspect autoimmune and immune-mediated diseases in animals with erosions and lcerations. However, these diseases are uncommon or rare.

APPROACH TO THE DIAGNOSIS

Diagnosis may be difficult. Ulcers and erosions have many possible causes. Therefore the diagnostic approach must be carefully planned and thorough (Figure 12-1).

History may yield important clues. Obese or short-legged breeds of dogs are predisposed to intertriginous (or body fold) pyoderma and urine scalding. Older animals are more susceptible to metabolic and neoplastic disorders. Concurrent systemic signs may indicate that lesions are the result of metabolic disease or a drug eruption (assuming the animal has received therapy). Determining whether pruritus is present and at which stage it developed is helpful. If early pruritus is present, then it is possible that this is a primary pruritic disease, such as that caused by hypersensitivity or ectoparasitism, and that the lesions are the result of self-trauma. Late onset of pruritus may be more difficult to assess and may arise in a large number of diseases. Chronic sun exposure, especially of poorly pigmented skin, may lead to actinic lesions including neoplasia.

General and dermatologic examination will greatly aid the establishment of a differential diagnosis and enable the clinician

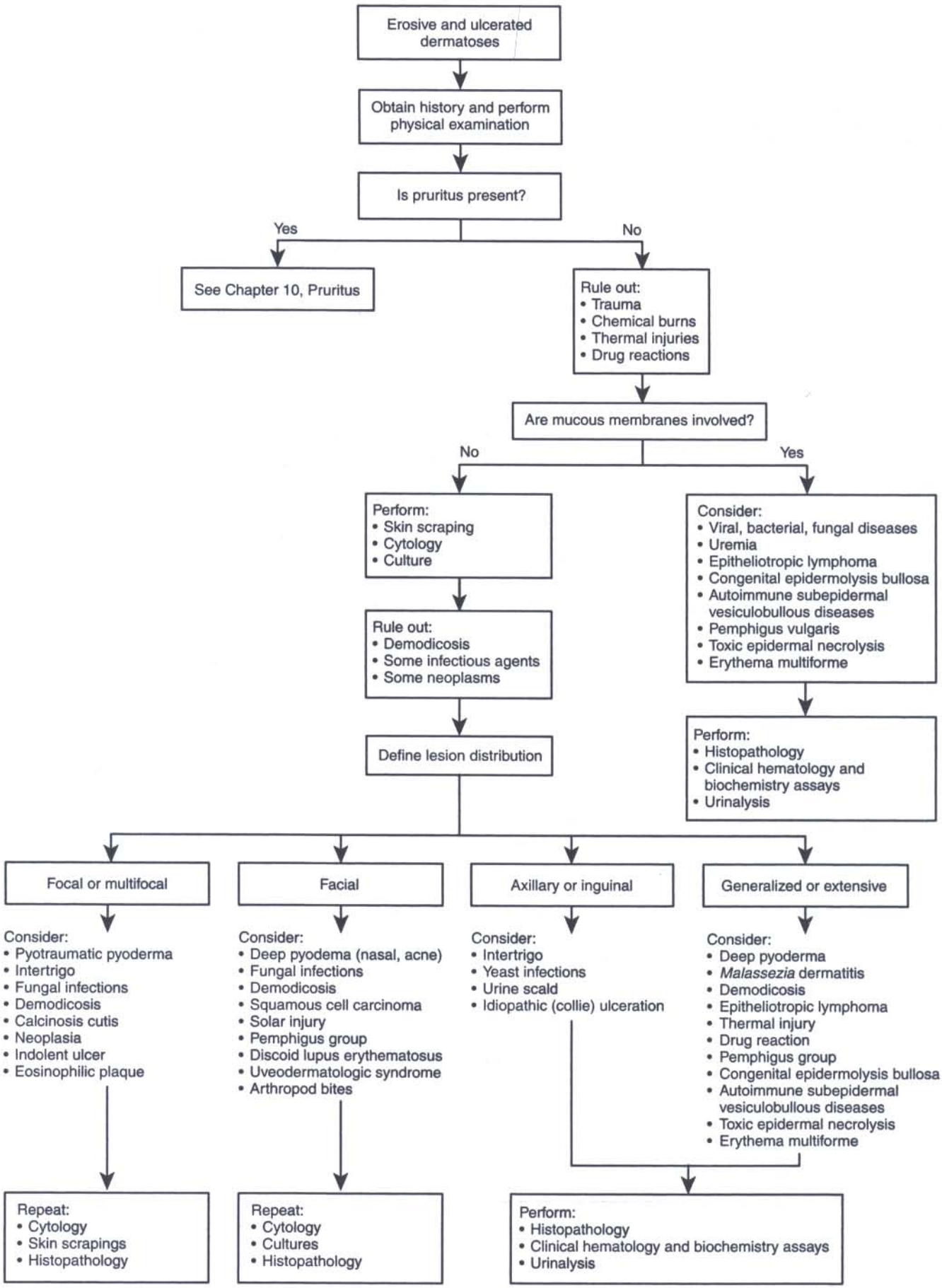


Figure 12-1 Algorithm for evaluation of erosive and ulcerated dermatoses.

to identify any concurrent systemic disease. The distribution of lesions may be extremely helpful (Box 12-2). Involvement of mucous membranes indicates that uremia, renal failure, or both; viral, bacterial, or yeast infection; certain immune-mediated disorders (bullous pemphigoid, pemphigus vulgaris), or epitheliotropic lymphoma is present.

Initial diagnostic tests such as cytologic examination of impression smears and microscopy of skin scrapings are useful. However, the majority of causes will be identified by histopathology, and biopsy specimens should be taken early in the development of this group of diseases.

INFECTIOUS CAUSES OF EROSIONS AND ULCERS

Viral Diseases

Feline calicivirus and feline herpesvirus (FHV) infections usually cause upper respiratory tract disease and conjunctivitis. Rarely, they may lead to cutaneous ulceration, typically on the feet. A tentative clinical diagnosis of feline calicivirus and FHV can usually be based on results of the history and physical examination.

Bacterial Disease

Pyoderma and other bacterial diseases may be difficult to recognize because these infections are pleomorphic. If doubt exists as to whether the lesions are the result of bacterial infection, then histopathology should be performed. Concurrent systemic antimicrobial therapy is indicated while awaiting the pathologist's findings. If histopathology results indicate that the lesions are bacterial in origin but little improvement has been seen after antimicrobial therapy, then it is likely that the infection is secondary. A second biopsy sampling is indicated after antibacterial therapy to allow examination of tissue without secondary infection.

Surface bacterial infections in dogs are characterized by erosion. Intertrigo (skin fold pyoderma) affecting lip, vulvar, facial, tail, or body folds is readily recognized clinically. Impression cytology and culture of the folds may reveal evidence of bacterial infection, usually *Staphylococcus intermedius*, but the yeast *Malassezia pachydermatis* may also be involved. Pyotraumatic dermatitis ("hot spots" or acute moist dermatitis) is another form of canine surface pyoderma that is readily recognized clinically. However, in some cases, the infection is deeper than it would appear on clinical examination (this is termed *pyotraumatic folliculitis*). The distinction between these two forms is made by histopathology and is important because glucocorticoid therapy is contraindicated in the deeper form.

Deep pyoderma in dogs may be characterized by erosion and ulceration; examples include nasal pyoderma and German shepherd dog pyoderma. These may be confused with immune-mediated disorders. As previously discussed, histopathology and antimicrobial therapy may be of value. Aerobic and anaerobic bacterial infection may affect the mucous membranes. Such infections are often secondary to dental disease, immunosuppression, and systemic diseases.

Opportunist or atypical mycobacterial infections may occur when feline skin is inoculated with soil or water harboring the organism via traumatic injury. Affected cats exhibit chronic nonhealing wounds and ulcers with draining tracts. Systemic signs are usually absent.

Fungal Disease

In recent years, infection of the skin surface associated with the yeast *M. pachydermatis* has been recognized in dogs. Ulceration is not a feature, but the affected skin may be eroded. Lesions usually occur in intertriginous regions, particularly in predisposed breeds (Basset hounds, West Highland terriers, and English cocker spaniels). The lesions are characterized by

Box • 12-2

Distribution of Ulcers and Erosions as a Diagnostic Clue

Axillary/Inguinal:
- Fungal (*Malassezia pachydermatis, Candida* spp.) (D)
- Idiopathic ulceration of collies (D)
- Intertrigo (D)
- Urine scald (D)

Focal/Multifocal:
- Calcinosis cutis (D)
- Demodicosis (D)
- Eosinophilic plaque (C)
- Indolent ulcer (C)
- Intertrigo (D)
- Neoplasia (D, C)
- Pyoderma (principally pyotraumatic dermatitis or folliculitis) (D)
- Systemic/subcutaneous mycosis (D, C)

Facial:
- Arthropod bites (D, C)
- Bullous pemphigoid (D, C)
- Deep pyoderma (D)
- Demodicosis (D)
- Dermatomyositis (D)
- Discoid lupus erythematosus (D)
- Linear IgA bullous disease (D)
- Pemphigus foliaceus/erythematosus (D, C)
- Solar injury (D, C)
- Squamous cell carcinoma (C)
- Systemic/subcutaneous mycosis (D, C)
- Uveodermatologic syndrome (D)

Mucocutaneous:
- Bacteria (aerobic/anaerobic) (D, C)
- Bullous pemphigoid (D, C)
- Bullous systemic lupus-type 1
- Epidermolysis bullosa aquisita (D)
- Epitheliotropic lymphoma (D)
- Fungal (*M. pachydermatis, Candida* spp.) (D)
- Mucocutaneous pemphigoid (D)
- Pemphigus vulgaris (D)
- Toxic epidermal necrosis/erythema multiforme (D, C)
- Uremia (D, C)
- Viral infection (calicivirus/herpesvirus) (C)

Generalized/Extensive:
- Bullous pemphigoid (D)
- Deep pyoderma (D)
- Demodicosis (D)
- Drug reaction (D, C)
- Epitheliotropic lymphoma (D)
- *Malassezia* dermatitis (D)
- Pemphigus group (D, C)
- Thermal injury (D, C)
- Toxic epidermal necrolysis/erythema multiforme (D, C)

D, Dog; C, Cat.

intense erythema, a yellow waxy crust, and malodor. Dermatophytosis may lead to eroded and ulcerated lesions in dogs and cats. Diagnosis is based on cytology, culture, and response to antifungal therapy.

Subcutaneous and systemic fungal infections are far less common. Impression smears and histopathology are indicated. Therapy is dependant on the organism involved.

OTHER CAUSES OF EROSIONS AND ULCERS

Parasitic Infections

Infestation with mites such as *Sarcoptes scabiei* or *Cheyletiella* spp. may lead to self-induced erosions and ulcers. Severe cases of demodicosis may, less commonly, lead to ulceration. Skin scrapings are diagnostic and mandatory.

Metabolic Disease

Calcinosis cutis is caused by accumulation of calcium in the skin, usually as a result of hyperadrenocorticism (naturally occurring or iatrogenic). Ulcers may develop over these mineral plaques. Histopathology is diagnostic. Treatment of the underlying systemic disease is usually curative.

Hepatic cirrhosis or pancreatic adenocarcinomata may lead to cutaneous ulceration that particularly affects the feet and perineum of older dogs. This disease has a range of synonyms, including hepatocutaneous syndrome, necrolytic migratory erythema, and metabolic epidermal necrosis.

Uremia as the result of renal failure may lead to oral ulceration. In cats, diabetes mellitus and hyperadrenocorticism may also lead to this phenomenon. Signs of systemic disease are usually present (e.g., anorexia, depression, dehydration). Halitosis is a feature. Urinalysis along with clinical biochemistry and hematology are usually diagnostic.

Neoplasia

Squamous cell carcinoma is a common feline neoplasm particularly affecting the extremities of white or lightly pigmented cats (e.g., ear tips, planum nasale). White English bull terriers are also predisposed. The prevalence of squamous cell carcinoma is greater in warmer climates. Waterproof, high sun protection factor cream should be applied to animals at risk. Ideally, access to sunshine should be restricted.

Epitheliotropic lymphoma leads to nodular, scaling, eroded and erythematous skin lesions in older dogs. Oral lesions (erythema, erosion) occur in the majority of cases. The prognosis is grave, with therapy having little influence on survival time.

Diagnosis of cutaneous neoplasia is by histopathology, although cytology of fine-needle aspirates and impression smears may be helpful.

Physical and Chemical Diseases

Such diseases can usually be diagnosed with history: exposure to extreme cold or scalding, recent treatment with medicaments, or (in the case of urine scalding) clinical examination. Solar-induced disease may be more difficult to diagnose because the onset is chronic and some manifestations of solar dermatoses may resemble other diseases.

Immune-Mediated and Autoimmune Diseases

Although this group is ascribed much significance by clinicians, these diseases are uncommon or rare. Lesions arise when tissue is damaged as a result of an inappropriate immunologic response. In autoimmune diseases, antibodies directed against a tissue component elicit an inflammatory response that may lead to cleavage of the epidermis from the underlying dermis (e.g., bullous pemphigoid, epidermolysis bullosa aquisita) or splitting within the epidermis itself (e.g., the pemphigus group). In some diseases, the precise pathologic mechanism is unknown (e.g., discoid lupus erythematosus).

The differentiation of the different immune-mediated diseases is important and made by histopathology. The different diseases respond to different forms of therapy, and the prognosis varies between them. If a definitive diagnosis is not obtained, then there is a risk of treating a benign disease too aggressively with immune-suppressive agents.

Miscellaneous Diseases

Dermatomyositis is a hereditary disorder primarily affecting the face and distal limbs of rough and Shetland collie (shelties) pups, leading to alopecia, erosions, ulceration, and scarring. It probably arises from immune-mediated vasculitis. Idiopathic ulceration is also seen in these breeds; previously it was thought that it may share its cause and pathogenesis with dermatomyositis. However, recent evidence suggests that it may be a form of lupoid dermatitis.

Idiopathic ulceration principally affects the ventral abdomen and groin and usually occurs in middle-aged rough and Shetland collie dogs. The prognosis is guarded because it is refractory to treatment in most cases.

Congenital diseases may affect the basement membrane and lead to ulceration and erosion. Examples include junctional epidermolysis bullosa and dystrophic epidermolysis bullosa.

CHAPTER 13

Pustules and Papules

Edmund J. Rosser, Jr.

Pustules and papules are the most common primary skin lesions in dogs. Bacterial skin diseases are the most frequent cause of these lesions. The discussions will be limited to bacterial skin diseases of the dog because the development of a pyoderma is an extremely rare event in the cat.

CUTANEOUS BACTERIOLOGY

Bacteria that are isolated from the skin of dogs are commonly divided into three categories: (1) resident organisms, (2) transient organisms, and (3) common pathogenic organisms. Resident bacterial organisms can be routinely and repeatedly isolated and cultured from the surface of the skin, hairshafts, hair follicles, nares, oropharynx, and anal ring of the dog and normally live in harmony with the host without causing clinical disease. The resident bacteria of the canine skin surface include coagulase-negative staphylococci (*Staphylococcus epidermidis, S. cohnii, S. saprophyticus, S. hominis, S. haemolyticus, S. capitis, S. warneri, S. xylosus, S. simulans,* and *S. sciuri*); coagulase-positive staphylococci *(S. intermedius)*; *Micrococcus* spp.; alpha-hemolytic streptococci; *Clostridium* spp.; *Propionibacterium acnes*; and *Acinetobacter* spp. The resident bacteria of canine hairshafts are *Micrococcus* spp., various gram-negative aerobes, *Bacillus* spp., and *S. intermedius*. *Propionibacterium acnes, Micrococcus* spp., streptococci, *Bacillus* spp., and *S. intermedius* have been isolated from within the hair follicles. The resident bacterium of the nares, oropharynx, and anal ring is *S. intermedius*. Transient bacterial organisms are not routinely or repeatedly isolated and cultured from the skin and haircoat of the dog. Under normal circumstances these organisms do not multiply on the dog but occasionally become pathogens by secondary invasion. They include *Escherichia coli, Proteus mirabilis, Pseudomonas* spp., *Corynebacterium* spp., and *Bacillus* spp.

Primary pathogenic organisms are capable of tissue invasion and creating disease. They are usually coagulase-positive staphylococci *(S. intermedius, S. aureus, S. hyicus)*, and *S. intermedius* is the most common isolate from canine skin infections.

PATHOPHYSIOLOGY

The bacterium *S. intermedius* is a normal resident of healthy canine skin, hairshafts, hair follicles, nares, oropharynx, and anal ring. They are also the most common causative organisms in superficial and deep pyodermas. These skin infections can be classified as *primary* or *secondary*. Secondary infections are undoubtedly the most common and are easily recognized by the tendency of the infection to be recurrent. Recurrence is the result of an underlying disease process allowing *S. intermedius* to become an opportunist and invade the stratum corneum, hair follicle, or both. These underlying disease processes may alter the skin directly as the result of local trauma, irritants, or scratching from parasitic and other pruritic skin diseases (see Chapter 10). Alternatively, the disease may act systemically to decrease resistance to cutaneous infections as in metabolic and immune-mediated skin diseases (see Chapter 269). Primary skin infections are so classified because once they are appropriately treated, they do not recur. However, it seems most likely that some transient insult occurs to the skin that allows *S. intermedius* to become a temporary opportunist and pathogen.

In either primary or secondary pyodermas, *S. intermedius* begins by overcolonizing the surface of the skin and either invading the stratum corneum (as in impetigo) or the hair follicle (as in superficial folliculitis). In cases of impetigo, the invasion of the stratum corneum results in the formation of primarily nonfollicular pustules (i.e., the pustules do not have a hairshaft in the center), which rupture and often form crusts and epidermal collarettes. The lesions are usually nonpruritic and tend to be associated with minimal inflammation. In cases of superficial folliculitis, the invasion of the hair follicle results in the formation of follicular papules and pustules (i.e., hairshafts are present in the center of the lesions) that also rupture and often form crusts and epidermal collarettes. The lesions are usually pruritic and associated with inflammation and erythema. The older lesions often evolve into annular areas of alopecia and hyperpigmentation.

Deep pyodermas invariably begin as a superficial folliculitis and occur in cases where the underlying disease processes have not been appropriately identified. The infection travels into the deeper portions of the hair follicle and subsequently ruptures the hair follicle into the surrounding dermis, causing a furunculosis. The infection may continue to invade the deeper dermal and subcutaneous tissues, resulting in cellulitis.

CLINICAL FEATURES

A *pustule* is defined as a small, elevated, purulent fluid-filled cavity in the epidermis that is less than 0.5 cm in diameter. The base of the pustule is often erythematous. Pustules are most commonly associated with a superficial pyoderma. A *papule* is defined as a small, elevated, solid skin lesion up to 0.5 cm in diameter caused by the infiltration of inflammatory cells. They are usually pinkish or reddish in color. When they are oriented around a hair follicle, they usually indicate a superficial bacterial folliculitis. They are also commonly observed in cases of scabies and flea allergy (see Chapter 10). The presence of pustules and papules caused by a bacterial infection is frequently associated with concurrent pruritus owing to the production of proteolytic enzymes by the bacteria present in these lesions (primarily *S. intermedius*). These lesions may then rupture spontaneously or be altered in their appearance as a result of pruritus-induced self-trauma. Therefore these primary lesions may be transient, leaving behind only the presence of secondary lesions such as erosions, crusts, epidermal collarettes, posttraumatic alopecia, and excoriations. As the disease becomes more chronic in nature,

additional skin changes may develop, such as hyperpigmentation and lichenification.

SUPERFICIAL PYODERMAS

Impetigo (Puppy Pyoderma)

Impetigo is most often observed in young dogs before puberty. This infection is considered to be an opportunistic or secondary pyoderma most frequently associated with poor nutrition, dirty environment, viral infections, ectoparasites, and intestinal parasitism. The disease is associated with the formation of superficial pustules that do not involve hair follicles and affects the inguinal and ventral abdominal regions (and occasionally the axillary region). Minimal erythema is noted, and the puppy is usually nonpruritic. Impetigo is often an incidental finding by the owner or is noticed on routine physical exam.

Superficial Folliculitis

A folliculitis is an inflammation of the hair follicle that can be caused by bacteria (staphylococcal folliculitis), fungi (dermatophyte folliculitis), and parasites (demodicosis, pelodera dermatitis).

Superficial bacterial folliculitis begins with the presence of pustules and papules initially affecting the inguinal and ventral abdominal regions. The papules and pustules are oriented around hair follicles and the dog is usually pruritic. As the disease progresses, epidermal collarettes form with varying degrees of central hyperpigmentation and marginal erythema, and additional areas affected may include the axillary regions and ventrolateral thorax. When the truncal skin is affected, the haircoat often takes on a "moth-eaten" appearance (especially in short-coated breeds of dogs).

DEEP FOLLICULITIS AND FURUNCULOSIS

Furunculosis is an inflammation of hair follicles with subsequent follicular rupture extending into the surrounding dermis and subcutaneous tissue. The lesions initially observed include papules, pustules, and epidermal collarettes followed by the presence of exudation, crust formation, and deep draining tracts. As the process of folliculitis and furunculosis continues and the lesions coalesce, areas may become nodular and indurated or a cellulitis may develop. Another lesion occasionally observed in these patients is a hemorrhagic bulla. The lesions are usually first noticed in inguinal, ventral abdominal, and axillary regions as a superficial folliculitis. However, when the underlying disease process is not appropriately treated, deep folliculitis and furunculosis may develop. With this complication, involvement of the entire ventrum or a generalized process may ensue. Occasionally the lesions are most severe over the pressure and wear areas of the body such as the elbows and lateral aspects of the stifle, hip, and chest region. In most cases, the lesions seem to be pruritic or painful.

Signs of systemic involvement may be evident, including anorexia, depression, weight loss, lethargy, and fever. This is often the indication of the development of bacteremia, septicemia, or both. A peripheral lymphadenopathy is also a common finding.

RECURRENT PYODERMAS

History and Physical Findings

Recurrent pyodermas may appear initially as a superficial folliculitis, deep folliculitis, or furunculosis (or a combination of these symptoms). Invariably, a recurrent pyoderma has some underlying reason for reappearing. Therefore the underlying problem needs to be identified and appropriately treated. One should first make certain that a recurrent pyoderma is not iatrogenic in nature. Iatrogenic recurrent pyodermas may be the result of previously inadequate drug therapy, including inappropriate antibiotic selection; inadequate dose, frequency and duration of antibiotic therapy; and the chronic use of corticosteroids as an adjunct to the treatment of a pyoderma.

Diagnostic Approach

The first part of the diagnostic approach to a patient with a pyoderma is to recognize the various lesions that indicate its presence. One of the commonly misinterpreted lesions on dermatologic examination is the epidermal collarette, especially when its margins are erythematous. It is often thought to be an indication of a dermatophyte (ringworm) infection but is more commonly an indication of a superficial spreading pyoderma. In addition, the presence of papules in patients with pruritus is frequently thought to be associated with primary allergic skin diseases and is treated solely with a corticosteroid. However, in many cases, closer inspection reveals the presence of a pinpoint pustule on top of the papule or a hairshaft exiting the center of the papule, which indicates the presence of a folliculitis. When one is uncertain as to whether the lesion present may be an indication of a bacterial skin disease, a skin biopsy should be performed.

When considering treatment of a dog with an antibiotic-responsive but recurrent pyoderma, the first step is to systematically evaluate the patient for some of the more common causes of a recurrence. One should consider obtaining the following tests: skin scrapings, flea combing, hair plucking and microscopic examination, skin surface impression cytology, cytology of pustules, and acetate (Scotch) tape preparations (Figure 13-1). When these test results are negative and the cytology or culture of pustules and papules indicate the presence of a pyoderma, an appropriate antibiotic must be selected. Either the antibiotic is empirically chosen (Table 13-1) or, preferably, is chosen based on the results of culture and susceptibility testing. The next step involves the use of the dog's response to therapy as an aid to the definitive diagnosis. In a majority of dogs with a recurrent pyoderma, some degree of pruritus is present. However, at this stage of the workup, the use of a corticosteroid (or any other antipruritic drug) needs to be avoided. The dog is then

Table • 13-1

Systemic Antibiotics Recommended in the Treatment of Staphylococcal Pyodermas

ANTIBIOTIC	RECOMMENDED ORAL DOSE
Clindamycin	5.5 mg/kg q12h, or 11 mg/kg q24h
Erythromycin	15 mg/kg q8h
Cephalexin	22 mg/kg q8h, or 33 mg/kg q12h
Cefadroxil	22 mg/kg q12h
Trimethoprim/ sulfadiazine	15–30 mg/kg q12h
Ormetoprim/ sulfadimethoxine	55 mg/kg on day 1, then 27.5 mg/kg q24h
Amoxicillin/clavulanate	13.75 mg/kg q12h
Enrofloxacin*	5–20 mg/kg q24h

*Only recommended in instances of recurrent pyodermas when culture and susceptibility testing indicate its required use.

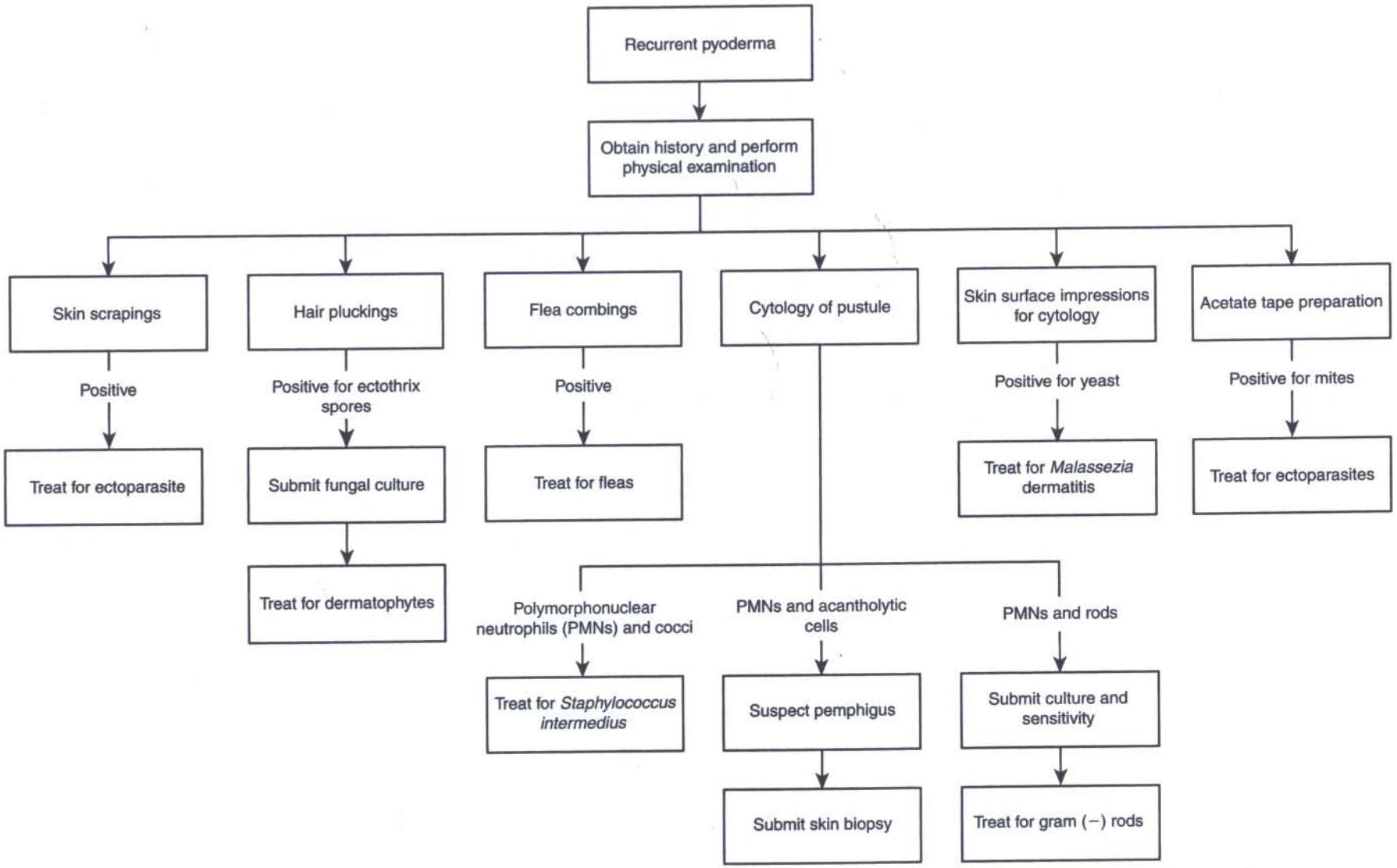


Figure 13-1 Algorithm for diagnosis and treatment of recurrent pyoderma. (From Rosser EJ, Littlewood J: *Practice resource manual: companion animal dermatology*, series I, module 1, Guelph, Ontario, 1996, Lifelearn Inc.)

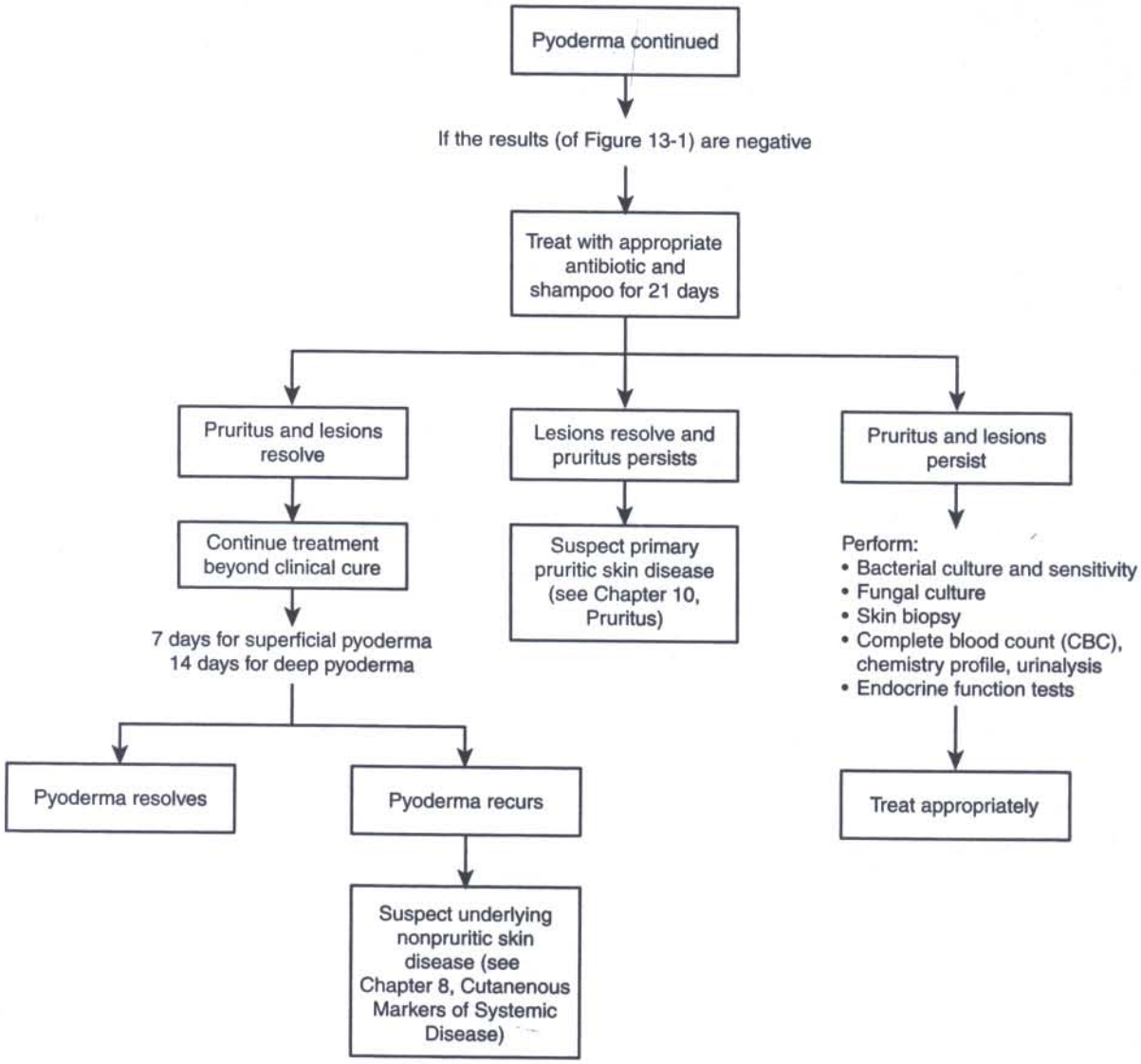


Figure 13-2 Algorithm for pyoderma continued. (From Rosser EJ, Littlewood J: *Practice resource manual: companion animal dermatology*, series I, module 1, Guelph, Ontario, 1996, Lifelearn Inc.)

treated *only* with the appropriate antibiotic and shampoo therapy (benzoyl peroxide shampoo) for a period of 3 consecutive weeks and then reevaluated (Figure 13-2). This initial duration of therapy is usually adequate in cases of superficial folliculitis but may need to be increased to 6 to 8 consecutive weeks in cases of deep folliculitis and furunculosis. If the recheck examination reveals that the pyoderma has noticeably improved or resolved but the pruritus has persisted, the dog needs to be further evaluated for the presence of an underlying primary pruritic skin disease including flea allergy dermatitis, atopic dermatitis, food allergy, scabies, demodicosis, allergic contact dermatitis, and seborrheic dermatitis. On the initial visit the owner should also be advised to observe the areas on the dog's body where the pruritus is persisting or most severe (i.e., the distribution pattern of pruritus) to assist the clinician in establishing the underlying differential diagnosis (see Chapter 10). However, if the recheck examination reveals that the pyoderma has resolved and the dog has become nonpruritic in response to the antibiotic and shampoo therapy alone, then it is necessary to establish whether the pyoderma is truly recurrent. In this case the appropriate antibiotic and shampoo therapy should be continued for a total treatment time of 8 weeks. After having done this, some patients with a history of a recurrent pyoderma will experience permanent resolution of their disease. If the pyoderma recurs after this treatment, then the following diseases should be ruled out: hypothyroidism, Cushing's disease, diabetes mellitus, reproductive hormone imbalances, demodicosis, cheyletiellosis, staphylococcal hypersensitivity, and cell-mediated immunodeficiencies (see Chapter 8).

CHAPTER • 14

Scaling and Crusting Dermatoses

Kinga Gortel
Jonathan D. Plant

PATHOPHYSIOLOGY

Scaling and crusting are common findings in many cutaneous diseases (Table 14-1). Scaling refers to the accumulation of loose fragments of cornified cells on the skin surface. Normal desquamation of cornified cells is not visible to the naked eye, so scales are only seen when loss occurs in larger flakes. Scales are usually secondary lesions in chronically inflamed skin but may also be primary lesions in conditions such as seborrhea and ichthyosis. Crusting occurs when dried exudates or secretions adhere to the surface of the skin. Crusts may be composed of pus, blood, serum, other exudates, or thick scales. They are also usually secondary, occurring on skin traumatized as a result of pruritus or in any pustular dermatosis. Crusts may be primary in some conditions such as miliary dermatitis and zinc-responsive dermatosis.

SIGNALMENT

Age

Puppies and kittens developing scaling within the first few weeks of life should be evaluated for transmissible infections and congenital dermatoses. Juveniles should be screened for infectious diseases, such as parasites, hereditary dermatoses, nutritional dermatoses, and environmental diseases. Differential diagnoses for similarly affected adult dogs and cats include the diseases listed for younger animals, as well as allergic, immune-mediated, endocrine, and metabolic diseases; keratinization disorders; and cutaneous neoplasia.

Breed

Breeds with an inherited predisposition to the development of primary scaling and crusting disorders include American cocker spaniels, English springer spaniels, West Highland white terriers, Basset hounds, Irish setters, Doberman pinschers, and Labrador retrievers. Breed predispositions are also noted in many other dermatoses that lead to scaling and crusting, including canine atopic dermatitis, hypothyroidism, and sebaceous adenitis.

HISTORICAL FINDINGS

The history can be helpful in narrowing the list of differential diagnoses in an animal with scaling or crusting. The age of onset should be established. The owner should also be questioned as to the seasonality of the scaling and crusting. An important consideration is the degree of accompanying pruritus. Diseases that are often severely pruritic include sarcoptic acariasis, atopic dermatitis, fleabite hypersensitivity, food hypersensitivity, *Malassezia* dermatitis, and cutaneous lymphoma.

PHYSICAL EXAMINATION

Lesions

Scaling and crusting are often encountered concurrently. The skin should be examined for pustules, papules, excoriation, erythema, ulceration, and the shape of crusts or scaly areas should be noted (e.g., epidermal collarettes).

Distribution

Scaling and crusting dermatoses may be generalized or have site predilections. Generalized conditions include dermatophytosis, cheyletiellosis, primary seborrhea, and sebaceous adenitis. Site predilections include the nasal planum (e.g., pemphigus foliaceus, discoid lupus erythematosus, squamous cell carcinoma), footpads (e.g., pemphigus foliaceus, zinc-responsive dermatosis, superficial necrolytic dermatitis, plasma cell pododermatitis), and ear pinnae (e.g., sarcoptic mange, ear margin seborrhea).

DIAGNOSTIC PLAN

Skin scrapings and cytology are simple and often useful for evaluation of dogs and cats with scaling and crusting (Figure 14-1). Skin scrapings are most useful for diagnosing demodectic mange in dogs and *Notoedres cati* in cats. They are less sensitive for canine *Sarcoptes scabiei*. *Cheyletiella* mites are easiest to find by acetate tape impressions.

Samples for cytologic examination of the skin may be collected directly from the surface of the skin by impression smears if the skin is greasy or moist or after the removal of crusts or adherent scales. If pustules are present, their content should be smeared on a slide. Waxy or dry samples benefit from gentle heat fixing. A modified Wright's stain (e.g., Diff Quick) is used to examine the slides. Cytology is most useful for confirming presence of bacteria and yeast. The inflammatory response of the skin can also be evaluated because neutrophils, eosinophils, and mononuclear cells are easily differentiated. The presence of numerous acantholytic cells among neutrophils suggests pemphigus but is occasionally encountered in other inflammatory conditions.

Examination for fungi should be attempted when dermatophytosis is suspected. Cats with scaling and crusting should always be checked for dermatophytes unless another cause is readily identified. A Wood's light examination should be performed. A dermatophyte test medium (DTM) fungal culture should always be inoculated if dermatophytosis is suspected. Direct examination of hair for dermatophytes is less sensitive.

Skin biopsy is needed to make a definitive diagnosis in some scaling and crusting disorders, including immune-mediated diseases, neoplastic conditions, and primary keratinization disorders. Crust and scale must be included in the

Table • 14-1

Scaling and Crusting Diseases of Dogs and Cats

DISEASE	LESIONS	SPECIES	SIGNALMENT	LESION DISTRIBUTION	FREQUENCY	PRURITUS	DIAGNOSIS
Bacterial							
Superficial folliculitis	Crusts, scales, collarettes, pustules	Dog > cat	Varies	Trunk	C	– to ++	CS, Cyt, BC, Bx
Deep pyoderma	Crusts, ulcers	Dog > cat	Varies	Trunk, feet	C	+	CS, Cyt, BC, Bx
Mucocutaneous pyoderma	Crusts, ulcers	Dog	German Shepherd or others	Lips, peribuccal	U	+ (painful)	CS, Bx
Pyotraumatic dermatitis	Moist crust, exudation, erythema	Dog	Any (often flea-related)	Face, neck, caudal trunk	C	+++	CS
Fungal							
Dermatophytosis	Crusts, scales, alopecia, erythema	Cat > dog	Young most frequently	Head, extremities, trunk	C	– to ++	DTM, Wood's light
Malassezia dermatitis	Crusts, scales, erythema, lichenification	Dog > cat	Adult most frequently	Axillary, groin, interdigital, facial	C	+++	Cyt
Parasitic							
Ctenocephalides felis (flea)	Scales, erythema	Dog > cat	Any	Lumbosacral, neck	C	+	CS, parasite exam
Sarcoptes scabiei	Crusts, scales, excoriations, alopecia, erythema	Dog	Any	Pinnal margins, lateral elbows, ventrum	C	+++	SS, response to therapy
Demodex canis	Crusts, scales, exudation, alopecia, erythema	Dog	Young or immunocompromised adults	From single lesions on the head to generalized	C	– to +	SS
Cheyletiella spp.	Scales	Dog, cat	Young most frequently	Dorsal trunk to generalized	U	– to ++	SS, tape impression
Notoedres cati	Crusts, scales	Cat	Any	Head, feet, generalized	U	– to +++	SS
Viral							
Feline leukemia virus (FeLV)	Crusts, scales, erosions	Cat	Any	Face, pinnae, perioral, feet, trunk	U	++	Serology, Bx

Allergic							
Atopic dermatitis	Erythema, alopecia, crusts (excoriation), scales, and others	Dog > cat	All, dogs often 1–5 years old	Face, ears, feet, ventrum	C	+ to +++	CS, IDST, IgE
Food hypersensitivity	Erythema, crusts (excoriation), and others	Dog, cat	All, any age	Any	U	+ to +++	Food trial
Flea bite hypersensitivity	Erythema, crusts (excoriation), and others	Dog, cat	All	Caudal dorsum, ventrum, thighs	C	++ to +++	Response to flea control
Miliary dermatitis	Small hemorrhagic crusts	Cat	All (often associated with fleas)	Dorsum	C	++	CS
Endocrine and Metabolic							
Hyperadrenocorticism	Alopecia, cutaneous atrophy, calcinosis cutis, crusts (pyoderma)	Dog > cat	Middle aged, older	Trunk	C	– (occ. +)	MDB, hormone assays, imaging, Bx
Hypothyroidism	Scaling, dry skin, pyoderma, +/– alopecia	Dog	Middle aged, often large breed	Generalized	C	–	MDB, thyroid assay
Necrolytic migratory erythema	Severe adherent crusting	Dog (cat)	Old	Muzzle, footpads, pressure points	R	+ to ++ (painful)	Bx, MDB, liver assays, imaging
Immune Mediated							
Pemphigus foliaceus	Crusts, pustules	Dog, cat	Any age and sex; Akita, chow chow, and others	Nasal planum, muzzle, pinnae, foot pads, trunk	U	– to +	Bx
Discoid lupus erythematosus	Crusts, depigmentation erosions, ulcers	Dog, cat	Collies, Shetland sheepdog, and others	Nasal planum, muzzle	U	–	Bx
Erythema multiforme	Crusts, vesicles erythema, target lesions, erosions, ulcers	Dog, cat	Any	Axillae, groin, mucocutaneous junctions	U	–	Bx
Congenital and Hereditary							
Primary seborrhea	Excessive scaling or greasy skin	Dog (cat)	Onset before 6 months, American cocker spaniel and others	Generalized	U	– to ++, esp. with secondary infections	Bx
Schnauzer comedo syndrome	Comedones that may become crusted	Dog	Miniature schnauzer	Dorsum	C	–	CS, Bx
Familial canine dermatomyositis	Alopecia, scaling, depigmentation	Dog	Onset before 6 months, collie, Shetland sheepdog, and others	Face, pressure points	U	–	Cs, Bx

Continued

Table • 14-1

Scaling and Crusting Diseases of Dogs and Cats—Cont'd

DISEASE	LESIONS	SPECIES	SIGNALMENT	LESION DISTRIBUTION	FREQUENCY	PRURITUS	DIAGNOSIS
Keratinization Defects							
Secondary seborrhea	Excessive scaling or greasy skin	Dog, cat	Any age	Depends on primary cause	C	– to +++ depending on cause	CS, any appropriate tests for primary disease
Vitamin A—responsive dermatosis	Marked follicular plugging, hyperkeratotic plaques	Dog	Cocker spaniel and others Adult onset	Generalized, more pronounced on ventrum	U	– to ++	CS, Bx
Ear margin dermatosis	Follicular casts and scaling	Dog	Dachshund and others	Ear margins, lateral and medial	U	–, may become painful	CS, Bx
Environmental							
Solar dermatitis	Erythema, scaling, may progress to exudation and crusting	Dog > cat	Light-haired animals, outdoor exposure	Pinnae, nasal planum (cat), bridge of nose, ventrum (dog)	C	– to +	CS, Bx
Nutritional							
Zinc-responsive dermatosis	Crusts, scales, erythema, alopecia	Dog	Siberian husky, Alaskan malamute; young adults	Periocular, perioral, mucocutaneous junctions, pressure points	U	– to +	Bx
Fatty acid deficiency	Scales	Dog, cat	Any	Generalized	U	– to ++	Dietary hx
Other							
Cutaneous lymphoma	Lesions highly variable but may include severe scaling	Dog > cat	Older animals	Generalized or localized	U	– to +++	Bx
Granulomatous sebaceous adenitis	Hyperkeratosis, alopecia, follicular casts, may be erythematous	Dog (cat)	Young to middle-aged, standard poodle, Akita, vizsla, and others	Face, trunk, pinnae, become generalized	C	– to ++	CS, Bx
Otitis externa	Scale, erythema, otic exudate	Dog > cat	Any	Pinnae, ear canal	C	++	Otoscopic examination, Cyt, BC

BC, Bacterial culture; *Bx*, skin biopsy; *C*, common; *CS*, clinical signs; *Cyt*, cytology; *DTM*, dermatophyte test medium fungal culture; *Hx*, history; *IDST*, intradermal skin test; *IgE*, allergen-specific serum IgE assay; *MDB*, minimum database; *NSF*, no significant findings; *R*, rare; *SS*, skin scraping; *U*, uncommon; +, positive; –, negative.

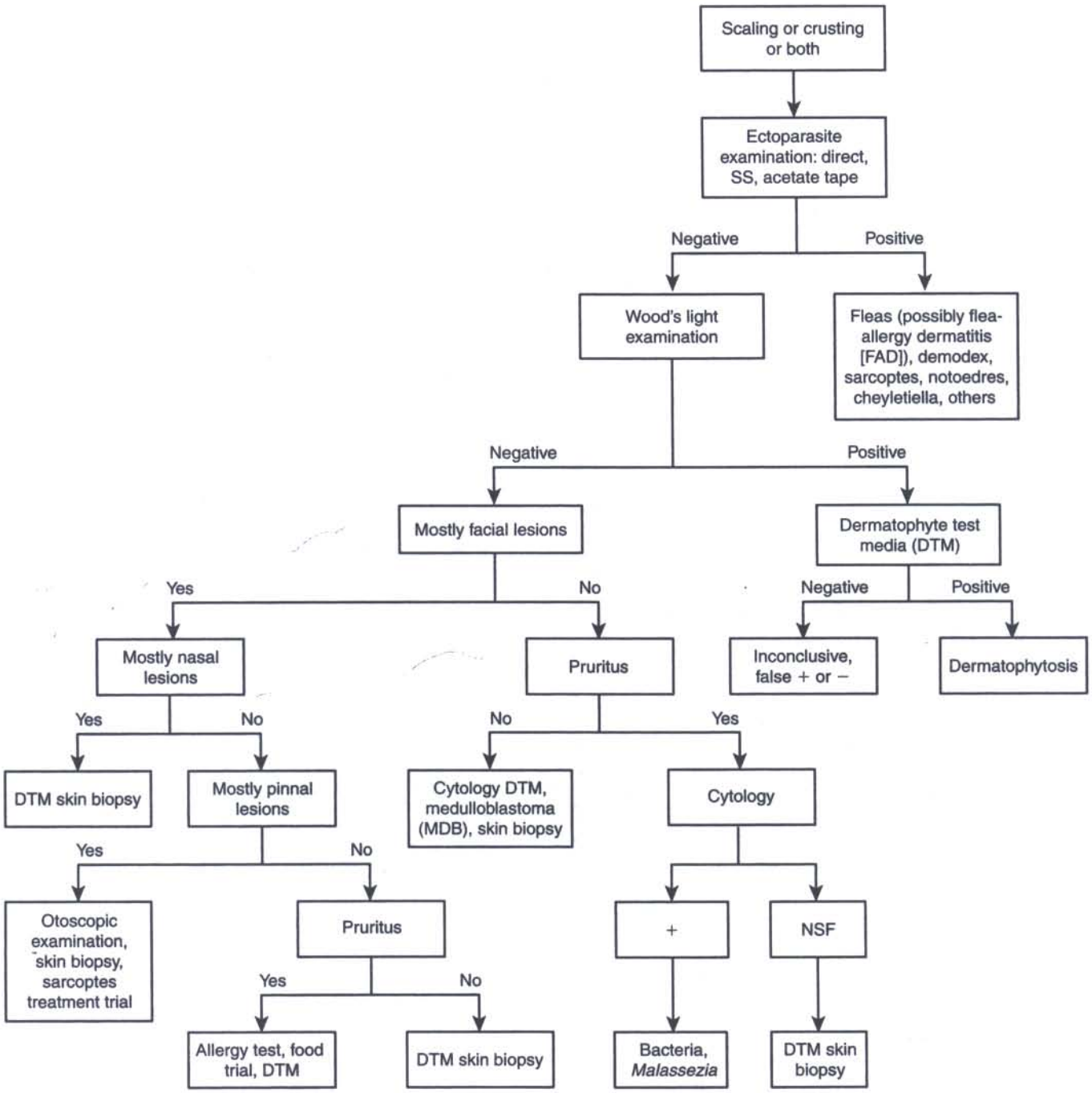


Figure 14-1 Diagnostic approach to scaling and crusting in dogs and cats.

biopsy, so the biopsy site should never be cleaned or scrubbed. Hair may be gently cut with scissors without disrupting any surface material.

A minimum database is most useful in middle-aged and older animals when endocrine or metabolic causes are suspected. Bacterial culture should be performed when bacteria are identified on cytology or when crusting does not completely resolve after appropriate antibiotic treatment for pyoderma.

TREATMENT

It is beyond the scope of this chapter to address the specific treatment of each disease that may result in scaling and crusting. In general terms, treatment can be divided into topical and systemic therapeutic approaches.

Topical Therapy

To reduce scaling and crusting, the goal is to normalize cell proliferation, differentiation, and desquamation and to reduce exudation from the skin surface. Active ingredients should be selected based on the underlying condition, and are most frequently applied as shampoos and conditioners. Active ingredients may be keratolytic, keratoplastic, degreasing, antimicrobial, antiparasitic, antiinflammatory, antipruritic, or moisturizing. Most animals with generalized scaling and crusting disorders will benefit from frequent bathing (twice a week or more).

Systemic Therapy

For secondary scaling and crusting, attempts should be made to correct the underlying cause. For primary scaling and crusting disorders of dogs, vitamin A or synthetic retinoid therapy are variably helpful. Vitamin A is given at a dose of 800 to 1000 mg/kg/day. The synthetic retinoid acetretin has been used to treat primary seborrhea in dogs at a dose of 1 mg/kg/day. The principal effect is to normalize epithelial keratinization. Possible adverse reactions include teratogenicity, keratoconjunctivitis, elevated liver enzymes, and hypertriglyceridemia. Its use is limited by expense.

CHAPTER 15

Changes in Pigmentation

Zeineb Alhaidari

Pigmentation changes are frequently seen in veterinary medicine; they not only have potential cosmetic importance but they could also imply medical or zootechnical consequences because possible causes include systemic diseases, genodermatoses, or both. Evaluation of pigmentation changes requires developing a differential diagnosis (Figure 15-1).

The term *leukoderma* refers to a loss of melanin pigmentation of the skin. The term *leukotrichia* or *poliosis* refers to a loss of melanin pigmentation of the hair. Similarly, *melanoderma* refers to an increased melanin pigmentation of the skin, and *melanotrichia* refers to an increased pigmentation of the hair.

HYPOPIGMENTATION

History

Breed

A marked breed predilection exists for most noninfectious focal hypopigmentation disorders.

- *Vitiligo*, characterized by the symmetrical development of achromic macules on the facial mucocutaneous junctions, has a breed predilection in the Tervueren, Rottweiler, Doberman pinscher, Newfoundland, Collie, German shorthair pointer, Old English sheepdog, and Siamese cat.
- The *uveodermatologic syndrome*, an autoimmune disorder targeting ocular and cutaneous melanocytes and resulting in uveitis and skin depigmentation, has been described mainly in northern breeds such as the Siberian husky, Samoyed, and Akita.
- *Acquired idiopathic hypopigmentation of the nose*, an idiopathic gradual loss of nasal planum pigment, is widespread in some canine breeds such as the Labrador retriever, Siberian husky, Samoyed, Poodle, and German shepherd.
- *Discoid lupus*, a presumed autoimmune photoaggravated disorder limited to the skin, affects mainly Collies and German shepherds.
- *Dermatomyositis* is a genodermatosis described in the Collie, Shetland sheepdog, and Beauceron shepherd breed. Crusting, ulceration, and depigmentation of the skin, affecting preferentially the face and extremities, are associated with varying degrees of muscle involvement.

Age of Onset

The age of onset is often helpful in the diagnosis of certain depigmenting disorders. An early age of onset usually suggests a genodermatosis. *Dermatomyositis* is classically first observed in 3- to 4-month-old puppies, with variably affected individuals in the litter. Symmetric unpigmented macules involving the mucocutaneous junctions of the face in a young dog, aged 8 months to 3 years, are highly suggestive of *vitiligo*. *Discoid lupus*, which has a similar clinical appearance to vitiligo, also affects dogs of a similar age. The old animal is more prone to develop *bullous autoimmune dermatoses* and neoplastic disorders such as *epitheliotrophic lymphomas*.

Evolution

Evolution of the hypopigmentation should be carefully documented. Circumstances of onset should be investigated. Local trauma, including physical or chemical causes, must be considered as a potential etiology of melanocyte dysfunction or destruction. Any drug administration preceding the onset of symptoms should be noted.

The nature and location of the initial lesion could be of major interest, especially in the differential diagnosis of nasal depigmentation. Unpigmented macules developing at the junction between the planum nasale and haired skin are highly suggestive of *bullous autoimmune diseases*. *Contact dermatitis* usually affects the rostral nares. Depigmentation developing on the floor of one nostril and associated with a purulent discharge is highly suggestive of *aspergillosis*.

Because *lupus erythematosus* or *pemphigus erythematosus* lesions are exacerbated with sun exposure, seasonality of symptoms is an interesting observation. Reported concurrent clinical signs, such as lameness, can be indicative of *leishmaniasis* or *systemic lupus erythematosus* (SLE). Ocular involvement suggests *uveodermatologic syndrome*, *leishmaniasis*, or *systemic mycoses*, such as *cryptococcosis* or *blastomycosis*. Weight loss, fever, and anorexia can be manifestations of *neoplastic diseases*, *SLE*, *bullous autoimmune disorders*, *systemic mycoses*, or *leishmaniasis*.

Physical Examination

Physical examination is the second important step in the diagnosis of pigmentary changes. The physical evaluation should help determine whether a disease is limited to the skin or multisystemic (see Figure 15-1). If the disease is limited to the skin and if leukoderma, leukotrichia, or both is the only skin lesion present, then one has to consider the topography of the lesions.

If the depigmentation is limited to the nose or facial mucocutaneous junctions, the persistence of normal nasal surface

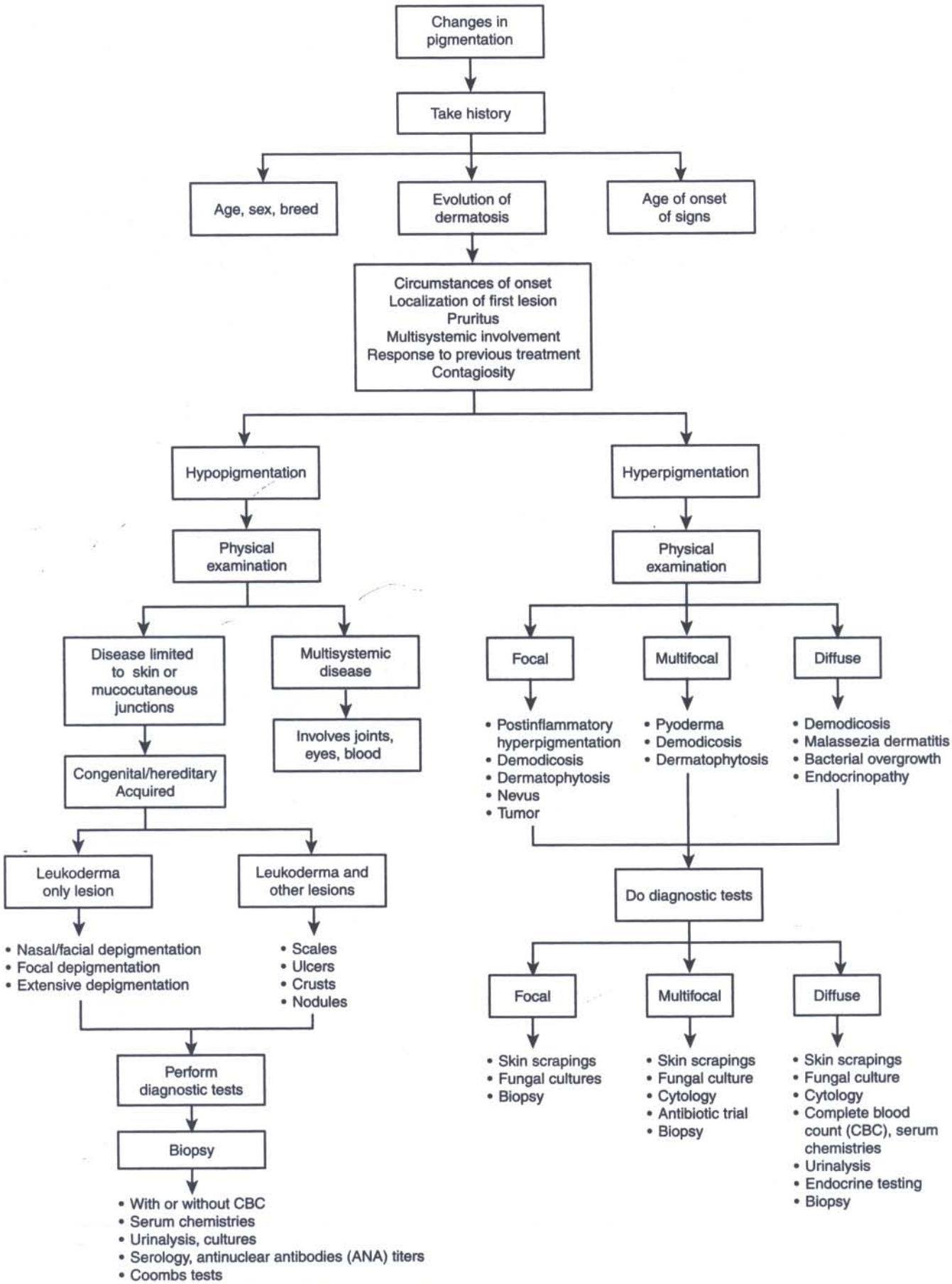


Figure 15-1 Algorithm for evaluation of changes in pigmentation.

architecture favors a noninflammatory cause, such as *vitiligo* or *acquired idiopathic hypopigmentation*. Alternatively, if the normal surface architecture has been altered, an inflammatory dermatosis should be suspected. However, ultraviolet radiation associated with sunlight can induce an actinic dermatitis on a lesion that is initially simply unpigmented, with subsequent erythema, ulcers, crusts, and disappearance of cutaneous surface markings.

If the unpigmented lesion is focal, then a history of *trauma* should be investigated. Extensive acquired leukotrichia can follow an immunologic attack directed primarily against the hair follicles in *alopecia areata*, resulting in alopecia and occasional regrowth of white hairs.

If leukoderma, leukotrichia, or both is associated with other skin lesions such as scales, ulcers, or crusts, *leishmaniasis* or *autoimmune dermatoses* should be considered.

Infiltrative lesions are usually indicators of *systemic mycoses* or *tumors*.

Multisystemic involvement is seen in *leishmaniasis, SLE, systemic mycoses,* or *tumors*. Arthritis and glomerulonephritis are frequent features of both *SLE* and *leishmaniasis*. Hematologic disorders, such as hemolytic anemia, leukopenia, and thrombocytopenia, can be associated with *SLE*. Nonregenerative anemia, leukopenia, and monocytosis frequently are observed in *leishmaniasis*. In the *uveodermatologic syndrome,* uveitis and subsequent glaucoma usually precede the cutaneous manifestations. The eye is also a frequent target in *leishmaniasis* and in *systemic mycoses,* such as *cryptococcosis* and *blastomycosis*.

Diagnostic Tests

Skin biopsy is the fundamental diagnostic procedure when faced with hypopigmentation (see Figure 15-1). Specimens should be taken both from the center and from the margins of lesions, especially if the disease is active and spreading. Biopsies can demonstrate the presence or absence of an inflammatory infiltrate and the presence or absence of melanocytes. The presence or absence of melanocytes is difficult to ascertain because special stains such as Fontana-Mason or dopa reaction cannot differentiate between nonfunctional and absent melanocytes. If inflammatory infiltrates and melanocytes are absent, one can suspect either *vitiligo* or a *postinflammatory depigmentation* with complete destruction of melanocytes. If melanocytes are present, *acquired idiopathic hypopigmentation* can be suspected. Inflammatory infiltrates are associated with several depigmenting diseases. Of particular interest are lichenoid infiltrates, which are chiefly lymphocytic in *lupus erythematosus* and *epitheliotrophic lymphomas* and are granulomatous in *uveodermatologic syndrome*. Infectious agents such as leishmania, mycobacteria, or fungal organisms are sometimes demonstrated on histologic sections of inflamed unpigmented lesions. If a pyogranulomatous or granulomatous nodular-to-diffuse infiltrate is observed, special stains should be requested in an attempt to identify the presence of microorganisms.

Depending on biopsy results, diagnosis will be completed by other tests such as complete blood count (CBC), serum chemistry profile, urinalysis, cultures, serologic testing for leishmaniasis or systemic mycosis, antinuclear antibodies dosage, and Coombs' test.

HYPERPIGMENTATION

History

Breed

Demodicosis and most *endocrinopathies* occur more frequently in specific breeds. Doberman pinschers, Shar Peis, West Highland white terriers, Scottish terriers, Boston terriers, Great Danes, and Weimaraners are breeds known to have a high prevalence of *demodicosis*. Great Danes, Irish setters, Doberman pinschers, and Old English sheepdogs are predisposed to *hypothyroidism*, whereas poodles, boxers, Boston terriers, beagles, and dachsunds are predisposed to *hyperadrenocorticism*.

Age of Onset

Age of onset is an important clue to the diagnosis of hyperpigmenting disorders. An infectious cause, such as *pyoderma, demodicosis,* or *dermatophytosis*, should be suspected primarily in young animals, whereas older animals may be at risk for endocrinopathies or tumors.

Evolution

The evolution of the hyperpigmentation should be carefully investigated. The age of onset and distribution of the initial lesions should be described. Any *trauma* can result in postinflammatory hyperpigmentation. Posttraumatic hyperpigmentation is observed more frequently in certain breeds such as the poodle (especially apricot or gray) or the Siamese cat. Scratching is a common cause of skin trauma. Thus any chronic pruritic skin condition (e.g., *atopy, adverse food reactions, pyoderma, Malassezia dermatitis, sarcoptic mange*) can potentially result in lichenification and hyperpigmentation. This makes pruritus a criterion of primary importance in the differential diagnosis of hyperpigmentation. Response to previous therapeutic trials, including doses and duration of therapy, should be reported. Spread to other animals in the environment or to owners increases the suspicion for contagious diseases such as *dermatophytosis* or *acariasis* (e.g., *scabies, cheyletiellosis*).

Physical Examination

When dealing with hyperpigmentation, the distribution of lesions is of major importance. If the lesion is solitary, the differential diagnosis should include *postinflammatory hyperpigmentation* (carefully review history), *demodicosis, dermatophytosis, nevus,* and *tumor*. If the lesions are multifocal and coin shaped with peripheral expansion, *pyoderma, demodicosis,* and *dermatophytosis* are primary suspects. In cases of diffuse nonpruritic hyperpigmentation, *demodicosis* and *endocrinopathies* should be considered. The latter are usually associated with systemic signs such as lethargy and obesity in the case of hypothyroidism, and polyuria/polyphegia (PU-PD) in the case of Cushing's syndrome.

Diagnostic Tests

Multiple skin scrapings are an extremely important diagnostic aid in almost every dermatologic case. They can give a quick, inexpensive, and easy diagnosis of demodicosis, scabies, or cheyletiellosis, although the latter two mites can be difficult to demonstrate. To confirm or eliminate the diagnosis of dermatophytosis, Wood's lamp examinations, direct examination of hairs or scales, and fungal culture should be performed in every case of focal, multifocal, or diffuse hyperpigmentation. Cytology is another easy test to use when dealing with hyperpigmentation. It can reveal yeast, such as *Malassezia pachydermatis,* or cocci. If the previous diagnostic tests fail to reveal a specific causative agent, an antibiotic trial is indicated when presenting with multifocal coin-shaped hyperpigmented lesions in dogs because pyoderma is common in dogs. Antibiotics with known activity against staphylococci, including beta-lactamase–resistant penicillins; first-generation cephalosporins, macrolides, and related molecules (i.e., lincomycin and clindamycin); potentiated sulfonamides; or fluoroquinolones should be prescribed for 4 to 6 weeks before rechecking the dog. In dogs with diffuse hyperpigmentation, a CBC, serum biochemistry panel, and urinalysis should be performed after skin scrapings have excluded the possibility of

demodicosis and cytology has excluded bacterial overgrowth of *Malassezia* dermatitis has been cytologically excluded. These diagnostic tests might provide helpful clues leading to the identification of specific underlying endocrinopathies. For example, increases in serum alkaline phosphatase, alanine aminotransferase (ALT), and cholesterol may raise the suspicion of hyperadrenocorticism. Thyroid function can be evaluated by a basal T_4 concentration, endogenous thyroid-stimulating hormone (TSH) level, or TSH response test. Adrenal function can be evaluated using adrenocorticotropic hormone (ACTH) stimulation, low-dose dexamethasone suppression, or urine cortisol: creatinine ratio tests. Sex hormone imbalances can be evaluated by basal estradiol and progesterone concentrations in female dogs and by human chorionic gonadotropin (HCG) stimulation tests in male dogs. The last and least rewarding procedure when dealing with skin hyperpigmentation is skin biopsy. A biopsy generally gives only vague clues or eliminates certain possible causes. It can, however, in conjunction with history and physical examination, furnish a high suspicion index for specific diseases such as *seasonal flank alopecia*. Seasonal flank alopecia is a cyclic follicular dysplasia characterized clinically by recurrent symmetric hyperpigmented alopecic flank lesions and an unpredictable prognosis. Biopsies demonstrate follicular atrophy and infundibular hyperkeratosis, which extend into the ostia of the secondary follicles and sebaceous ducts, mimicking the appearance of a malformed foot.

As always in dermatology, a definitive etiologic diagnosis is a mandatory prerequisite to successful management. Pigmentation changes, including both hypopigmentation and hyperpigmentation, are no exceptions.

CHAPTER 16

Fleas, Flea Allergy, and Flea Control

Candace A. Sousa

Flea infestations of pets and the home environment are a common occurrence. Fleas are responsible for the production and transmission of several diseases of humans and their pets. The flea that causes most of the problems is *Ctenocephalides felis felis*, the common cat flea. In one study it accounted for 92% to 99% of the fleas found on dogs and cats, respectively.[1]

The flea passes through four stages in its life cycle. It undergoes a complete metamorphosis at each stage.[2] At any time approximately 57% of the fleas are eggs, 34% are larva, 8% are pupa, and only about 1% are present as adults. The life cycle can be completed in as little as 12 days or take as long as 174 days and is dependent on the ambient temperature and humidity.[3]

Flea eggs are oval, pearly white, nonsticky, and about 0.5 mm in length.[4] The egg hatches between 1 and 10 days of being deposited on the host and falling off into the environment, depending on the ambient temperature and humidity (ideal conditions are 70% relative humidity and 35° C (95° F).[2–4]

Flea larvae emerge from the eggs after hatching. The larva of C. *felis felis* has three stages or larval "instars." The larvae are about 2 mm long, slender, white, and covered with short hairs. They feed on organic debris and blood-containing feces from adult fleas. The larvae are negatively phototactic (move away from light) and positively geotactic (move toward the ground).[2,4] Therefore when indoors the larvae avoid direct sunlight and move under furniture, appliances, and into carpet fibers. Outdoors, they move into shaded areas under bushes, trees, and leaves. Five to 11 days are required for the larvae to molt twice, during which they grow to about 5 mm in length. The larvae are extremely susceptible to heat and desiccation. They can survive only if the relative humidity is greater than 50% or when soil moisture is between 1% to 20%.[3]

Temperatures greater than 35° C (95° F) and less than 3° C (35° F) for more than 40 hours per month are also deleterious to survival. The mature larvae produce a sticky cocoon in which to pupate. Environmental debris may adhere to the cocoon, which helps it go undetected and provides excellent protection against insecticides. Pupation lasts from 5 to 9 days. Environmental locations suitable for a high rate of larval survival are termed *hot spots* or *source points*.

The preemerged adult flea is the stage that can extend the longevity of the flea. They can survive for up to 140 days in the cocoon if protected from desiccation. In the cocoon they are also protected from most insecticides. Physical pressure and changes in light, temperature, and carbon dioxide are thought to be stimuli for emergence of the adult flea.

Newly emerged fleas can survive in the environment from 10 to 62 days, again depending on the temperature and humidity.[8] Once on the host, the flea begins feeding within seconds and becomes an obligate parasite. The animal's grooming activity is the primary cause of mortality of ectoparasites. The flea feeds by piercing the skin of the host and inserting the tip of the labrum epipharynx to extract capillary blood.[5] Saliva is introduced by way of the salivary pump and used as an anticoagulant.[4] The female flea consumes an average of 14 µl of blood per day (equivalent to 15% of her body weight).[6] About 72 female fleas will remove 1 ml of blood daily. Male fleas consume less blood than females but feed more frequently.[2] Once fleas feed and initiate reproduction, they become dependent on a constant source of blood or they will die within a couple of days. During feeding, female fleas excrete large quantities of incompletely digested blood ("flea dirt") in long tubular coils or fine pellets.[2]

The first of multiple matings occurs on the host within 8 to 24 hours. Egg production begins within 36 to 48 hours of the first blood meal, reaches maximum production between 4 and 9 days, and may continue for more than 100 days. Egg production peaks at 40 to 50 per day and averages 27 eggs per day for the first 50 days. A single female flea may deposit over 2000 eggs during her lifetime.[4,7]

Flea allergy dermatitis (FAD) is the most common veterinary dermatologic condition in the world. It begins with the

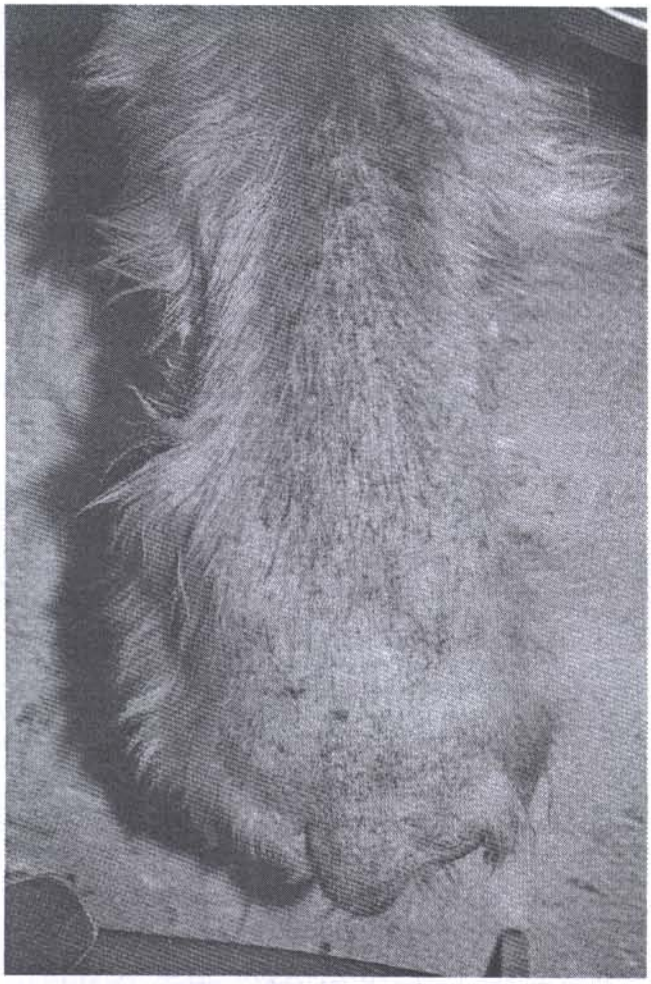


Figure 16-1 Dorsal lumbosacral region of an Afghan hound with FAD. Note the distribution of the alopecia. Skin is erythematous and crusted.

bite of a flea. The saliva of the flea contains amino acids, aromatic compounds, fluorescent materials, polypeptides, and phosphorus.[9] In the dog the antigenic substances carry a molecular weight of 18,000–45,000 Da with the major allergen weighing 30,000–32,000 Da.[10] Dog owners notice scratching, chewing, licking, biting, and other signs of pruritus. Sixty-one percent of flea-allergic dogs develop clinical signs between 1 and 3 years of age.[11] As animals age, with continued exposure to fleas, the degree of hypersensitivity may wane. FAD is uncommon in dogs less than 6 months of age. Patients usually have papules, crusts, salivary stains, excoriations, and erythema in a wedge-shaped pattern over the lumbosacral region, caudal thighs, proximal tail, ventral abdomen, and around the umbilicus. With chronic itching the areas become alopecic, lichenified, and hyperpigmented and the dog develops an odor related to secondary infections with *Staphylococcus intermedius* and *Malassezia pachydermatis*.

A diagnosis of FAD is based on the age of onset of the pruritus, the distribution of the pruritus and clinical signs, and the observation of fleas, flea feces, or both. Many dogs that are allergic to the bite of a flea have very few fleas on them at any time because their excessive grooming activity removes the fleas. Cats are especially efficient at removing fleas. Some of those patients will have recurrent tapeworm *(Dipylidium caninum)* infestations from ingestion of the fleas. The diagnosis of FAD can be confirmed with an intradermal skin test with flea antigen.

Treatment of FAD is a 3-step process. Most important is the elimination of the fleas from the animal and prevention of reinfestation with the use of both on-animal and -premise flea control. The second step involves providing the animal with relief from the allergic reaction and pruritus. Moderate doses of short-acting oral corticosteroids used for 5-10 days will usually be sufficient. Lastly, any secondary infections need to be treated with the appropriate oral and/or topical medications.

The goals of flea control are to eliminate the adult fleas on *all* the animals in the house and immature fleas in the environment. The best approach incorporates mechanical, physical, and chemical measures. Source points should be identified and treated aggressively. Carpets, pet bedding, and resting areas in the home should be well vacuumed using a vacuum with a power head. Pet bedding should be washed. Dead vegetation should be cleaned away from animal resting areas outside. A wide variety of chemicals can be used on pets and in the environment; however, no single, "miracle" flea product exists that can be used on both animals and their surroundings.

Botanical products are the closest things we have to "natural" insecticides. *Pyrethrins* are derived from a certain species of chrysanthemum. Six naturally occurring pyrethrins exist. They are minimally toxic to mammals (oral LD50 in rats, 1500 mg/kg body weight).[12] Because pyrethrins are unstable in the presence of ultraviolet light, moisture, and air, most are found combined with synergists (e.g., piperonyl butoxide) that inhibit oxidative and hydrolytic degradation of the compounds. *Pyrethroids* (e.g., permethrin, sumethrin, resmethrin, d-trans-allethrin,

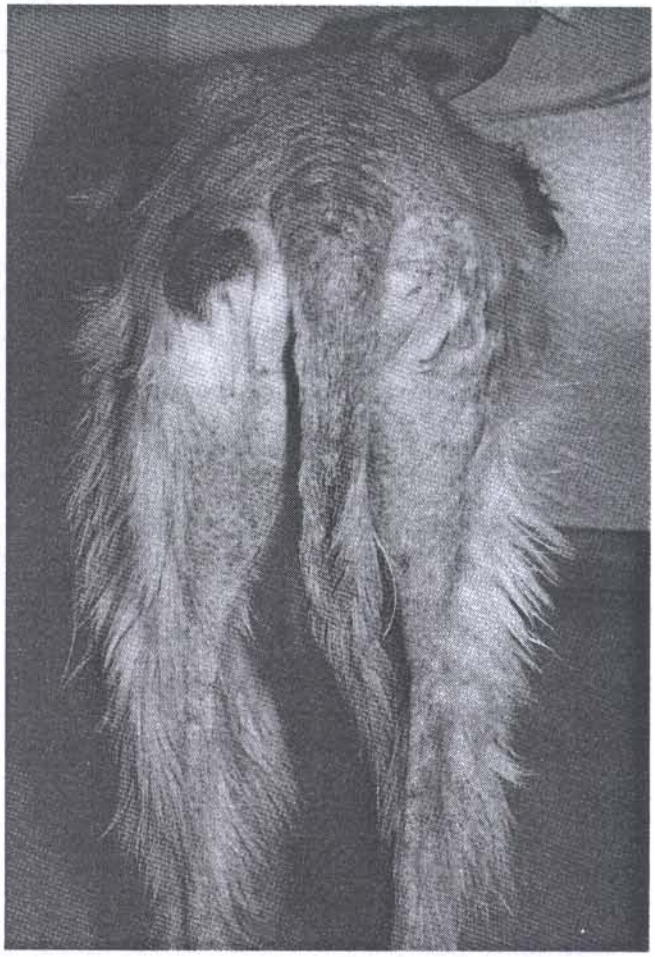


Figure 16-2 Same dog as in Figure 16-1. Dermatitis extends onto the caudal thighs.

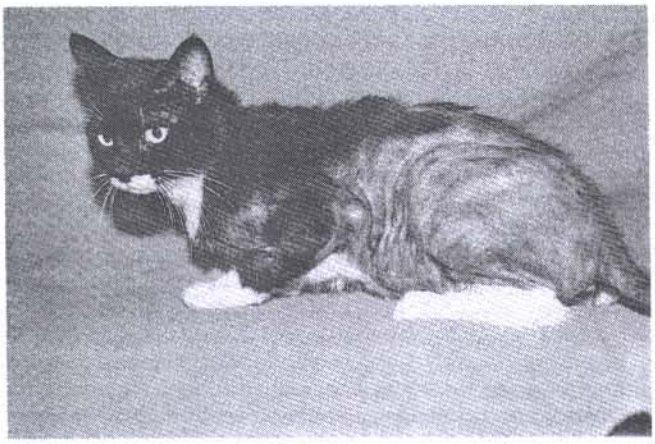


Figure 16-3 Cat with FAD. Pruritus has resulted in partial alopecia of the entire caudal half of the trunk.

tetramethrin, fenvalerate) are synthetic insecticides derived from the molecular structure or sharing the same mechanism of action of pyrethrins. They are more stable than pyrethrins but are slightly more toxic. The mechanism of action of pyrethroids is based on changes in ion conductance, mainly through delayed closing of the sodium activation gate of the nerve cells.[13]

Rotenone is an extract of the root of the derris plant and contains two active ingredients. It is slightly more toxic than pyrethrins and is very toxic to fish.[12] It is safe for use in small animals but not used in many products. *D-limonene* and *linalool* are derived from citrus pulp. They have a solvent action on the cuticular lipids of the exoskeleton of the flea that results in desiccation and death of the flea.[14] They are relatively effective but very short acting, and there have been reports of severe toxic reactions in cats.

Carbamates (e.g., carbaryl, propoxur, bendiocarb) and *organophosphates* (e.g., malathion, ronnel, chlorpyrifos, fenthion, dichlorvos, cythioate, diazanon, propetamphos, phosmet) are cholinesterase inhibitors. They act mainly as adulticides but are potentially very toxic to pets, particularly to cats and young animals. These ingredients are found in a variety of formulations for use on the animal and in the environment. Cythioate and fenthion are also formulated as systemic insecticides.

Nitenpyram (Capstar™, Novartis Animal Health) is a neonicotinoid that acts at the nicotinic acetylcholine receptor of insects. It has a very low mammalian toxicity. It is supplied as an oral medication that can be given to dogs and cats to kill adult fleas within 6 hours after administration. The product is rapidly eliminated in the urine and does not kill new fleas after 24 hours of administration.

Imidacloprid (Advantage™, Advantix™, Bayer) is a topical adult flea killer that acts by binding to nicotinergic receptors in the nervous system of the insect. Claims are that most fleas are killed within 24 hours, before they have a chance to lay eggs. It is used as an on-animal spot treatment once a month and is very safe for use on mammals; however, it can be washed off if the pet is bathed, which will decrease its efficacy.

Fipronil (Frontline®, Frontline Plus®, Merial) is another topical adult flea killer that is found as both a spot treatment and spray. It is a phenylpyrazole and acts by blocking the passage of chloride ions through gamma-aminobutyric acid (GABA)– regulated chloride channels. It is highly specific to invertebrates. One hundred percent of adult fleas are killed within 24 hours. Once used, claims are made that fleas will be killed for up to 3 months and that after 48 hours the animal can be bathed as often as needed without affecting the efficacy of the product because the active ingredient is incorporated within the sebaceous secretions. Frontline Plus® also contains methoprene, which acts to prevent the production of viable flea eggs and larvae.

Selamectin (Revolution®, Pfizer Animal Health) is an FDA-approved avermectin that is applied as a spot-on product once monthly to dogs or cats. A single application kills more than 98% of the fleas within 24-36 hours. The flea-killing effects persist for 1 month, even with bathing. Selamectin also has ovicidal and larvicidal activity against fleas.

Sodium polyborate (SPB) is a powder that is used in the indoor environment to interrupt the flea life cycle. It is believed that the flea larvae ingest the powder and are killed before they can pupate. Elimination of fleas in the indoor environment may require 3 to 6 weeks. SPB has a high margin of safety around mammals (oral LD50 in rats, 3479 mg/kg).

Insect growth regulators (IGRs) (e.g., methoprene, fenoxycarb, pyriproxyfen) mimic the juvenile hormone that the flea larvae produce during pupation. When the egg and larvae are exposed to this hormone, the egg will not hatch and the larvae will not pupate. These products have no effect on pets and people because these hormones are specific for insects. (Oral LD50 in dogs for methoprene, 5000 to 10,000 mg/kg; oral LD50 for fenoxycarb in rats, 16,000 mg/kg) IGRs are commonly found in both on-animal and in-premises products.

Insect development inhibitors (IDIs) (i.e., lufenuron, Program®, Sentinel®, Novartis Animal Health) are chitin synthesis inhibitors that prevent the flea larvae from hatching from the egg. The product is fed to pets once monthly and deposited in the fat stores of treated animals. It is slowly released from tissues, allowing maintenance of effective blood levels of drug for weeks after administration. The female flea ingests the product when feeding where it becomes incorporated into the flea egg. These products will not kill the adult flea. No known contraindications or side effects exist in mammals, and lufenuron is very safe (oral LD50 in rats > 2000 mg/kg).

Many formulations exist for the deliverance of the insecticides to the pet. Shampoos act to mechanically remove the fleas, but because they are rinsed off, they have minimal residual action. This problem with residual flea control can be overcome by using a final rinse (dip) that contains an insecticidal product. Many flea sprays are alcohol-based and quickly kill adult fleas. Unfortunately, most contain pyrethrins, and unless the chemical is microencapsulated, their duration of action is less than 1 day. Powders, foams, concentrated solutions (spot treatments), and collars are all available that are formulated with a variety of chemicals; several of the chemicals are also sold in oral formulations.

In the indoor environment, hand spraying either by a professional or the owner is the preferred method of delivering the chemicals. This allows the product to be applied directly on the areas most frequented by the pets ("source points"). Large pieces of furniture must be moved to ensure that the spray reaches the areas of larval migration.

Outdoors, sprays are very useful and their application should be concentrated in the areas frequented by the animals, especially those that are shaded, have a mild temperature, and contain organic matter.

CHAPTER 17

Other External Parasites

Karen L. Campbell

External parasites are major causes of distress and disease in dogs and cats. Some parasites cause only mild irritation, whereas others are associated with severe inflammation and secondary infections. Many ectoparasites serve as vectors or intermediate hosts of other diseases. It is important to know the clinical features, identification, and appropriate treatments for external parasites affecting dogs and cats (Table 17-1).

FAMILY DEMODICIDEA

Demodex spp. live as commensals in the skin of most mammals. Most species (including *D. canis* and *D. felis*) spend their entire life cycle in the hair follicles and sebaceous glands of their host. A few species (including *D. gatoi* and the short-tailed demodectic mite of dogs) are found within the epidermis. It is thought that most follicular infections develop during the early weeks of life, with the commensal population in bitches and queens being transferred to in-contact areas of puppies and kittens. However, the short-tailed forms of the mites may be transferred between adult animals of the same species.

Localized demodicosis in dogs is most common in puppies between 3 to 6 months of age. Skin lesions develop secondary to localized overgrowth of mites on the face or forelimbs and consist of one or more localized areas of alopecia, erythema, and scaling. Clinicians make the diagnosis by doing deep skin scrapings and finding the characteristic "cigar-shaped" mites with short, stubby legs. Counts should be made of all life stages (eggs, larvae, nymphs, and adults). Dogs with normal immune systems will naturally resolve early, localized lesions. Factors that may predispose dogs to *Demodex* overgrowth include other parasites, poor nutrition, immunosuppressive drug therapy, and stress—these factors should be identified and corrected. Specific antimite therapy is rarely warranted. Topical benzoyl peroxide gel or lotion may be applied once daily to help prevent secondary bacterial infections and aid in mite removal from the follicles. Skin scrapings should be repeated in 4 weeks. If lesions are still present and the mite count is still high with a large proportion of immature forms, the condition may be progressing to generalized demodicosis. Rotenone or benzyl benzoate-containing lotions or creams may be applied to the lesions once daily.

Generalized demodicosis in dogs may be classified as juvenile onset (affecting dogs 3–18 months of age) or adult onset (affecting middle-aged to older dogs, often immunocompromised animals with underlying hyperadrenocorticism, hypothyroidism, diabetes mellitus, immunosuppressive drug therapy, or neoplasia). Clinical signs are variable and may start with localized lesions that spread. Patchy to multifocal alopecia, erythema, and silvery-gray scales are common. The affected skin may become lichenified, hyperpigmented, pustular, and crusted or ulcerated. Secondary bacterial infections may progress to life-threatening sepsis. Peripheral lymphadenopathy is common. Deep skin scrapings will reveal numerous demodectic adults, nymphs, and larvae or ova (or both). Mixed infections with *D. canis* plus short-tailed and long-bodied forms of *Demodex* mites may be identified by their characteristic microscopic features. An assessment of the general health of the dog should be made, and any underlying diseases or concurrent infections should be treated.

With the recent withdrawal of Mitaban® (amitraz, Fort Dodge) from sale in the United States, no licensed products are approved for use in treating demodicosis. It should be noted that amitraz is an Environmental Protection Agency (EPA)-registered pesticide in the United States; although alternative forms of amitraz are available, it is a violation of United States federal law to use an EPA-registered pesticide in a manner inconsistent with its labeling. Both ivermectin and milbemycin are effective alternatives to amitraz in the treatment of generalized demodicosis; however, high doses and long courses of therapy are required. Ivermectin toxicosis is well recognized in collies and has also been reported in many other breeds of dogs. It is recommended that therapy be initiated with 0.05 mg/kg PO on days 1 to 2, with an increase to 0.1 mg/kg PO on days 3 to 4, and continuing to increase by increments of 0.05 mg/kg until 0.4 mg/kg/day is reached. Ivermectin should be discontinued immediately in any dog showing depression, ataxia, mydriasis, or other signs of toxicity. Collies and other breeds that cannot tolerate high doses of ivermectin may be treated with milbemycin oxime. A recommended protocol for milbemycin is 0.5 mg/kg PO days 1 to 2, with increases of 0.5 mg/kg increments until 2.0 mg/kg/day is reached. Signs of milbemycin toxicosis include mydriasis, ataxia, lethargy, and stupor. Therapy should be continued until two negative skin scrapings have been obtained at monthly intervals.

Localized demodicosis is rare in cats and usually affects the eyelids, periocular region, ear canal, or head and neck. Lesions include patchy alopecia with scaling and crusting or a ceruminous otitis externa (pruritus is variable). Clinicians make the diagnosis by finding mites on superficial and deep skin scrapings, ear swabs, or both. Treatment may include topical rotenone or lime sulfur solution.

Generalized demodicosis is rare and less severe in cats than in dogs. It may be associated with an underlying immunosuppressive or metabolic disease such as feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), toxoplasmosis, systemic lupus erythematosus, or diabetes mellitus. Clinical signs include variable pruritus; multifocal, patchy, or symmetrical alopecia with or without erythema; scaling; crusting; macules; and hyperpigmentation. Clinicians make the diagnosis by finding mites on superficial *(D. gatoi)* or deep *(D. felis)* skin scrapings. Most cats will respond favorably to weekly dips with 2% lime sulfur solution. *D. gatoi* may be contagious, thus in-contact cats should be evaluated and treated if infected.

FAMILY SARCOPTIDAE

Sarcoptes scabiei var *canis* primarily affects dogs but can also cause disease in cats, foxes, and humans. Dogs can be infested with mites from foxes and humans. The life cycle is approximately 21 days and completed on the host. Off-host survival time depends upon the relative humidity and temperature. Adult mites are small (200 to 400 µm), oval, and white with two pairs of short legs. The pretaris have long, unsegmented pedicels. The anus is at the posterior edge of the body. The mites initially affect relatively hairless areas of skin such as the ear pinnae and elbows. Female mites burrow through the epidermis at a rate of 2 to 3 mm/day. They lay their eggs in the resulting tunnel. Eggs hatch into larvae that burrow to the surface of the skin where they feed. Many dogs develop a hypersensitivity reaction to mite antigens. As few as 10 to 15 mites may produce severe clinical signs in a hypersensitive individual. Clinical signs include an intensely pruritic, nonseasonal dermatitis with papules, excoriations, and hair loss. Affected areas typically develop a thick yellowish crust. Lesions may rapidly generalize, but the dorsum is usually spared.

Diagnosis is based on history of a contagious, nonseasonal, intensely pruritic dermatitis involving the pinnal margins, elbows, hocks and ventral abdomen, and chest plus finding mites or mite eggs or feces in superficial skin scrapings. A presumptive diagnosis is made based on response to treatment trials. Effective licensed treatments include weekly applications of 2% lime sulfur solution or monthly applications of 6 to 12 mg/kg selamectin. Effective extra label treatments include ivermectin 0.2 to 0.3 mg/kg PO every 7 days for four to six treatments or milbemycin oxime at 2 mg/kg PO every 7 days for four to six treatments. As in the treatment of demodicosis, it is advisable to initiate treatment with either ivermectin or milbemycin at much lower doses with daily increases until the target dose is reached without evidence of side effects. The target dose is then given once weekly for at least 3 weeks past resolution of clinical signs. In-contact dogs should be treated to eliminate possible asymptomatic carriage of the mites.

Notoedres cati primarily parasitizes cats but may also affect foxes, dogs, rabbits, and humans. Notoedric mange is highly contagious and frequently occurs in epizootics in endemic areas. The mites are smaller than *S. scabiei*, have medium-length unjointed sucker-bearing stalks on their legs, more body striations, and a dorsal anus. Clinical signs include intense pruritus and dry, crusted lesions that first appear on the medial edges of ear pinnae and spread over ears, head, face, and neck. Some cases also involve the feet and perineal regions. Diagnosis is confirmed by finding the mites, nymphs, larvae, and ova in superficial skin scrapings. Traditional therapy is 2% lime sulfur solution applied weekly for 4 to 8 weeks. Other effective treatments include selamectin (6 to 12 mg/kg topically every 30 days), ivermectin (0.3 mg/kg PO or SQ every 14 days for two treatments), or doramectin (0.3 mg/kg SQ once).

FAMILY PSORPTIDAE

Otodectes cynotis infests the external ear canal and adjacent skin of dogs, cats, foxes, and ferrets. The prevalence in feral cats in the United States has been reported at 25% to 37%. Although ear pruritus and copious production of a dark "coffee grounds-like" cerumen are common, 10% of infested animals may exhibit no clinical signs. Diagnosis is made by finding mites on otoscopic examination or on microscopic examination of material from ear swabs or ear flushes (flushing the ear canal with 1 to 2 ml of mineral oil may have a higher mite yield than use of a cotton swab that traps mites in its fibers). Adult mites are 300 to 400 µm, white, with a terminal anus and four pairs of legs. All legs of the male have short, unjointed stalks with suckers. Only the front two pairs of legs of female mites have suckers; the fourth pair of legs are rudimentary and do not extend beyond the body margin. The mites feed on epidermal debris and tissue fluid. Hosts may develop hypersensitivity reactions to mite antigens. Topical ceruminolytics should be used to remove cerumen and debris from the external ear canal. Topical otic acaricidal products are effective as is topical selamectin. Systemic ivermectin has been used with variable results. Fipronil spray or spot-on may also be effective; however, fipronil should *not* be used in the ear itself. In-contact animals should be evaluated and treated as appropriate for the species.

GENUS LYNXACARUS

Lynxacarus radovski is a hair-clasping, fur mite of domestic cats. These mites have elongated bodies, 430 to 520 µm long, with a flaplike sternal extension containing the first two legs that are used to grasp the hair of the host. The mites may be found in such large numbers as to give a "salt and pepper" appearance to the haircoat. Some cats develop widespread papular crusts, whereas others show no clinical signs from the infestation. Clinicians make the diagnosis by collecting the mites from acetate tape impressions, hair plucks, or superficial skin scrapings. Effective treatments include topical pyrethrin sprays, 2% lime sulfur dips, or systemic ivermectin. The mite is contagious to other cats and may cause a papular rash in humans; it is not considered contagious to dogs.

FAMILY CHEYLETIELLA

Cheyletiella spp. mites are easily recognized by their big palpal claws, M-shaped gnathosomal mouthparts, and comblike tarsal appendages. The sensory organs on genu I may be used to identify different species. The sensory organ of *C. yasguri* (primary host is dog) is heart shaped, of *C. blakei* (primary host is cat) is cone shaped, and of *C. parasitovorax* (primary host is rabbits) is globe shaped. These three mite species are freely contagious from one host species to another and can transiently affect humans. The mites do not burrow but move rapidly in pseudotunnels in epidermal debris. The entire life cycle is completed on the host. The ova are smaller than louse nits and are attached to host hairs by fine fibrillar strands. Adult female mites may live up to 10 days in the environment. Clinical signs associated with infestation include a dorsally oriented dry scaling and variable pruritus. Some cats develop miliary dermatitis. Diagnosis is made by finding mites or ova on acetate tape impressions, on superficial skin scrapings, or in fecal flotations. Affected and in-contact dogs, cats, and rabbits should be treated with topical parasiticides (e.g., 2% lime sulfur dip, fipronil, pyrethrin, selamectin). Systemic ivermectin is also effective. Treatment should be continued for 4 to 8 weeks, and the environment should be also be treated with an acaricidal spray approved for use in homes.

FAMILY TROMBICULIDAE

Larvae of the family *Trombiculidae* (chiggers) are parasitic, whereas the nymphs and adults are free living. The six-legged larvae are bright red or orange and may be found on the skin or in the ears of dogs and cats. Chiggers remain on the skin for several days, their saliva disintegrates the host skin cells, and a tube called a *stylostome* is formed that holds the mite to the skin until feeding is completed or the mite is dislodged by the

host's scratching or biting. Chiggers may be found on skin scrapings. Topical fipronil is an effective treatment.

FAMILY IXODIDAE

Ixodid (hard) ticks possess a sclerotized dorsal shield plate on the idiosoma known as a *scutum*. These ticks are intermittent feeders, remaining attached for several days. The number of hosts upon which they feed varies from one to three among the different species of ticks. Ticks are important as vectors of protozoan, viral, and rickettsial diseases. Some are also involved in producing tick paralysis. When animals are infested with a small number of ticks, manual removal can be accomplished by soaking the tick in alcohol, grasping the head with a forceps, and applying firm traction. With heavier infestations the animal may be treated with fipronil or a pyrethrin or pyrethroid (dogs only). Amitraz collars may be used to prevent tick attachment. Environmental control includes mowing and cutting of brush and grass, plus use of environmental pesticides approved for control of ticks.

Rhipicephalus sanguineus is the brown dog tick. It is a three-host tick with all life stages feeding on dogs and occasionally humans, cats, rabbits, and horses. It is identified by its inornate scutum, ventral plates on males, and presence of festoons. *Dermacentor variabilis* is the American dog tick. It is also a three-host tick. The principal hosts of the larvae and nymphs are field mice and other small rodents. The principal host of the adult is the dog, but other mammals and humans may also serve as hosts. Its is identified by its ornate scutum with eyes and festoons. The males lack ventral plates. *Dermacentor andersoni* is the Rocky Mountain wood tick. It is a three-host tick. The adults feed on wild and domestic herbivores. Larvae and nymphs feed on rodents. It is identified by its ornate scutum with legs having the same pattern of brown and gray as the body.

Amblyomma americanum is the Lone Star tick. It has a single white spot on the scutum of the reddish brown adult female. The adult male is small with two pairs of symmetrical spots near the head and pale strips on its sides. It is a three-host tick with larvae and nymphs feeding on rodents, rabbits, and birds. Adult ticks feed on larger mammals. *Ixodes dammini* is the deer tick. It is a three-host tick with larvae and nymphs feeding on rodents and the adults on white tail deer or other mammals. It is a small, inornate tick that lacks eyes and festoons. It is the primary vector of *Borrelia burgdorferi*.

FAMILY ARGASIDAE

Argasid ticks are soft bodied and lack a scutum. The only argasid tick of importance in small animals is the spinose ear tick, *Otobius megnini*. Adult ticks are not parasitic; however, larvae and nymphs infest the external ear canals of dogs and rarely cats. Clinical signs include an acute onset of otitis externa with severe inflammation and waxy exudate. Diagnosis is made by visualizing the mites and removing them.

ORDER PHTHIRAPTERA

Lice are highly host specific, with their life cycles completed on the host. Most can only survive a day or two off a host. The body of a louse is divided into a head, thorax, and abdomen. The body is flattened dorsoventrally and has stout legs and claws for clinging tightly to hair, fur, or feathers. Two suborders exist: (1) the sucking lice *(Anoplura)* and (2) the biting lice *(Mallophaga)*.

Sucking lice have mouthparts adapted for sucking the blood of the host. *Linognathus setosus*, the "long-nosed" louse, is the only sucking louse found on dogs. These lice are bluish black and have dark-blue eggs. These lice are relatively slow moving and easy to capture using flea combs or acetate tape. Biting lice have relatively larger heads and ventrally located mouthparts. The claws are smaller than those of sucking lice. The only louse found on cats is *Felicola subrostrata*. The most common biting louse on dogs is *Trichodectes canis*. This louse is short, broad, yellowish in color, and can be a vector for *Dipylidium caninum*. A second biting louse affecting dogs is *Heterodoxus springer*, found only in tropical and subtropical regions. Biting lice can move rapidly and are harder to capture than sucking lice. During a life span of approximately 1 month, female lice lay 200 to 300 operculate eggs ("nits") that are glued to the hair of the host. Light infestations may be asymptomatic. Heavier infestations with *Linognathus* can cause blood-loss anemia, whereas heavier infestations with biting lice produce irritation and pruritus. Pediculosis can result in miliary dermatitis in cats or a pattern of alopecia and excoriations similar to fleabite dermatitis in dogs. Lice are easily killed by 2% lime sulfur dips, pyrethrin or carbaryl powders or sprays, and most other parasiticides used for fleas. Grooming equipment should be thoroughly cleaned.

ORDER DIPTERA

Diptera is one of the largest orders in class Insecta, with over 120,000 species. All of these species have a complex (complete) metamorphosis. In some species the adults are parasitic on mammals, whereas in other species the larvae are parasitic.

Flies of the genus *Phlebotomus* in the Old World and *Lutzomyia* in the New World are of primary importance as vectors of the protozoan *Leishmania* spp. The fly bites themselves are not associated with significant disease; however, the protozoan often leads to the development of a chronic, exfoliative dermatitis of the face, pinnae, and feet of infected dogs and may also produce severe systemic disease.

Mosquitoes are in the family *Culicidae*. Most animals develop a pruritic papule at the site of a mosquito bite. Some animals (most commonly cats) develop a hypersensitivity reaction to the antigens in mosquito saliva and develop a pruritic, erosive, crusting dermatosis on the bridge of the nose, papular to nodular lesions on ear pinnae, and hyperkeratosis with swelling of footpads. The lesions may be characterized histologically as a diffuse eosinophilic dermatitis, an eosinophilic furunculosis, or an eosinophilic nodular dermatitis with collagen degeneration. Mosquitoes are also important as vectors of *Dirofilaria immitis*.

Flies of the families *Simuliidae* (black flies), *Tabanidae* (horse flies), and *Muscidae* (stable flies, horn flies, houseflies) frequently attack the ear pinnae of dogs housed outdoors. The ear tips, margins, or folds may develop erythema and hemorrhagic crusts. Affected dogs should be housed indoors and treated with topical antibiotic-corticosteroid cream or lotion until the lesions heal and the source of the flies has been eliminated.

Myiasis occurs when fly eggs are laid in damp areas of the skin or haircoat, and the larvae develop in the underlying tissue of the host. True screwworms, *Cochliomyia hominivorax*, can attack healthy tissue. Blowflies (*Calliphora*, *Lucilia*, *Protophormia*, and *Phormia*) feed on dead tissue, whereas flesh flies *(Sarcophaga*, *Wohlfahrtia)* can attack living tissue. Proteolytic enzymes produced by the larvae are highly destructive and can result in "punched-out" round holes in the skin. Treatment includes débridement of wounds, supportive care, and control of any underlying or predisposing factors (e.g., injuries, urinary incontinence, diarrhea, unkempt haircoat).

Table • **17-1**

Scheme for Identification of Arthropod Ectoparasites of Dogs and Cats

Adults with Eight Legs, Two Body Divisions (Cephalothorax, Abdomen), No Antennae, Simple Eyes, and No Wings	**Class *Arachnida***
Flattened dorsoventrally, mouthparts of chelicera, hypostome, palp	Suborder *Metastigmata* (ticks)
Dorsal shield (scutum)	Family *Ixodidae*
Inornate scutum, anal groove forming an arch, lack festoons	Genus *Ixodes*
Inornate scutum, has festoons, basis capituli is hexagonal	Genus *Rhipicephalus*
Ornate scutum, has festoons, basis capituli is rectangular	Genus *Dermacentor*
Ornate scutum, has festoons, mouthparts are longer than basis capituli, the second palpal segment is twice as long as the third	Class *Amblyomma*
Soft bodied	Family *Argasidae*
Mite with respiratory pore in middle of body	Suborder *Mesostigmata*
Chelicerae long and styletlike, 750–1000 μm body, long legs, red color after feeding, found near bird roosts or nests	Genus *Dermanyssus*
Mite without a respiratory pore	Suborder *Astigmata*
Round body 400–430 μm, terminal anus, short stubby legs with long unsegmented pedicels	Genus *Sarcoptes*
Round body 200–500 μm, dorsal anus, legs with medium-length unsegmented pedicels	Genus *Notoedres*
Oval body 300–400 μm, terminal anus, anterior legs are long with short unsegmented pedicels and large suckers, rear legs have suckers in males and are rudimentary with whiplike setae in females	Genus *Otodectes*
430–520 μm elongated body, flaplike sternal extensions, terminal suckers on all legs, found "clasping" hairs on cats	Genus *Lynxacarus*
Mite with stigmata opening on the gnathosoma	Suborder *Prostigmata*
100–400 μm slender "cigar-shaped" body	Family *Demodicidae*
Found in hair follicles of dogs	*Demodex canis*
Found in subcorneal location in dogs, stubby body	*Demodex* unnamed species
Found in hair follicles of cats	*Demodex felis*
Found in subcorneal location in cats, stubby body	*Demodex gatoi*
400 μm oval body with large palpal claws, *M*-shaped gnathosomal mouthpart	Family *Cheyletiellidae*
Found on cats, cone-shaped sensory organ on genu I	*Cheyletiella blakei*
Found on dogs, heart-shaped sensory organ on genu I	*Cheyletiella yasguri*
Found on rabbits, globose-shaped sensory organ on genu I	*Cheyletiella parasitovorax*
Adults with Six Legs, Three Body Parts (Head, Thorax, and Abdomen)	**Class Insecta**
Adults wingless, laterally flattened	Order *Siphonaptera* (fleas)
Head with genal and pronotal combs	Genus *Ctenocephalides*
Flat head (length of head ≥ twice height of head)	*Ctenocephalides felis*
Round head (length of head < twice height of head)	*Ctenocephalides canis*
No combs on head, angular forehead	Genus *Echidnophaga*
No combs on head, rounded forehead	Genus *Pulex*
Adults wingless, flattened dorsoventrally, stout legs with claws	Order *Phthiraptera* (lice)
Long nose, sucking mouthparts	Suborder *Anoplura* (sucking lice)
On dog	*Linognathus setosus*
Wide head, biting mouthparts	Suborder *Mallophaga* (biting lice)
On cat	*Felicola subrostrata*
On dog in United States (broad body)	*Trichodectes canis*
On dog in tropics (slender body)	*Heterodoxus spiniger*
Adults with one pair of wings	Order *Diptera* (flies)

The family Oestridae consists of bot flies. The only bot fly of importance in small animals is *Cuterebra*. The adult fly resembles a bumble bee and lays its eggs along rabbit runs and near rodent burrows. As animals brush past, the eggs hatch and the larvae crawls onto the host's fur and enters a body opening or wound. Larvae migrate subcutaneously and produce a nonpainful nodular swelling that fistulates. Lesions are most commonly found on the head, neck, or trunk during late summer to early fall. Treatment involves enlarging the hole and carefully extracting the larva.

HELMINTH PARASITES

Hookworm dermatitis develops when larvae of *Ancylostoma braziliense, A. caninum,* or *Uncinaria stenocephala* enter the

skin of areas in direct contact with the ground. Clinical signs include red papules progressing to erythematous, thickened, alopecic areas of skin on the feet, sternum, ventral abdomen, posterior thighs, and tail. Diagnosis is based on history of contact with hookworm ova-containing feces, contaminated soil, or organic material. Treatment involves appropriate anthelmintic treatment of all dogs in the kennel or household, environmental decontamination, and symptomatic treatment.

Pelodera dermatitis occurs when larvae of *Pelodera strongyloides* invade the hair follicles of skin in contact with damp soil or decaying organic debris. Clinical signs include mild-to-intense pruritus with erythema, papules, and crusting of skin in contact with the ground (feet, legs, ventral abdomen, and tail). Diagnosis may be made by finding the 600 to 650 μm larvae on skin scrapings. Treatment involves removal of the contaminated bedding or soil and dipping the dog in a parasitic dip (e.g., 2% lime sulfur).

Dracunculus insignis is a parasite of dogs and wild carnivores. The intermediate host is a *Cyclops* ingested from contaminated water. The larvae develop in the host, and adults are located in subcutaneous tissues of the abdomen and limbs. A nodule forms at the site and fistulates. When the nodule contacts water, the female worm comes to the surface and releases large numbers of larvae. Surgical excision of the worms is the treatment of choice.

CHAPTER • 18

Edema

Marc R. Raffe
Jennifer Roberts

INTRODUCTION

The well-being of cells and tissues depends not only on an intact circulation to deliver oxygen and nutrition but also on intercompartmental fluid homeostasis. Approximately 60% to 70% of lean body weight is water; of this value about two thirds is contained in the intracellular space and one third in the extracellular space. Most extracellular water (approximately 70%) is contained in the interstitium, a matrix of connective tissue and gel-like substrate that is the area between the vascular compartment and the cell membrane.

Under normal conditions, continuous water movement occurs across fluid spaces. Water is shifted from the vascular network into the interstitium; ultimately it crosses cell membranes to become incorporated in the intracellular cytoplasm or is returned back to the vascular network. Water return to the vascular space is controlled by transcompartmental pressure changes induced by the presence of large molecular weight proteins (colloids) in the vascular network. Because of a slight pressure difference between the hydrostatic force displacing water from the arterial-capillary network and the colloidal force promoting water return to the capillary-venous network, residual water remains in the interstitial compartment. This residual volume is drained back into the systemic circulation by lymphatic tributaries. Under normal conditions, no net transfer of water across tissue compartments occurs (Figure 18-1).

When this relationship is disturbed, increased water retention in the interstitial compartment often results. Abnormal collection of water in the interstitial space is defined as *edema*. Collection of water in body cavities (hydrothorax, hydropericardium, ascites) and generalized profound subcutaneous swelling (anasarca) are included in the edema category.

PATHOGENESIS

As previously noted, a defined physiologic relationship governs intercompartmental water balance. This relationship, known as *Starling's law of the capillary*, represents two major factors in water distribution: hydrostatic and oncotic (osmotic) forces. The relationship between hydrostatic and oncotic forces have been extensively investigated and is described as the following mathematical relationship:

$$\text{Net filtration} = Kf[(P_{cap}-P_{if})-(\pi_p-\pi_{if})]$$

where Kf represents net capillary wall permeability, P_{cap} represents hydrostatic pressure generated by the heart, P_{if} represents hydrostatic pressure generated by tissues, π_p represents oncotic forces in plasma, and π_{if} represents oncotic forces in tissues generated by protein and mucopolysaccharides (see Figure 18-1).

Under normal conditions, negative pressure is present in the interstitium. Negative pressure is maintained by the combination of oncotic forces and lymphatic drainage, with a combined drainage capacity that exceeds hydrostatically induced shift of water from the intravascular compartment. When factors associated with this relationship are changed, the outcome is often abnormal interstitial water retention creating a positive interstitial pressure. The conversion from

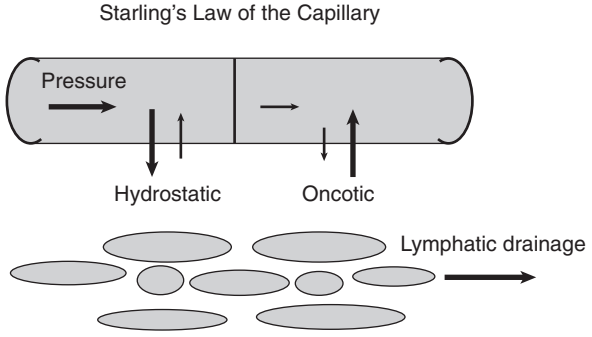


Figure 18-1 Starling's law of the capillary.

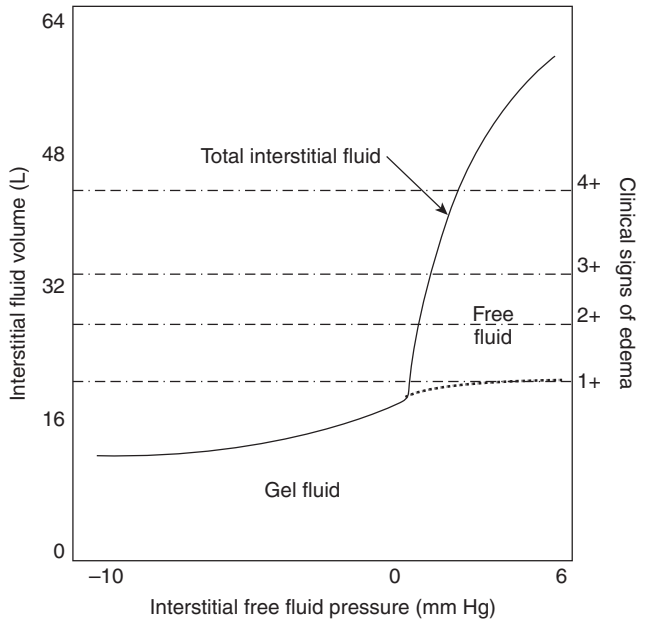


Figure 18-2 Effect of increasing interstitial fluid pressure on volumes of total interstitial fluid, gel fluid, and free fluid.

negative to positive interstitial pressure is believed to be a key factor in edema formation (Figure 18-2). Pathophysiologic changes commonly associated with edema formation include increased vascular permeability, decreased protein and mucopolysaccharide concentration in the interstitial matrix, and reduced lymphatic drainage. Five categories of edema have been described based on changes in Starling's law of the capillary: (1) increased hydrostatic pressure, (2) reduced osmotic pressure, (3) lymphatic obstruction, (4) sodium retention, and (5) inflammation. Specific clinical syndromes associated with each category are listed in Table 18-1.

CLINICAL PRESENTATION AND DIAGNOSIS

Edema is a secondary feature of many clinical presentations. Historical findings suggestive of edema include limb swelling, increase in abdominal girth, and postural related dyspnea. Physical findings include limb swelling in gravity-dependent regions, swelling of the ventral aspect of the mandible, prepuce, scrotum or mammary glands, periorbital swelling, increased breath sounds characterized by rales and rhonchi, and fluid presence in the abdomen or thorax. Superficial edema in subcutaneous tissue can be confirmed by applying digital pressure over the swollen area. Displacement of interstitial water leaves a finger-shaped depression that refills after a short time. This finger-shaped depression is called "pitting edema."

Diagnostic procedures are focused on confirming edema presence and determining possible cause. Evaluation of the physiologic components of water balance (plasma protein concentration, erythrocyte mass, serum electrolyte levels, and system blood pressure) are important to determine which factor or factors associated with water balance are affected. Evaluation of underlying inflammation (white blood cell [WBC] count, differential, platelet count) is warranted in specific underlying causes.

Table • **18-1**

Causes of Edema

CAUSE	CONTRIBUTING FACTOR	SPECIFIC CLINICAL SYNDROMES
Increased hydrostatic pressure	Impaired venous return	Congestive heart failure
		Constrictive pericarditis
		Ascites (cirrhosis)
		Venous obstruction or compression (thrombosis, external pressure, extremity inactivity)
	Small-caliber arteriolar dilation	Heat
		Neurohumoral dysregulation
Reduced plasma osmotic pressure	Hypoproteinemia	Protein-losing glomerulonephropathy (nephrotic syndrome)
		Cirrhosis (ascites)
		Malnutrition
		Protein-losing gastroenteropathy
Lymphatic obstruction		Inflammatory
		Neoplastic
		Postsurgical
		Postirradiation
Sodium retention	Excessive dietary intake with renal insufficiency	
	Increased tubular sodium reabsorption	Renal hypoperfusion
		Increased renin-angiotensin-aldosterone secretion
Inflammation	Acute inflammation	
	Chronic inflammation	
	Angiogenesis	

Modified from Mitchell RN, Cotran RS: Hemodynamic disorders, thrombosis, and shock. In Cotran RS et al, editors: *Robbins pathologic basis of disease*, ed 6, Philadelphia, 1999, WB Saunders.

Electrocardiographic and echocardiographic imaging is indicated in cases where edema may be associated with primary or secondary heart failure. Ultrasonographic imaging of the peritoneal space, thoracic space, and pericardial space is warranted if physical finding indicate cavity-based fluid collection.

Collection of edema fluid and fluid analysis may be helpful in determining the underlying disease process. The clinicopathologic features of edema fluid are typically a protein-poor transudate with a specific gravity less than 1.012 that has poor cellularity. In inflammation, increased protein content is noted; fluid is generally an exudate with a specific gravity greater than 1.020 and has the presence of inflammatory cell morphology (macrophages, degenerated white blood cells).

TREATMENT

Treatment of life-threatening edema is an immediate goal irrespective of cause. Typically these presentations are associated with primary heart failure. Administration of parenteral furosemide or vasodilator drugs (or both) is considered the primary step for emergency management. The rationale for furosemide selection includes its known actions producing increased renal sodium excretion facilitating edema mobilization from interstitial sites, pulmonary and systemic vasodilatation, and increased lymph flow in the thoracic duct. All of these responses positively affect transcompartmental water balance and reduce edema formation, especially in the lung. Vasodilators (hydralazine, nitrates) are used to reduce edema; they produce their primary actions through relaxation of systemic arterioles and venules promoting redistribution of central blood volume and reducing hydrostatic pressure. In fulminant cardiac failure, a sympathomimetic such as dobutamine (1 to 5 μg/kg/min constant rate infusion [CRI]) is started and titrated to achieve positive inotropic response. This will improve the Starling's relationship and help to mobilize edema.

Nonemergent edema management is achieved by using goal-directed therapeutic intervention to rebalance the Starling's relationship. Furosemide or other potent loop diuretics (bumetanide, spironolactone, triamterene, amiloride, and thiazide-class) may be used to promote edema mobilization by initiating physiologic responses previously noted for furosemide. Administration of plasma products (fresh plasma, fresh frozen plasma, and cryopoor plasma), hetastarch, or dextran 70 will increase intravascular oncotic pressure and favor water redistribution from the interstitial to intravascular compartment. These products are considered in cases demonstrating decreased oncotic pressure (hypoproteinemia), decreased osmotic balance (anemia), or increased endothelial permeability (inflammation). Decreasing osmotic forces by dietary modification to reduce sodium and chloride intake or through use of loop diuretics to increase sodium and chloride loss is an additional consideration in primary cardiac disease patients.

PROGNOSIS

The prognosis for successful management of edema is based on the ability to treat and resolve the underlying clinical disorder. Edema secondary to inflammatory states, colloid imbalance, or primary cardiac disease is often successfully managed or resolved. Edema secondary to lymphatic pathology often requires long-term management to successfully correct.

CHAPTER • 19

Hepatocutaneous Syndrome

Catherine Outerbridge

Hepatocutaneous syndrome (HS) is an uncommon skin disease associated with systemic metabolic disease. It has also been called *superficial necrolytic dermatitis* (SND), *metabolic epidermal necrosis*, *diabetic dermatopathy*, and *necrolytic migratory erythema* (NME). This disease was first described in a dog in 1968. The first English language reference comparing the disease to the human disease NME was in 1986, when the disease was described in four dogs with diabetes mellitus and was thus first called *diabetic dermatopathy*. The disease has been most commonly described in older dogs, although a histologically equivalent disease occurring in cats and the black rhinoceros has been reported. The etiopathogenesis of this disease is unclear, but it is likely multifactorial. Because different disease processes appear to cause similar histologic skin lesions, it might be more correct to refer to the skin disease as either *SND* or *metabolic epidermal necrosis*.

COMPARATIVE ASPECTS WITH NECROLYTIC MIGRATORY ERYTHEMA AND THEORIES OF PATHOGENESIS

NME is a histologically similar disease that is seen in humans. Most often NME occurs in association with a glucagon-secreting tumor. Glucagonoma syndrome in humans is characterized by the skin lesions of NME, hyperglycemia resulting from carbohydrate intolerance or diabetes mellitus, weight loss, hypoaminoacidemia, and anemia. Humans with NME usually have a profound hypoaminoacidemia, presumed to result from the catabolic gluconeogenic effects of glucagon. However, NME has been diagnosed in some humans with normal plasma amino acid concentrations, and these have often been patients with nonglucagonoma-associated disease. Nonglucagonoma-associated NME has been reported in humans with celiac disease, chronic malabsorption, cirrhosis,

nonalpha islet cell tumors, pancreatitis, hepatitis, inflammatory bowel disease, and heroin abuse.

Unlike people with NME, association with glucagonoma has not been consistently demonstrated in the majority of dogs with the skin lesions of SND. Afflicted dogs commonly have a characteristic concurrent hepatopathy, thus the use of the name HS. The hepatic pathology seen in dogs with HS has not been reported to occur in those dogs with confirmed glucagonoma-associated SND. In addition to the association with hepatic pathology, some dogs with the skin lesions of SND have a history of phenobarbital or primidone administration, mycotoxin ingestion, or gastrointestinal signs and malabsorption.

The severe vacuolar liver disease seen in the majority of dogs with the skin lesions of SND and the association in some dogs with concurrent diabetes mellitus suggests that an underlying hormonal or metabolic disturbance is occurring in dogs with HS. Diabetes mellitus has been reported to occur in 25% to 40% of dogs with HS.

Hypoaminoacidemia has been documented to occur in all dogs with SND skin lesions that have, thus far, had concentrations of plasma amino acids measured. Most dogs had nonglucagonoma-associated disease or HS, and only two dogs were confirmed to have a pancreatic tumor. The pattern of the plasma amino acid panels in dogs with SND appears to be significantly different from that seen in dogs with acute or chronic hepatitis.

The liver plays a critical role in amino acid balance. In chronic and acute hepatitis, compromised hepatic metabolism results in increased concentrations of many plasma amino acids. However, this is not seen in dogs with SND because the majority of individual plasma amino acid concentrations are less than 60% of normal. Total amino acid concentrations documented in dogs with SND are approximately 30% of the concentrations documented in healthy dogs or dogs with acute or chronic hepatitis. These differences suggest that the pathogenesis of hypoaminoacidemia in dogs with SND cannot be explained by compromised hepatic metabolism. The ratio of branch chain amino acids (BCAA) to aromatic amino acids (AAA) has been recognized as an indicator of hepatic insufficiency, and this ratio decreases with the severity of hepatic dysfunction or portal-systemic shunting. The mean BCAA:AAA ratio in dogs with SND in a recent study was 2.6:1.0, which is not indicative of severe hepatic dysfunction. It seems probable that an as yet unexplained increase in hepatic catabolism of amino acids might account for the severity of the hypoaminoacidemia documented in the dogs with SND. Intravenous administration of amino acids initially bypasses the portal circulation resulting in the delivery of amino acids to peripheral tissues before hepatic uptake and catabolism can occur. The fact that some dogs respond better to therapy with intravenous amino acid infusions rather than oral protein hyperalimentation supports the hypothesis that dogs with SND have increased hepatic catabolism of amino acids.

The etiopathogenesis of the hepatic pathology seen in the majority of dogs with SND remains unknown, and it is unclear what metabolic pathway or pathways may link liver or pancreatic disease with the skin lesions seen in SND. Hyperglucagonemia, if it were present, could explain the risk for the development of diabetes mellitus and hypoaminoacidemia seen in dogs with SND. Glucagon secretion can increase threefold without significant increases in peripheral plasma glucagon concentrations. Glucagon is not a hormone routinely measured in dogs, and assays may not detect all biologically active metabolites of glucagon. The catabolism of almost all amino acids is influenced by glucagon except tryptophan. Tryptophan concentrations are not significantly decreased in dogs with SND. It is possible that a disturbance in glucagon metabolism may have a role in the HS form of SND.

The actual etiopathogenesis for the skin lesions seen in dogs with SND or in humans with NME is not known. Humans with NME have had resolution of their lesions after surgical excision of their glucagonoma or after the use of somatostatin analogues. This suggests that hyperglucagonemia may have a direct role in the development of the skin lesions. It has been suggested that in NME, hyperglucogonemia results in increased epidermal arachidonic acid, and the resultant metabolites are responsible for the inflammatory changes in the skin. However, evidence exists that glucagon alone cannot explain the development of NME lesions in all affected humans because some have had resolution of skin lesions despite increased glucagon concentrations. Approximately 50% of humans with nonglucagonoma-associated NME have plasma glucagon concentrations within reference limits. Some patients with nonresectable pancreatic tumors have had NME skin lesions resolve with administration of intravenous amino acids. This finding, along with the hypoaminoacidemia seen in the majority of glucagonoma NME patients has led to the hypothesis that increased gluconeogenesis triggered by hyperglucagonemia results in low plasma amino acid concentrations, epidermal protein depletion, and then the skin lesions of NME. Hypoaminoacidemia was proven to result from increased hepatic clearance in one human patient with a glucagonoma. Essential fatty acid and zinc deficiencies have both been proposed to contribute to the development of NME because the histologic appearance of skin lesions in patients with zinc deficiency or essential fatty acid deficiency shares some similarities to those seen in NME. Some patients have had improvement of their NME skin lesions after zinc or essential fatty acids (EFA) supplementation, but neither has proven to be helpful for long-term resolution of the skin lesions in NME.

In dogs with SND, pancreatic tumor excision or treatment with somatostatin has resolved skin lesions. Because different disease processes appear to be able to produce the same characteristic histologic skin lesion, this suggests that they may perhaps all result in a common metabolic disturbance. The fact that severe hypoaminoacidemia is documented to occur in all cases of SND in which plasma amino acids have been measured, regardless of associated disease, makes it likely that this metabolic derangement is directly contributing to the cutaneous lesions seen in affected dogs.

CLINICAL PRESENTATION

The disease is typically diagnosed in older dogs. The mean age of affected dogs is 10 years of age, with a range of 4 to 16 years. Male dogs comprise 64% of reported cases. Shetland sheepdogs, West Highland white terriers, Cocker spaniels, and Scottish terriers may have a predisposition to develop HS because they appear to be overrepresented (Table 19-1).

The most common clinical sign is the development of visually distinctive skin lesions with a characteristic distribution. The skin lesions in dogs with HS may precede any other clinical signs. Skin lesions include erythema, crusting, exudation, ulceration and alopecia involving footpads, periocular or perioral regions, anal and genital regions, and pressure points on the trunk and limbs. A marked crusting, fissuring, and ulceration of the footpads is suggestive of SND (Figure 19-1). Secondary cutaneous infections with bacteria, yeast *(Malassezia, Candidia)*, or dermatophytes, particularly involving the feet, are often present in dogs with SND. Lameness secondary to footpad lesions, inappetence, and weight loss can also be associated with SND. Polydipsia and polyuria may be present when concurrent diabetes mellitus or significant liver dysfunction is present.

Table • 19-1

*Survey of Breeds of Dogs Affected with Hepatocutaneous Syndrome Based on Reported Cases**

	NUMBER		NUMBER
Mixed breed	25	Bichon frise	1
Terrier mix	6	Cairn terrier	1
Shetland sheepdog	11	Cavalier King Charles spaniel	1
Cocker spaniel	11	Golden retriever	1
West Highland white terrier	10	Keeshond	1
Scottish terrier	5	Labrador retriever	1
Jack Russell terrier	5	Maltese	1
German shepherd	5	Miniature poodle	1
Border collie	4	Old English sheepdog	1
Lhasa apso	3	Pomeranian	1
Beagle	3	Rough collie	1
Welsh corgi	3	Samoyed	1
Schipperke	2	Springer spaniel	1
American Eskimo	1	Standard poodle	1
Australian shepherd	1	Yorkshire terrier	1

*110 compiled cases.

Histopathologic findings of representative skin biopsies are unique and confirm the diagnosis. These findings include a marked parakeratotic epidermis with striking inter- and intracellular edema, keratinocyte degeneration in the upper epidermis, and hyperplastic basal cells that create the characteristic "red, white, and blue" histologic lesion. The evaluation of serum biochemistry panels often demonstrates an increase in liver enzyme activities and a decrease in serum albumin concentration. Serum bile acid evaluations are abnormal in about half of affected dogs. A review of reported cases found hypoaminoacidemia in all dogs, elevated glucagon in 4 out of 4 dogs that had a glucagonoma, and increased serum insulin concentrations in 8 out of 11 dogs.

Abdominal ultrasound may demonstrate a unique "honeycomb" pattern to the liver consisting of variably sized hypoechoic regions surrounded by hyperechoic borders. Hepatic histopathology often documents a distinctive vacuolar hepatopathy with parenchymal collapse. Grossly, the liver may appear irregular, have multiple nodules, and be mistaken for being cirrhotic. There exists some contradiction as to whether the hepatic lesions in HS reflect true cirrhosis. Despite some histologic descriptions of micronodular cirrhosis, one study, using special stains, confirmed only a minimal increase in collagen within portal areas. Extensive fibrosis and reduced liver size characteristic of chronic cirrhosis is not seen in HS.

The prognosis for dogs with SND is generally poor and the majority of dogs have survival times of less than 6 months. However, 20% of the dogs in a recent study were maintained for 12 months or more with oral protein hyperalimentation and periodic parenteral IV amino acid infusions.

DIAGNOSIS

Diagnosis of HS is based on obtaining skin biopsies with the typical histopathologic changes. The characteristic dermatohistopathology can be focal within a given lesion. Whenever possible, multiple representative samples should be obtained and submitted. Biopsies should be chosen, if possible from easily accessible sites, and attempts to avoid general anesthesia should be taken because these dogs are not often good candidates for anesthesia. The documented occurrence of abnormal laboratory findings as listed in Table 19-2 should increase the clinical suspicion of HS in dogs with compatible cutaneous lesions. If abdominal ultrasound is available, it can provide further support for the diagnosis if the characteristic "honeycomb" pattern is documented. If this ultrasonographic pattern to the liver is not visualized in a dog with a confirmed histologic diagnosis of SND, evaluation for a possible pancreatic tumor is necessary. Pancreatic tumors may not be readily

Table • 19-2

Percentage of Reported Cases (101 Dogs) Displaying the Commonly Reported Clinical and Laboratory Findings in Dogs with Hepatocutaneous Syndrome

CLINICAL FINDINGS	%	LABORATORY FINDINGS	%
Hyperkeratotic and fissured footpads	94%	Elevated serum alkaline phosphatase	98%
Perioral or periocular skin lesions	62%	Elevated serum alanine transferase	71%
Perianal or perineal skin lesions	33%	Anemia	37%
Elbow skin lesions	30%	Hypoalbuminemia	33%
Perivulvar or scrotal or preputial skin lesions	28%	Diabetes mellitus	33%

visible with an abdominal ultrasound examination, so measurement of plasma glucagon is also recommended. If plasma glucagon concentrations are abnormally increased or a pancreatic mass is visible on ultrasound, the option for exploratory laparotomy and tumor excision can be considered. However, postoperative morbidity and mortality have been high. Plasma amino acids, if measured, should document a characteristic severe hypoaminoacidemia.

MANAGEMENT

The most effective symptomatic or palliative therapy for dogs with HS appears to be the administration of intravenous amino acids. A number of amino acid solutions are commercially available. Administration of a total dose of 25 ml/kg of a 10% Aminosyn (Abbot Labs, N.C. and Ill.) solution, administered over 6 to 8 hours and repeated at 7- to 10-day intervals has been recommended. Both Travasol 8.5% without electrolytes (Baxter Healthcare Corp., Clintec Nutrition Company, Deerfield, Ill.) and ProcalAmine 3% amino acids with 3% glycerin and electrolytes (B. Braun Medical Inc., Irvine, Calif.) can also be used for intravenous infusions in treating dogs with SND. These hypertonic amino acid solutions should be administered via a central vein to diminish the chance of thrombophlebitis. Inducing a hyperosmolar state is possible if administration is too aggressive. Dogs should be watched for neurologic signs, and the infusion discontinued if these occur. If compromised hepatic or renal function is present the administration of intravenous amino acids may exacerbate hepatic encephalopathy or augment increases in blood urea nitrogen (BUN). Such dogs warrant close monitoring with serial measurements of ammonia, BUN, and osmolality during intravenous amino acid administration. Some dogs show dramatic improvement in attitude with resolution of skin lesions after receiving amino acid infusions. As yet no defined protocols exist for the administration of amino acid infusions in these dogs, and repeat infusions are performed bimonthly, monthly, or when clinical signs return.

Oral nutritional support should include a high quality protein diet that can be additionally supplemented with an amino acid powder such as Promod (Ross Laboratories, Columbus, Ohio), at a dose of one scoop per 10 pounds. Unless significant hepatic dysfunction with hyperammonemia has been documented necessitating a low protein diet, most dogs with HS cannot be fed enough protein to overcome the hypoaminoacidemia occurring in this disease. Zinc and essential fatty acid supplementation is often recommended, in part because of the reported initial improvement in some people with NME. Feeding egg yolks (3 to 6 per day) has been reported to result in clinical improvement in some dogs. This provides some additional protein but may also include micronutrients that may have some role in this disease.

Secondary infections should be treated with appropriate antibiotic and antifungal therapy, with careful consideration of those drugs that may be hepatotoxic or require hepatic metabolism. Topical therapy with antibacterial and antiyeast shampoos can also be of benefit in some dogs in helping to manage secondary infections.

Therapy with glucocorticoids is not recommended. Although antiinflammatory therapy for the skin lesions may be of some benefit, the risk of precipitating or exacerbating diabetes mellitus in these dogs makes the use of glucocorticoids contraindicated.

Physique

CHAPTER 20

Obesity

A Disease to Be Recognized and Managed

Rebecca L. Remillard

It is estimated that 24% to 30% of the pet population in the United States seen by veterinarians is overweight or obese. This information, together with an estimated number of pets and veterinarians in the United States, suggests that a single veterinarian may see as many as 840 of these overweight or obese animals per practice. The cause of obesity as a primary disorder is simply that an animal is receiving more calories than it is expending, and body fat mass increases. Obesity may also be a secondary condition in animals with hypothyroidism, hyperadrenocorticism, or insulinomas. Treating these endocrinopathies rarely reduces, so a weight loss program may be necessary. However, the incidence of obesity as a primary disorder exceeds the incidence of the endocrinopathies associated with obesity.

HEALTH RISKS

Several health risks are associated with obesity as evidenced from long-term studies in cats and dogs. Grossly obese pets have increased prevalence of impaired gaits, traumatic and degenerative orthopedic disorders, and overweight puppies are more likely to develop clinical signs of orthopedic disease. Dogs obese at 1 year of age have a greater risk for developing mammary cancer later in life, and overweight dogs have an increased risk of developing cystic transitional cell carcinoma. Overweight pets have reduced activity, decreased heat tolerance, and they show visible signs of aging earlier than ideal-weight animals. Other health problems commonly noted in obese pets include dyspnea, congestive heart failure, dystocia, and nonallergic dermatologic problems. As we have learned from rodent and canine studies, lean or optimal weight pets may live on average 1 to 2 years longer than overweight pets. Therefore weight control is not only a quality of life issue but also one that may increase longevity. Calorie restriction is the only factor known to increase median life span.

Overweight and obese dogs and cats commonly have primary and secondary health issues. Studies have demonstrated significant weight changes in research dogs and cats using commercially available diets designed for weight loss. These therapeutic weight loss diets are marketed solely to veterinarians.

RECOGNITION

Body weight alone does not indicate whether that weight is appropriate for the particular patient. Knowing a dog's weight to be 50 lb (23 kg) or a cat to be weighing 12 lbs (5.5 kg) means that animal might be underweight, at optimal weight, or overweight. Writing a body condition score next to the weight puts that weight in perspective, which allows visualization regarding how the weight is carried on that skeletal frame. Scoring body condition is similar to the visual effect of breed (e.g., a 50-lb beagle conjures a very different picture than a 50-lb Newfoundland).

Body Condition Scoring

Body condition scoring (BCS) is a useful tool that estimates an animal's body fat content, taking into account the animal's frame size independent of body weight. Several different numbering systems (using 3-, 5-, or 9-point categories) and wall charts are available. A clinician must learn by experience what visual and palpable characteristics correspond with a given BCS; however, once learned, BCS has been demonstrated to be a reliable indicator for determining body composition. BCS is a useful tool in evaluating weight changes within an individual and as a means of communicating between clinicians.

The 5- or 9-point systems seem to be most commonly used. A 5-point system is most useful to novices using whole numbers (1/5 is emaciated, 3/5 is ideal, 5/5 is grossly obese), but with practice, the scores will be recorded to the nearest half score (e.g., 4.5/5). Experienced clinicians frequently use the 9-point system, in which scores are recorded to the nearest whole number (1/9 is emaciated, 5/9 is ideal, 9/9 is grossly obese). Using the 5-point system scored to the nearest half score actually is the 9-point system.

A pet in optimal body condition has "normal body contours and silhouettes, bony prominences that can be readily palpated but not seen or felt above skin surfaces, and intraabdominal fat insufficient to obscure or interfere with abdominal palpation." Body condition can be defined as the ratio of body fat to nonfat tissues and hence does estimate percent body fat. Fat mass expressed as a percentage of body weight can also be a useful tool in convincing owners their pets are overweight. Body composition studies in dogs and cats suggest that animals assessed to be in optimal body condition have 15% to 25% body fat. Dogs and cats with a BCS of "ideal" will have 15% to 25% body fat, those considered overweight will have 26% to 35% body fat, and those deemed obese will have more than 35% body fat. Some pets may have well more than 40% body fat (e.g., the cat with a 10-lb frame weighing 20 lbs is probably carrying 10 lbs of fat). Therefore it is correct to say that when assigning the maximum BCS, the pet has at least 40% body fat.

Dogs with an ideal BCS of 4 to 5 lived 15% longer than dogs of the same breed, living in the same environment, and

eating the same diet but having a BCS of 6 to 7 (using the 9-point system). Hence, weight reduction programs should be discussed and implemented when the BCS is 6/9 or greater because the percent body fat will then be greater than 25%. The benefits derived from controlling body weight and condition are thought to be realized at any time throughout life; hence benefits can be gained by reducing the weight of any pet at any age.

MANAGEMENT

Before beginning a weight loss program, it is essential to ensure that the obesity is of primary origin and not the result of an endocrinopathy. Body weight may not naturally correct after such treatments have been instituted. A reduced calorie intake may still be needed after initializing treatment for an underlying endocrinopathy. A complete physical examination, with routine serum, blood, and urine analysis should be done. If necessary, additional diagnostics should be done to further evaluate any abnormal clinical findings of the cardiovascular, gastrointestinal, liver/pancreas, renal/urinary, musculoskeletal, or other organ systems. A dietary history is of limited value because most clients cannot recall the names or amounts of food fed to their pets. The most essential dietary information needed is an estimate of the current amount of calories fed so that appropriate restriction may begin. Most owners of pets with a BCS greater than or equal to 6/9 feed ad libitum, suggesting that a specific feeding amount divided into two meals per day would be an excellent starting point. Some owners requesting a weight loss plan have already begun to limit the pet's calorie intake with no success; hence the first feeding recommendations must be a further restriction of calories. Several different methods can be used to restrict calorie intake.

Short-Term Starvation

Starvation as a method of weight loss cannot be used in cats because of the risk of inducing hepatic lipidosis. Starvation has been used as a form of weight loss in dogs. However, this method creates not only a caloric deficiency but also a deficiency of all other nutrients. Most pronounced would be a protein deficiency (skeletal muscle wasting will occur as a result of the need for synthesis of essential proteins). Body weight lost will then be comprised of fat, muscle, and to a lesser extent bone. Less obvious will be the water-soluble vitamin and trace mineral deficiencies created because little to no body storage of these nutrients takes place, and a daily intake is necessary for ongoing metabolic processes. The goal of weight loss is to reduce the body fat content while maintaining other body tissues and metabolism. Deficiencies of amino acids, vitamins, and trace minerals are needed to properly and fully catabolize and therefore reduce fat stores. No veterinary protein, vitamin, or mineral supplement exists that will adequately supply 100% of the daily requirement of these essential nutrients. Starvation creates nutritional deficiencies across all metabolic processes and is therefore not an acceptable form of weight reduction from a physiologic perspective. The inhumane aspects of this method are obvious. Additionally, short-term starvation does not teach the owner how to properly feed and manage their pet in the long-term once the proper weight has been achieved.

Feeding Less of Current Food

It is not uncommon to hear a practitioner advocating, "Simply feed less of his regular food," as a method of weight loss. If the volume of "regular food," usually an over-the-counter (OTC) pet food product not designed for weight loss, is reduced by 25% or less, there may be little nutritional harm done to a normal healthy overweight adult dog over a short period (weeks), depending on the OTC product used. However, if the volume of regular food has to be reduced by more than 30% to get weight loss, nutritional deficiencies will occur. For example, feeding 30% fewer calories of an OTC adult premium maintenance dog food to a 50-lb overweight dog produces a protein intake 5.6% below current canine feeding recommendations. As the restriction continues, more nutrients become deficient. Therefore when more than a 25% restriction of calories is necessary, changing the pet food product is absolutely necessary. An OTC diet labeled "light," "lite," "lean," "less," or "reduced calorie or fat" is formulated for weight maintenance, not weight reduction. Some properly formulated OTC "reduced calorie" diets may be fed at 25% less than the recommended feeding; however, unless one is comfortable with the calculations or has some assurance from the manufacturer, it is not advisable as a general rule.

Properly formulated weight loss diets are specifically designed to be low in calories with increased concentrations of all other nonenergy nutrients. In other words, the nonenergy nutrients are in a higher proportion to calories consumed in a weight reduction diet than in the OTC adult maintenance or reduced calorie foods. One only wants to create a caloric deficiency and not other nutrient deficits during weight loss according to Association of American Feed Control Officials (AAFCO) allowances. Feeding fewer or no treats, snacks, or table foods is appropriate because these do not affect the daily nutrient intake balance. Changing treats to high-water (squashes) or fibrous (broccoli) vegetables is also acceptable because they contain no calories to be counted.

Feeding High-Fiber Diets

There has been some debate regarding the effectiveness of diluting dietary calories with dietary fiber, water, and air. Water and air are quickly removed from the gastrointestinal tract and do not contribute substantially to a feeling of gastrointestinal fill; hence they have a minimal sustained effect on decreasing food intake. Dietary fiber has been shown to decrease food intake.

Fibers are complex carbohydrates that cannot be digested by endogenous enzymes within the small bowel but can be fermented to varying degrees in the colon. Fiber is classified by physiochemical and analytic properties. Dietary fiber, including soluble versus insoluble fiber, dilute diet calories, increase satiety, and limit food consumption by increasing digested bulk and prolonged distention of the gastrointestinal tract. The difference between soluble and insoluble fiber is based upon their solubility in water; although the fiber types affect the gastrointestinal rate of transit differently, transit time through the entire gastrointestinal tract is increased approximately the same for both soluble and insoluble fibers. Some dog studies showed no effect on caloric intake when foods contained 12% to 14% of dry matter as soluble or insoluble fibers, but dogs did consume significantly less of a food containing 21% insoluble fiber. These same dogs also ate less food when offered a second meal 30 to 45 minutes after consuming the high-fiber food. Overall, study results indicate beneficial effects of dietary fiber in foods intended for weight loss. Most commercial weight loss diets contain primarily insoluble fiber at greater than 10% (and sometimes as high as 30%) of the dry matter. Increased fecal bulk is to be expected, and sometimes the increase frequency of defecation is not acceptable to the owner. In this case a lower-fiber diet (10% to 15%) has to be used for weight loss.

Weight Loss Protocol

Several methods can be used to calculate food doses for weight loss. An equation for weight loss must require fewer calories consumed than are currently expended. Different pet food companies offering weight loss products and programs use different methods, and some calculation methods are more successful than others.

Method 1: The daily caloric intake for weight loss is 50% of the maintenance calories at dog's current weight. This method has not produced a rate of weight loss sufficient to meet owner's expectations or inspire interest in continuing the program in clinical trials.

Method 2: The daily caloric intake for weight loss is a percentage (40% to 60%) of the maintenance energy requirements at the target, desired, or optimal body weight. This method has produced a rate of weight loss acceptable to owners.

Method 3: The daily caloric intake is calculated based upon maintenance energy requirement (MER) at the current weight minus a desired percent body fat loss per day, which could be adjusted depending upon individual animal response. This method has been shown to produce a rate of weight loss acceptable to owners. Several pet food manufacturers have these weight loss calculations available in simple, user-friendly programs that can be run on most personal computers (IBM or Macintosh).

Consistently delivering or feeding fewer calories to the pet is of course the responsibility of the owner. Owner (family) compliance is the single most important aspect in an obese pet losing weight; this is simple to say but very difficult to deal with in the single 20-minute office visit. Approximately 55% of the overweight feline and canine patients are not brought back for a recheck weight loss visit. Pets who returned for three or more recheck visits did successfully lose weight. Recheck visits every 4 to 8 weeks are essential because the caloric intake must be reduced (recalculated) to continue weight loss or the weight will stabilize. Some weight loss packages put together by pet food manufacturers aid owner compliance by providing a well-demarcated feeding cup or cans and printed instructions.

In summary, losing excess body fat has been shown to decrease morbidity and increase longevity in pets. BCS systems and computerized weight loss programs are now available as useful clinical tools. Veterinarians should be regularly discussing weight control with owners and helping those with pets with BCS greater than 5/9 because the majority of pets are now neutered and have less exercise and because pet food companies strive to make their OTC products ever more palatable.

CHAPTER 21

Cachexia

Thomas Schermerhorn

A standard definition for cachexia is difficult to provide. In clinical practice, *cachexia* is the term used to describe the weight loss, loss of muscle, and anorexia that accompany many chronic disease conditions. However, it is important to recognize that cachexia is not simply caused by inadequate nutrient intake and that cachexia and starvation are not equivalent physiologic processes. In humans, two biochemical features distinguish malnutrition caused by cachexia from that caused by starvation. First, unlike starvation, cachexia is associated with a pronounced acute phase inflammatory response, characterized by production of proinflammatory cytokines such as interleukins (IL-1 and IL-6, among others) and tumor necrosis factor alpha (TNF-alpha).

Cytokines stimulate the production of ubiquitin, a protein that binds to other proteins and stimulates their metabolism via the cellular proteasome system. Activation of the ubiquitin-proteasome system does not occur during starvation. Increased resting energy expenditure is the second feature of cachexia that distinguishes it from starvation. Resting energy expenditure increases as a consequence of altered protein, fat, and carbohydrate metabolism.

A diagnosis of cachexia should be considered for any dog or cat with marked weight loss, severe muscle loss, and decreased appetite in the setting of a chronic inflammatory response. By this definition, cachexia is not a specific diagnosis but an indication of a state of disordered metabolism that can be caused by a variety of diseases.

When evaluating an emaciated dog or cat, it is important to determine, from diagnostic and therapeutic standpoints, whether the condition has developed as a result of inadequate nutrient intake (maldigestion, malabsorption, or underfeeding, for example) or represents true cachexia.

HISTORY

Dogs and cats with cachexia may be brought to veterinarians principally for weight loss or for signs associated with an underlying condition. Careful history taking should include questions about appetite, caloric intake, daily exercise, and environment. Some animals with cachexia have weight loss with preservation of appetite; the loss of body condition may be noted before the onset of anorexia in some cases. Dogs and cats with malnutrition as a result of starvation, malabsorption, or maldigestion typically have a good appetite. However, the level of appetite is variable in animals with cachexia, ranging from normal to complete anorexia. Lethargy, weakness, and exercise intolerance may be marked and in some cases are worse than would be expected if simply the result of poor physical condition. The dietary history should be carefully reviewed and include the type and quantity of food offered (including any dietary supplements provided), the possibility that other pets at home might be competing for food, and the pet's level of appetite. It is important to distinguish those animals that have an appetite but cannot prehend or swallow food from those who have no appetite but can chew and swallow normally. Diagnostic considerations suggested by various patient history findings are presented in Box 21-1.

PHYSICAL AND LABORATORY FINDINGS

Cachexia has few specific indicators other than the marked loss of body condition that is a characteristic finding; muscle may be lost disproportionately to fat in some animals with cachexia. Similarly, laboratory findings are not specific for cachexia.

Box • 21-1

Diagnostic Considerations for Patients with Marked Weight Loss

Dietary History—Inadequate
Starvation
Underfeeding
Poor quality food

Dietary History—Adequate
Environmental/housing factors
  Competition for food from other pets
  Limited access to food
Oral and dental disease
Impaired use of nutrients
  Specific nutrient deficiency
  Maldigestion of any cause
  Malabsorption of any cause
  Diabetes mellitus
  Protein-losing disease
    Nephropathy
    Gastroenteropathy
  Cardiac disease*
Elevated metabolism
  Hyperthyroidism
  Chronic fever of any cause*
End-stage renal disease*
Neoplasia*
Chronic infection*
Chronic inflammation of any cause (e.g., immunologic disease*)

*Diseases typically associated with cachexia in humans and animals.
Note: Patients may present with or without a loss of appetite.

Serum protein levels are variable even in the presence of a systemic inflammatory response. For example, elevated fibrinogen levels (as a component of the acute phase response) in humans with neoplasia may be offset by reduced albumin synthesis. Increases in hormone concentrations, such as cortisol and insulin, may be observed in animals with cachexia; these changes may result from or be the cause of cachexia-induced alterations in metabolism. In general, an individual patient's physical and laboratory findings will be representative of the underlying disease rather than specific indicators of cachexia. No compelling reasons exist to perform specific laboratory tests to make a diagnosis of cachexia. Instead, cachexia is largely a clinical diagnosis that is made when appropriate physical findings are present in a dog or cat with a disease associated with a chronic inflammatory response.

DIAGNOSTIC PLAN

A general algorithm for making a diagnosis of cachexia is shown in Figure 21-1. It is important to recognize cachexia because animals with this condition may not respond as expected to therapeutic interventions and nutritional support.

THERAPY

Successful therapy of the primary disorder is the most efficacious means of reversing the metabolic abnormalities that underlie the development of cachexia. Nutritional support is the cornerstone of specific therapy for cachexia. Hypercaloric feeding is intended to supply the dog or cat with sufficient calories to meet increased maintenance caloric needs (because of hypermetabolism), prevent additional weight loss, and promote weight gain. Unfortunately, hypercaloric feeding alone may not be sufficient therapy for animals with true cachexia. People with cachexia who receive hypercaloric feeding gain weight, but the increase in body weight is almost exclusively the result of an increase in adipose tissue without

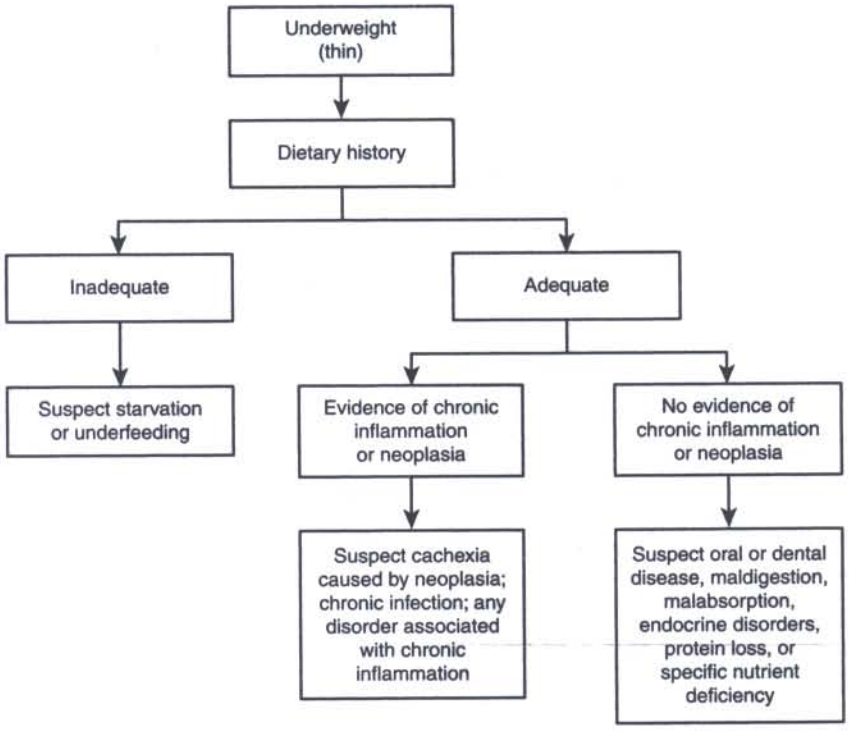


Figure 21-1 Algorithm for making a diagnosis of cachexia.

change in lean body mass. Thus it appears that simple feeding therapy may not be sufficient in all situations to reverse the abnormal protein catabolism that accompanies cachexia. Additional therapies that have been used for cachexia in humans that may prove useful for the treatment of animals include appetite stimulants, anabolic agents, antiinflammatory drugs, and cytokine inhibitors. Although some of these drugs have been extensively used for other indications in small animals, information is limited about their efficacy when used for cachexia.

CHAPTER • 22

Failure to Grow

Sherri L. Ihle

Growth is a complex process that results in an increase in size of an individual. In dogs and cats, growth primarily occurs during the first 6 to 24 months of life. When an animal does not increase in size at the normal rate or to a normal extent, a "failure to grow" is identified. The owner of the affected pet may notice the problem and bring the animal to the veterinarian, or the animal's small size may be first noticed during a routine physical examination. In veterinary medicine, determination of normal growth is sometimes difficult because breed sizes vary and mixed breed pets predominate. Comparing littermates, when possible, can be helpful in making and assessing the individual's growth rate and pattern.

PATHOPHYSIOLOGY

Genetic, hormonal, metabolic, and nutritional factors influence growth. To meet its full genetic potential, an animal must have growth hormone (somatotropin) to stimulate insulin-like growth factor-I (IGF-I) production, which in turn stimulates skeletal growth, protein synthesis, and cell proliferation. Full IGF-I activity requires the presence of thyroid hormone. The animal must also consume sufficient calories and nutrients; digest, absorb and retain the nutrients; transport the nutrients to the necessary tissues; and be able to use the nutrients for metabolic maintenance and growth. A defect in any of the previously mentioned processes can disrupt, delay, or stop normal growth (Box 22-1; Figure 22-1).

Genetic Abnormalities of Bone Growth

An inherited endochondral ossification defect in chondrodystrophic animals results in angular limb deformities and subnormal height.

Deficient Nutrient Intake

Gastrointestinal parasitism, resulting in a "relative" deficiency in nutrition, is the most common cause of reversible retarded growth in puppies and kittens. If an insufficient amount of food or food of poor quality is consumed, nutrients will not be available to provide substrates and energy for tissue growth. Oral disease may cause pseudoanorexia. Regurgitation or vomiting because of esophageal or gastric disorders results in insufficient food reaching the intestines for digestion and absorption. Maldigestion or malabsorption can result in decreased uptake of nutrients. Renal, hepatic, cardiac, inflammatory, and hypo-adrenal disease can suppress the appetite.

Box • 22-1

Causes of Growth Failure in Dogs and Cats

Small Stature and Poor Body Condition
- Dietary problem
  - Underfeeding
  - Poor quality diet
- Cardiac disorder
  - Congenital anomaly
  - Endocarditis
- Hepatic dysfunction
  - Portosystemic vascular anomaly
  - Hepatitis
  - Glycogen storage disease
- Esophageal disease
  - Megaesophagus
  - Vascular ring anomaly (e.g., persistent right aortic arch)
- Gastrointestinal disease
  - Parasites
  - Inflammatory bowel disease
  - Obstruction (e.g., foreign body, intussusception)
  - Histoplasmosis
- Exocrine pancreatic insufficiency
- Renal disease
- Renal failure (congenital or acquired)
  - Glomerular disease
  - Pyelonephritis
- Inflammatory disease
- Hormonal disease
  - Diabetes mellitus
  - Hypoadrenocorticism
  - Diabetes insipidus
  - Juvenile hyperparathyroidism (dogs)

Small Stature and Good Body Condition
- Chondrodystrophy
- Hormonal disease
  - Congenital hypothyroidism
  - Congenital hyposomatotropism (pituitary dwarfism)
  - Hyperadrenocorticism

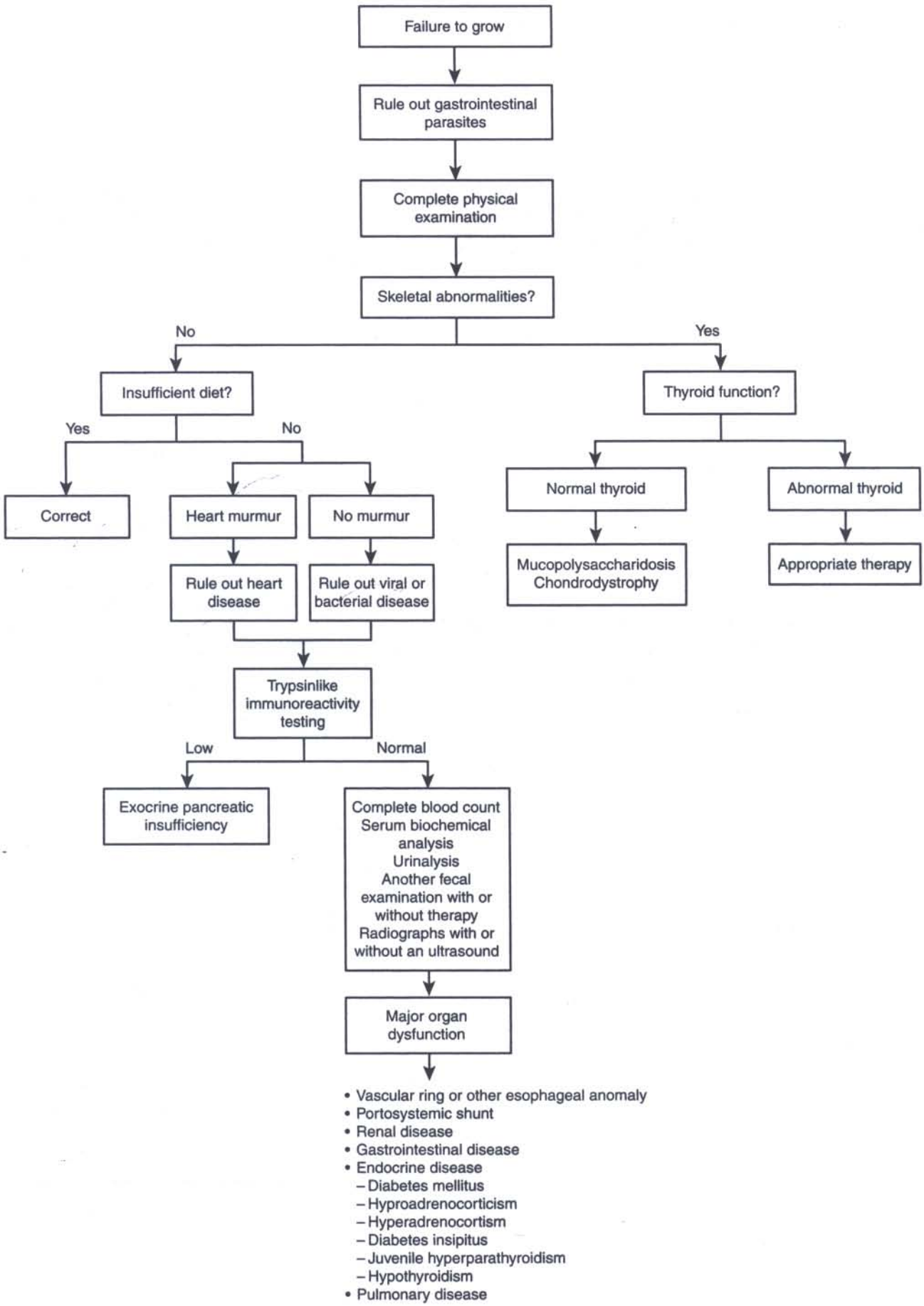


Figure 22-1 Algorithm for diagnostic evaluation of the dog or cat with failure to grow.

Absorption and transport of nutrients from the intestines to other tissues can also be inadequate with cardiac disease.

Caloric or Nutrient Loss

Fever can result in excess caloric loss as body heat. In diabetes mellitus, glucose is lost in the urine. Protein and salts can also be lost in the urine in animals with glomerular and renal tubular disease, respectively. Several intestinal disorders can result in protein-losing enteropathy. As previously noted, parasitism is the most common cause of "lost" nutrients.

Abnormal Metabolism

Carbohydrate metabolism can be altered in inflammatory disease, renal disease, and hepatic disease. Protein production can also be decreased with hepatic disease. Hypothalamic or pituitary aplasia or neoplasia (e.g., craniopharyngioma) can result in low growth hormone and IGF-I concentrations. Hypothyroidism can decrease the activity of growth hormone. Because insulin has a positive effect on IGF-I production, insulin deficiency caused by diabetes mellitus or malnutrition can slow growth. Cortisol excess, whether endogenous or exogenous in origin, can inhibit the secretion of growth hormone. An extremely rare form of juvenile hyperparathyroidism in German shepherds has also been reported to cause stunted growth.

HISTORICAL FINDINGS

The animal with subnormal growth may be brought to the veterinarian for that problem or the small body size may be noted during a routine examination. In either case, the owner of the dog or cat should be questioned as to the size of the pet's parents and littermates, if known. If the parents and littermates are also at the lower end of the range of breed size, the small stature of the pet may not be worrisome. However, if the pet is noticeably smaller than its littermates, the problem should be investigated. When the family history is unknown, the pet's size should be compared with others in the breed. For the mixed breed dog, the predominant breed should be determined based on physical characteristics, and that breed's average size should be the standard for comparison.

Duration of the Problem

Determining whether the animal's growth has been slow since birth or whether it was normal and then suddenly seemed to stop can be helpful. In the former case, congenital defects should be strongly considered, whereas in the latter case, acquired disorders must also be considered.

Diet

A detailed nutritional history should be obtained as to type of food, amount of food consumed, appetite, and feeding schedule. A less palatable or poor quality diet may not be eaten well or may be poorly used by the animal. A poor appetite despite the feeding of a palatable, high-quality food suggests the presence of a systemic illness causing inappetence or anorexia. Conversely, if the animal is always hungry and internal parasites have been ruled out or treated, underfeeding (because of inadequate owner knowledge of the pet's nutritional needs), a disorder causing a "relative" lack of calories (e.g., exocrine pancreatic insufficient), or an increased nutrient loss (e.g., diabetes mellitus, renal disease, intestinal disease) should be considered.

Concurrent Clinical Signs

The owner should also be questioned about the presence or absence of other clinical signs, which may help define the cause of the problem. Regurgitation usually indicates a pharyngeal or esophageal problem. Vomiting suggests a gastrointestinal problem or systemic illness (e.g., renal disease, hepatic disease, hypoadrenocorticism). Diarrhea or voluminous stools may be seen with disorders causing maldigestion (e.g., exocrine pancreatic insufficiency) or malabsorption (e.g., severe parasitism, inflammatory bowel disease, histoplasmosis). If polyuria is present, diabetes mellitus, renal disease, hepatic dysfunction, or hypercalcemia (juvenile hyperparathyroidism) should be considered. Seizures, episodic abnormal behavior, vomiting, and diarrhea may be signs of hepatic dysfunction. Exercise intolerance or syncope can suggest a congenital cardiac abnormality. Poor response to housebreaking measures or to obedience training, or a lack of normal puppy play activities can suggest the mental dullness of congenital hypothyroidism, or the encephalopathy of hepatic failure. Poor response to housebreaking measures may also be seen with ectopic ureters or the polyuria of kidney abnormality. Glucocorticoid therapy for an unrelated problem may have slowed the pet's growth. Although the absence of these historical findings does not eliminate these disorders as possible problems, their presence can guide the diagnostic plan.

PHYSICAL EXAMINATION FINDINGS

Although some animals examined as a result of poor growth will have no other clinical abnormalities, in many animals a thorough physical examination can provide valuable clues as to the organ system or systems responsible for the problem. The animal's general appearance and body condition should be assessed. A short animal with a poor body condition is more likely to have a nutritional, metabolic, or cardiac abnormality, whereas a short animal with a good body condition is likely to have a hormonal problem or be chondrodysplastic (see Box 22-1). Chondrodysplastic animals and many animals with congenital hypothyroidism will also have an abnormal skeletal conformation (e.g., angular limb deformities). Symmetrical truncal alopecia, the prolonged presence of a soft puppy haircoat, or thin scaly skin suggests a thyroid or growth hormone deficiency or cortisol excess. Mental dullness can be seen with hypothyroidism or hepatic encephalopathy. Hepatic failure can also result in cortical blindness.

The head and neck should be examined for pale mucous membranes (anemia of chronic disease), icterus (hepatic disease), oral pain (dysphagia), and lymphadenopathy (inflammatory disease). The thorax should be carefully ausculted for a murmur (congenital cardiac disease, other cardiac dysfunction), bradycardia (hypoadrenocorticism), or abnormal lung sounds (pulmonary disease). On abdominal palpation, enlarged or shrunken kidneys can indicate a renal problem, and hepatomegaly can suggest hepatic disease or dysfunction. Thickened bowel walls may be felt in the presence of inflammatory bowel disease, or a mass lesion may be palpated in the pet with a foreign body or intussusception.

DIAGNOSTIC PLAN

Decisions concerning the initial diagnostic plan should be based on the animal's body condition and any abnormalities identified from the history and physical examination (see Figure 22-1). Food consumption should always be evaluated (see Historical Findings). If food intake is in question, a brief *feeding trial* can provide information on appetite and caloric consumption in relation to change in body weight. Multiple *fecal examinations* and possible deworming should be performed to eliminate severe parasitism as the cause of malnutrition. If the animal has been given a medication that may have slowed growth, the medication should be discontinued, if possible, and subsequent growth monitored. A *complete blood count* (CBC) should be evaluated for anemia, inflammation,

or eosinophilia. Results of a *serum biochemical profile* can suggest renal, hepatic, or gastrointestinal disease; diabetes mellitus; hypoadrenocorticism; hyperadrenocorticism; hypothyroidism; or hyperparathyroidism. A *urinalysis* may show proteinuria, isosthenuria, hyposthenuria, glucosuria, or inflammatory sediment. *Radiographs* can be used to detect a cardiopulmonary abnormality, organomegaly, a small liver or kidneys, intestinal foreign body, or skeletal abnormalities. *Ultrasonography* may help to further characterize radiographic abnormalities and detect structural abnormalities within an organ. An *electrocardiogram* may be helpful in assessing potential hyperkalemia (in an emergency) and congenital cardiac abnormalities. *Radiographic contrast studies* can be used to characterize congenital cardiac abnormalities, to identify portosystemic vascular anomalies, and to detect partial gastrointestinal obstructions. *Hepatic function tests* can identify the need for further investigation of the liver. *Gastrointestinal function tests* (e.g., serum trypsinlike immunoreactivity, serum cobalamin and folate) can be used to identify occult gastrointestinal disease causing maldigestion or malabsorption. *Biopsy* may be needed if gastrointestinal, hepatic, or renal disease is identified. *Hormonal tests* can be used to detect hypothyroidism, hyperadrenocorticism, hypoadrenocorticism, and hyperparathyroidism; an assay for growth hormone is not currently available on a commercial basis, but an IGF-I assay is available for the dog.

TREATMENT

Treatment of the animal that exhibits growth failure varies widely based on the underlying pathology. Some disorders can be well managed medically, and others require surgical correction.

CHAPTER 23

Swollen Joints and Lameness

Richard E. Goldstein

Lameness is a common reason for dogs to be taken to a veterinary practitioner. Although lameness has numerous causes, this chapter will address lameness associated with nontraumatic inflammatory disease of the joints. Assessment for swelling or pain of accessible joints should be a routine component of the physical examination of dogs and cats. Arthritis can be categorized based on cause.

Degenerative joint disease is caused by chronic changes to the joint capsule, cartilage, and synovium associated with minimal to no active inflammation. Degenerative joint disease, although painful, is typically not associated with systemic inflammatory signs. Inflammatory joint diseases can be classified as septic or nonseptic (immune mediated). Inflammatory joint disease is typically associated with one or more of the signs consistent with those of systemic disease. These usually include fever, leukocytosis, inappetence, or lethargy. Arthritis can also be classified based on the number of joints involved. Monoarthritis implies involvement of a single joint, whereas polyarthritis involves multiple joints.

SEPTIC ARTHRITIS

Septic arthritis is defined by presence of bacteria in the synovial or joint fluid, observed on cytologic evaluation or with bacterial culture. Septic arthritis occurs as a result of hematogenous (more common in neonates) spread or external penetrating wounds. It is not always possible to distinguish septic arthritis from immune-mediated arthritis, especially when multiple joints are involved or no obvious penetrating wound is seen. Joint fluid cultures, although worthwhile, are frequently negative even when bacteria are evident on cytologic examination. Neutrophils predominate in the joint fluid of infectious and immune-mediated arthritis. Degenerative changes in neutrophils, however, are more indicative of a septic process. The number and type of joints involved may help the clinician differentiate septic from nonseptic arthritis. Single joint involvement and involvement of proximal joints (hip, shoulder, stifle, and elbow) are usually septic. Multiple, distal joint (carpi, tarsi) involvement, is most commonly seen immune-mediated disease. When a septic process is possible, a period of antimicrobial therapy can be recommended, even if no bacteria are observed on joint fluid cytology and joint fluid cultures are pending or negative.

IMMUNE-MEDIATED POLYARTHRITIS

Immune-mediated polyarthritis is the most common polyarthritis in companion dogs and cats. A type III hypersensitivity reaction, in which immune complexes are deposited in the synovial membrane and an inflammatory cascade is initiated, is thought to be the cause. The immune stimulus is frequently unknown, hence the commonly used term "idiopathic polyarthritis." Immune-mediated polyarthritis can be categorized both radiographically and histologically into the common nonerosive form and the uncommon erosive condition.

EROSIVE POLYARTHRITIS

Erosive polyarthritis in dogs may have similarities with human rheumatoid arthritis. These similarities include the progressive, severe, deforming course of the disease and the erosive radiographic appearance of affected joints. In humans, specific antibodies, collectively known as *rheumatoid factor* (RF), are commonly identified. An IgM antibody, considered the canine RF, has been identified in some dogs with erosive arthritis. Although the term *rheumatoid arthritis* has been used

in veterinary medicine, it is preferable to use the descriptive term *erosive arthritis* in dogs.

RF is a nonsensitive and nonspecific marker of erosive or immune-mediated arthritis in dogs, making the assay's clinical utility questionable. Radiographic findings commonly seen in dogs with this form of arthritis include erosions involving the articular surface or the loss of trabecular bone density in the epiphyses. The destructive process is progressive. Radiographically, this process appears in the subchondral or juxtaarticular bone as poorly demarcated radiolucent foci. Erosive arthritis has been reported in many breeds but is thought to occur more frequently in small breed dogs, 2 to 6 years of age. A specific form of erosive arthritis has been reported in greyhounds.

Erosive polyarthritis has been reported in cats and has been termed *progressive feline polyarthritis*. This is a disease that occurs more commonly in male cats between 1.5 and 5 years of age. It may be an immune-mediated hypersensitivity type III reaction to chronic viral immune stimulation, secondary to chronic feline syncytium-forming virus infection. Two forms of the disease exist: (1) the deforming type, a severely erosive condition that is similar to canine erosive arthritis, and (2) the more common proliferative form. Both forms can be associated with severe systemic signs of disease, including lymphadenopathy, swollen joints, and muscle wasting.

NONEROSIVE POLYARTHRITIS

This is the most common form of immune-mediated polyarthritis in dogs and cats. The source of the antigenic stimulation is usually not known. Nonerosive polyarthirtis has been reported to occur secondary to chronic infectious disease, systemic lupus erythematosus (SLE), lymphocytic plasmacytic synovitis, use of certain drugs, and malignancies. It may also be a component of immune-mediated diseases, such as inflammatory bowel disease or chronic hepatitis.

Clinical signs typically include cyclic fever, lethargy, anorexia and varying degrees of pain, lameness and swollen joints. A stiff gait characterized as "walking on egg shells" is frequently observed, but some affected dogs have a normal gait. The distal joints (carpi and tarsi) are most commonly affected. Pain, redness, and swelling range from severe to absent. Some dogs exhibit pain that is difficult to localize. Others have signs of back or neck pain. This could be a result of inflammation of the vertebral articulations or concurrent meningitis. Lymphadenopathy and muscle wasting can be profound. Nonerosive polyarthritis can be seen in any breed at any age but most commonly occurs in young dogs (between 1 and 6 years of age). The condition appears to be overrepresented in German shepherds, Doberman pinschers, collies, spaniels, retrievers, terriers, and poodles. Specific syndromes involving immune-mediated polyarthritis have been identified in certain breeds of dogs, such as swollen hock syndrome in Shar Peis and arthritis in Akitas.

Infectious disease can cause a secondary immune-mediated polyarthritis as a result of chronic immune stimulation inducing immune complex deposition in the synovial tissue. Diseases frequently associated with secondary immune-mediated polyarthritis include heartworm disease, rickettsial disease such as ehrlichiosis, Rocky Mountain spotted fever, Lyme disease, and others. Chronic bacterial infections such as discospondylitis, pyelonephritis, prostatitis, and endocarditis can also cause a secondary immune-mediated polyarthritis.

Systemic lupus erythematosus is suspected when polyarthritis is accompanied by immune-mediated hemolytic anemia, thrombocytopenia, glomerulonephritis, or immune-mediated dermatopathies. The value of antinuclear antibody (ANAs) testing is controversial. This syndrome is thought to occur more commonly in females and in German shepherds, collies, Shetland sheepdogs, beagles, and poodles.

Lymphocytic-plasmacytic synovitis has been reported most commonly in German shepherds and other large-breed dogs. This condition is thought to be associated with degenerative joint disease, such as arthritis in the stifle joint after rupture of the cranial cruciate ligament. The diagnosis can be confirmed with histologic evaluation of the synovium.

Drug-induced immune-mediated polyarthritis appears to be rare. It has been reported to occur as a result of trimethoprim-sulfadiazine therapy in a group of Doberman pinschers. Immune-mediated polyarthritis has been suspected in some cases after vaccinations (e.g., vaccinations for lyme disease).

Inflammatory joint disease (septic or immune mediated) should be suspected in the following instances (Figure 23-2):

- The dog or cat with joint pain, joint swelling, generalized pain, or reluctance to rise.

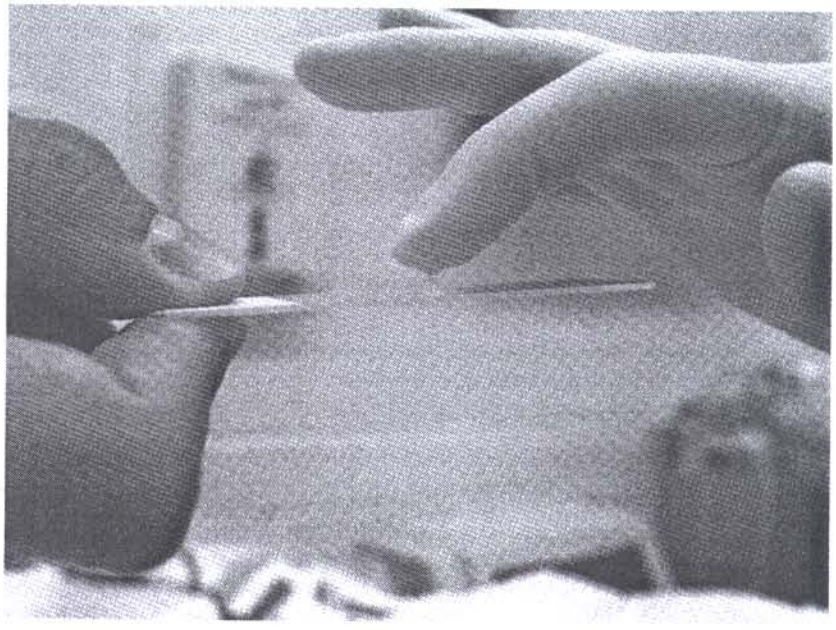


Figure 23-1 A demonstration of the method to grossly assess joint fluid viscosity. A drop is placed on a glass slide. It is gently touched with a fingertip that is then slowly moved away. The reader should note the strand of viscous fluid typical for normal joint fluid viscosity.

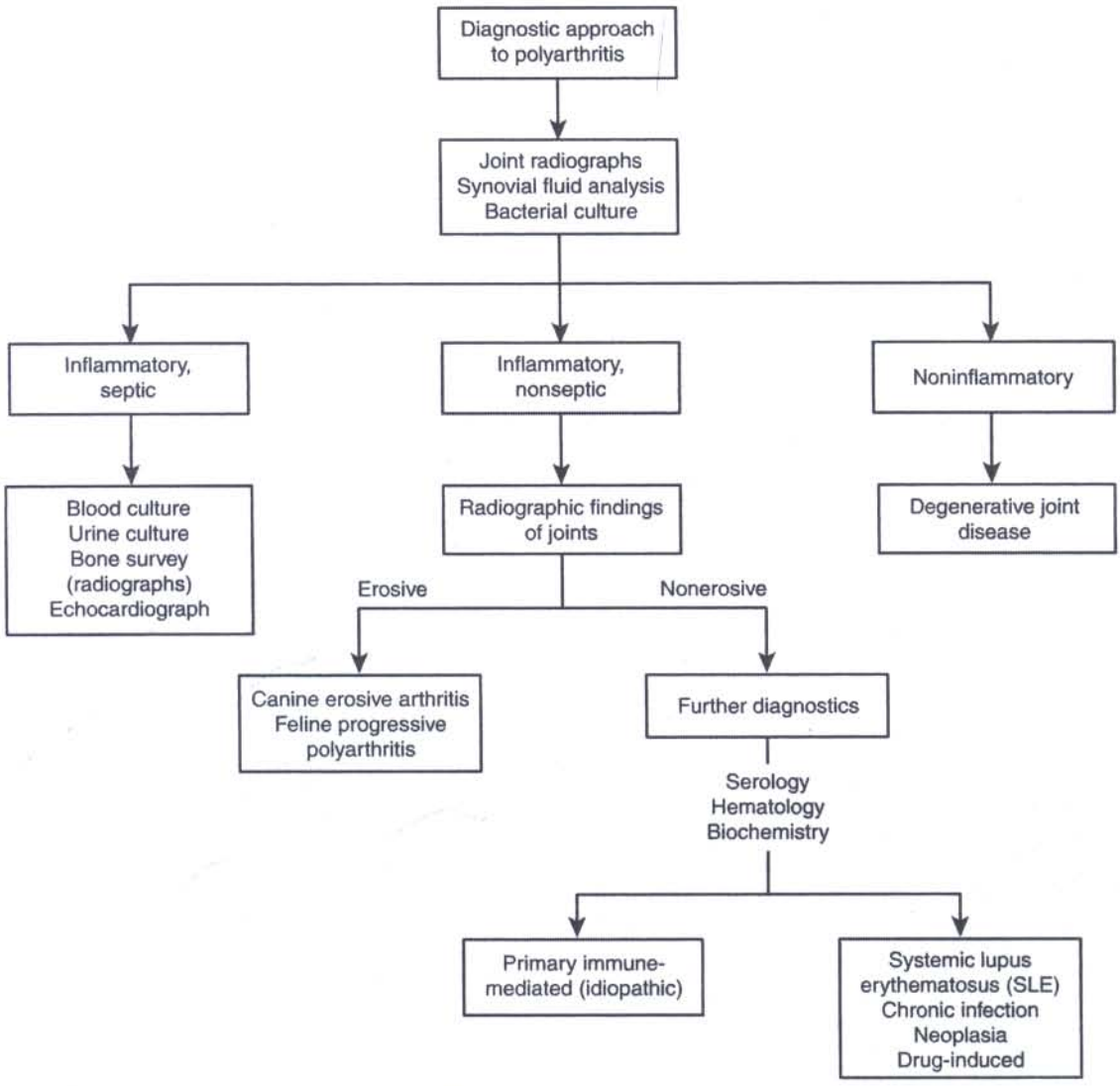


Figure 23-2 Algorithm for diagnostic approach to polyarthritis.

- Joint pain or swelling that is apparent during the physical examination.
- The dog or cat that has abnormalities that could result from a systemic inflammatory condition: fever or leukocytosis.
- When immune-mediated disease is suspected in other organ systems (i.e., immune-mediated hemolytic anemia, thrombocytopenia, steroid responsive sterile meningitis, glomerulonephritis).

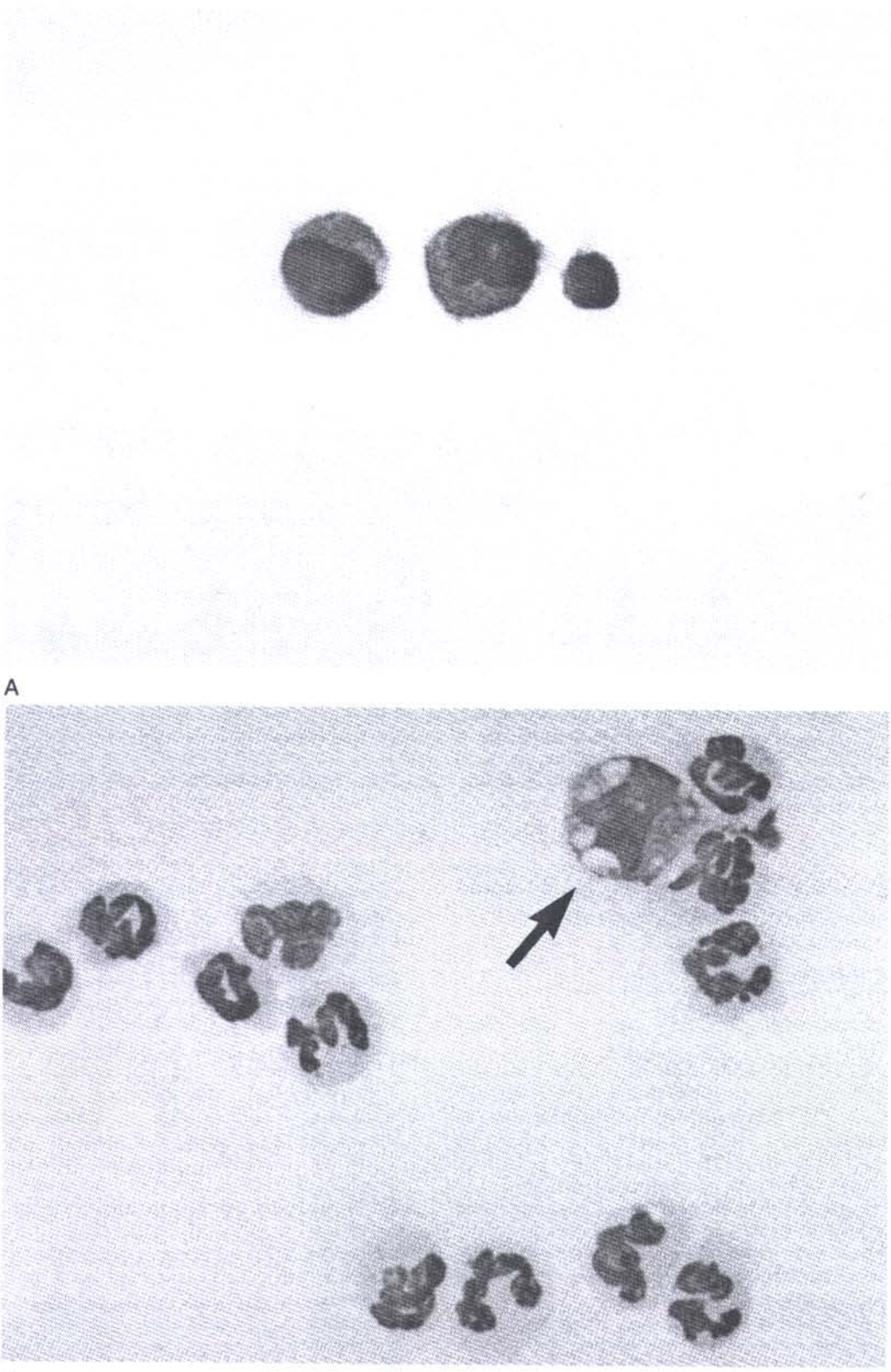
ARTHROCENTESIS AND JOINT FLUID ANALYSIS

Joint fluid analysis is the single most important test performed in the diagnosis of inflammatory arthritis. Joint taps are usually simple to perform and are associated with minimal morbidity or complications (see Chapter 74). Aspiration of synovial fluid (joint taps) and cytologic analysis are necessary to define the involvement of a joint (Figure 23-3). Affected joints, even severely affected, may not appear swollen or painful. Joint taps should also be performed as part of the diagnostic investigation of a fever or leukocytosis of unknown origin or when other immune-mediated disease is suspected. In a recent study, 20% of dogs with a fever of unknown origin had immune-mediated polyarthritis. Unfortunately, the information clinicians can obtain from joint fluid analysis is limited. Increased numbers of neutrophils appear in joint fluid of both septic and immune-mediated arthritis, making the differentiation between the two difficult, and joint fluid cultures are frequently negative even in the obvious presence of bacteria.

Multiple joints should always be sampled, including those that do not appear to be clinically involved in the disease process. It is recommended that both carpi and both tarsi joints be sampled along with at least one elbow and stifle. Hip and shoulder joints are not commonly tapped unless they appear to be diseased.

GROSS EXAMINATION

Fluid from a normal joint is clear, light straw colored and has a sticky viscous feel, forming a strand when a drop is paced between a fingertip and the thumb, which are then slowly pulled apart, or between a glass slide and a fingertip, which is slowly moved away from the slide (Figure 23-1). More than a few drops should not be easily obtained from a normal joint. If the fluid is discolored, turbid, lacks viscosity, or is aspirated in

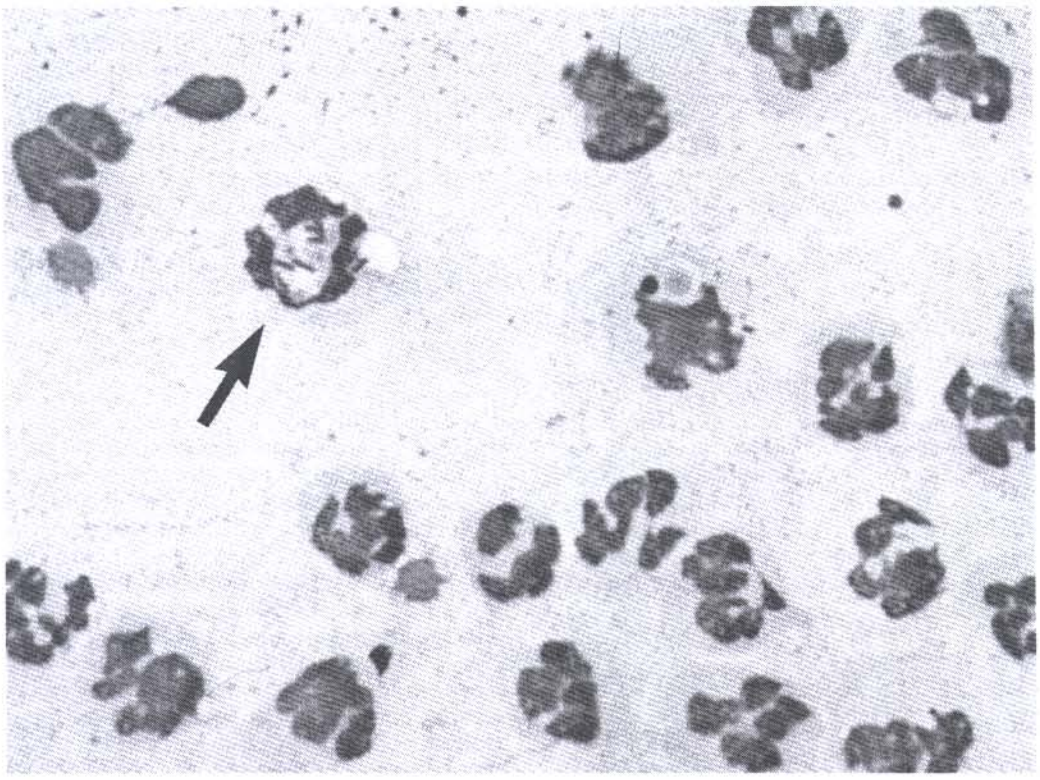


A

B

Figure 23-3 A, Normal: Two quiescent mononuclear phagocytes *(larger)* and a small mature lymphocyte are seen in this low-cellularity direct smear of normal canine synovial fluid. These are the predominant cell types in health in all species. B, Nonseptic arthritis: Numerous well-preserved neutrophils and a macrophage *(arrow)* are seen in this highly cellular direct smear of synovial fluid from a cat with immune-mediated polyarthritis. Neutrophils typically are less than 10% in health.

Continued



C

Figure 23-3, cont'd C, Septic arthritis: Numerous neutrophils and a few red blood cells (RBCs) are seen in this highly cellular direct smear of synovial fluid from a dog with septic arthritis. The reader should note cellular debris in the background and several degenerate neutrophils, including one that contains several bacterial rods *(arrow)*. (Courtesy Dr. Tracy W. French, Dip. ACVP, Cornell University.)

excessive amounts, then joint disease is likely. Blood contamination, only partially mixed in with the joint fluid, may occur.

CYTOLOGIC EVALUATION

Normal joint fluid contains less than 2500 to 3000 white blood cells (WBCs) per milliliter and few red blood cells (RBCs). At least 90% of white cells in normal joints are mononuclear. Inflamed joints (septic or immune mediated) will typically have over 5000 WBCs and over 10% neutrophils. The WBC or neutrophil count can be estimated by multiplying the average number of cells seen in each high-power field by 1000. The presence of bacteria or degenerate changes in the neutrophils is suggestive of septic and not immune-mediated arthritis, as is a positive bacterial culture. WBC counts can be markedly increased with septic or immune-mediated disease processes, approaching 100,000 WBC/ml of joint fluid including over 90% neutrophils.

If sufficient joint fluid is obtained, then additional testing of the fluid is possible, including protein content, glucose concentrations, and a mucin clot test. Clinically these tests are not often performed and are thought to have little additional value if cytology and culture have been performed.

ADDITIONAL TESTING

A minimum data base, including a complete blood count (CBC), a serum biochemistry profile, and a urinalysis is recommended in any dog or cat with suspected inflammatory arthritis. Radiographs of the joint are indicated if septic or erosive arthritis is suspected. A search for possible sources of bacterial infection should be undertaken if septic arthritis is suspected and no obvious penetrating wound or source of infection is evident. This search could include blood and urine cultures, thoracic and abdominal radiographs, and spinal radiographs to identify discospondylitis, abdominal ultrasound, and possibly cardiac echocardiogram for bacterial endocarditis.

If immune-mediated polyarthritis is suspected, then a search for the source of chronic immune stimulation and additional manifestations of immune-mediated disease should be undertaken. The chronic immune stimulation could be a primary immune disorder (idiopathic) or a result of chronic infection, inflammation, or neoplasia. Additional diagnostics in this case could include the previously mentioned testing listed for septic arthritis, a Coombs' test, and serology for ANAs and RF. Serology for exposure to rickettsial agents such as *Ehrlichia* species, *Borrelia*, systemic fungal infections, and for occult heartworm infestation may be indicated, depending on the prevalence in the region and a possible travel history. Positive results of any of these tests must be taken as part of the entire clinical picture. Positive Coombs' test, RF, and ANA are all nonspecific findings perhaps strengthening the possibility of more general immune-mediated disease or SLE. Positive titers to the previously mentioned infectious agents are likely indicative of exposure and not necessarily active disease. In the case of Lyme disease, if the pet has been vaccinated, then Western blot analysis can differentiate between antibodies produced as a result of the vaccine and those produced by natural exposure.

CHAPTER • 24

Body Odors

Karen A. Moriello

Webster's Dictionary defines odor as "*That characteristic of a substance which makes it perceptible to the sense of smell whether it be pleasant or unpleasant.*" From a clinical perspective, the definition of *odor* would have to be expanded to include whether the odor is *normal* or *abnormal*. Whether clinicians realize it or not, the use of smell is an intricate part of the physical examination process. Depending upon the disease process, it can also be involved in the diagnostic, therapeutic, and monitoring process.

PEOPLE, PETS, VETERINARIANS, AND THE BODY ODOR ISSUE

Body odor has a biologic purpose. In general, smell and body odor for all species are important in species recognition, social interactions, and mate selection. In the animal phylum, changes in body odor and pheromones are driven by genetics and evolutionary trends. In the human species, one other major driving force exists—changing social trends. For example, body odor in one era may be considered normal or even desirable but in another deemed socially unacceptable. The issue of environmental odors (i.e., room odors) is almost equally important to people. Manipulation of personal and environmental odors (out of the "unpleasant" and into the "neutral or pleasant" spectrum) is an important social trend (and a commercial industry). Further complicating this issue is the increased recognition that body odor may be an early warning sign of health issues (e.g., fruity apple odor of ketoacidosis as the result of diabetes mellitus or starvation) or a human health hazard (e.g., mold). Veterinarians increasingly have to navigate the issue of "the pet's body odor" with clients. This is difficult at times because the current norm is "pleasant odor" or "no odor." The clinician's task is to determine whether the body odor in question is a sign of disease or whether it is within the realm of normal for the pet in question. If the latter is true, then clinicians must find a way to make the pet's odor more acceptable to the owner.

PATHOPHYSIOLOGY OF BODY ODOR

Body odor in animals varies with species, breed, sex, age, and overall health. In the healthy dog or cat, skin secretions contain insignificant amounts of odorous substances. Skin odor is the result of bacterial decomposition of secretions from sebaceous glands, epidermal lipids, and epitrichial and atrichial sweat glands. Epitrichial glands are present on haired skin just below sebaceous glands and open onto the surface via the piliary canal. These glands are largest and most numerous in mucocutaneous junctions, interdigital spaces, and over the dorsal back and lumbosacral areas. Not surprisingly this is often where odor concentrates in pets. Atrichial glands are located only on footpads. Sweat contains unsaturated fatty acids, ammonia constituents, and their volatile salts. Sebum and epidermal lipids on the skin surface are degraded by lipases of gram-positive bacteria to glycerol and unsaturated fatty acids, which are further metabolized to odorous compounds. It is these by-products that give sebum its antibacterial and antifungal properties. Some of the acids produced by the degradation of these lipids, butyric and caproic acids, are quite volatile and emit a cheesy rancid odor. Oral odor may be associated with systemic illnesses, such as uremia, diabetes mellitus, or periodontal disease. Malodor associated with periodontal disease is due to the production of volatile sulfur components. Oral odors are most often the result of by-products of bacterial metabolism resulting from bacteria colonization of plaque, gingival sulci, and the dorsal surface of the posterior tongue. Oral odors may also be the result of something the pet has ingested (e.g., fecal material).

CLINICAL APPROACH TO THE PROBLEM OF BODY ODOR

The starting point of any medical visit is the owner's complaint. In general, pets with the problem of body odor fall into one of four broad categories (see the following) as determined by the history and physical examination. In the case of body odor, what the clinician simply sees and smells may accomplish the initial sorting. After this, the clinician can then determine how best to proceed (see Box 24-2). In most cases the veterinarian needs to determine if underlying cause is due to a systemic disease, pure dermatologic disease, external factors, or lack of client education.

"Normal pets" are considered to be malodorous by the client but not by the clinician. In general, the clinician's initial assessment is that the pet's body odor is within the normal range for the *species* (e.g., cat owners first acquiring a dog may not be aware of species differences), *age* (e.g., puppies have a unique odor), *sex* (e.g., intact tom cats are more odorous than neutered male cats), *breed* (e.g., hound dogs' odor versus poodles'), *hair length*, etc. Furthermore, a thorough literal "sniff exam" (nose to tail, dorsum to ventrum, feet, and ears) of the patient reveals no unusual odors. Finally, no evidence of a dermatologic or medical disease exists. The *key sorting aspect* of this group is that the veterinarian considers the animal to smell normal, and no history or physical evidence of illness or skin disease exists. In these situations, client education and suggestions for bathing routines that are tolerable and safe for the pet are indicated.

The clinician should be aware of two subsets in the normal pet group. The first is a subset of normal pets with owners who complain of odors that "come and go." In these situations the cause may be anal sac expression, something the dog ate (e.g., onions, garlic), flatulence, "wet dog" smell, a change in the dog's regular dog food (some specialty diets, especially fish

based, cause the dog to "smell fishy"). In warm weather, many dogs will drool excessively, and this will mat the haircoat around the face, chest, and forelegs, leading to an offensive odor. Warm weather often results in increased moisture on the skin, and this can lead to bacterial degradation and odor. In addition, many owners of dogs with allergic skin disease report acute episodes where the skin becomes warm, the dog "literally sweats" and then is very odorous.

The second subset includes those pets that smell normal to the clinician, but the owner reports that there has been a change in how the dog smells. It is critical to carefully examine these patients for evidence of subtle signs of skin disease because these owners may be reporting a valid finding. A recent study found that 86% of owners that were blindfolded and only allowed to use their sense of smell were consistently able to differentiate their dog's body odor from that of another simply by sniffing a blanket. This finding amazed both owners and investigators. What is pertinent to veterinarians is that owners may very well "know" what their dog smells like when it is normal and when it is not.

Malodorous Pet with an Obvious Cause

These are patients with unmistakable odor from urine, feces, skunk, flatulence, and "I rolled in the compost heap" odors. This group could also include the pets with obvious skin or medical problems, where the source of the odor (infected fracture, ears, seborrheic skin, pyotraumatic dermatitis, and so on) is easily found. Animals with severe halitosis are also included here (Box 24-1). The *key sorting aspect* of this group is that the clinician immediately knows where the odor is coming from, what is causing it, what needs to be done to eliminate it, and whether or not further medical or dermatologic diagnostics are needed. In these situations, client education may be as simple as recommendations on how to remove the odor (e.g., skunk) or more complicated discussions on the need to treat existing infections and perform appropriate diagnostic tests to investigate the underlying cause.

Malodorous Pets with Obvious Systemic Illnesses

These are patients that are malodorous, but more importantly are systemically ill. This might be determined by historical or physical examination findings (or both); changes in body odor might have been what prompted the client to finally bring the animal for examination. The *key sorting aspect* of this group is an obvious state of ill health associated with the body odor. In general, cats rarely are presented for the problem of body odor. When they are, it is usually for one of three reasons. First, a strong odor emanates from an ear, mouth, or body region. This should prompt the clinician to look for infections, injuries, neoplasia, myiasis, etc. Second, the cat is soiling itself with urine, feces, or both or not removing it from the haircoat. This could be for any number of reasons, such as physical inability to groom (e.g., obesity, arthritis) or neuromuscular injury. Third, the cat could just be generally odorous to the client. These cats usually have stopped grooming themselves, and their haircoat is matted or greasy. This situation should prompt the clinician to look for a systemic illness (e.g., hyperthyroidism, diabetes mellitus, neoplasia). Dogs with systemic illness may be mildly or severely malodorous. Mild odors are usually caused by concurrent skin infections triggered by debilitation. The skin odor in these patients usually is not noticeable to the clinician until the dog is physically examined. Severely odorous dogs almost always have the odor localized to one area (e.g., mouth odor caused by uremia), a site of injury and infection (open fracture with secondary infection), or excrement on their haircoat because of some cause of immobility. In these situations, client education must focus on a need to aggressively pursue the cause of the illness, whereas the odor issue is addressed as part of the therapy for the health and well-being of the patient (e.g., treatment of urine or fecal soiling).

Box • 24-1

Common Causes of Halitosis in Dogs and Cats*

Oral Diseases
Periodontal disease (gingivitis, periodontitis, abscessation)
Neoplasia (melanoma, fibrosarcoma, squamous cell carcinoma)
Foreign body or trauma (fractures, electrical cord injury)
Pharyngitis
Stomatitis, lymphocytic-plasmacytic feline stomatitis

Respiratory Diseases
Rhinitis and/or sinusitis
Neoplasia
Pneumonia or pulmonary abscess

Dermatologic Diseases
Lip fold pyoderma
Ulcerative mucocutaneous pyoderma
Feline or canine eosinophilic granulomas
Pemphigus complex, bullous pemphigoid, lupus erythematosus
Drug eruptions
Cutaneous lymphoma
Exposure to dimethyl sulfoxide (DMSO)

Metabolic Diseases
Renal failure/uremia
Diabetic ketoacidosis

Gastrointestinal Diseases
Megaesophagus
Inflammatory bowel disease
Exocrine pancreatic insufficiency

Neoplasia
Constipation (cats)

Dietary
Aromatic foods (onions, garlic)
Fetid foodstuffs (e.g., ingestion of carrion)
Coprophagy

Grooming Behavior
Anal sacculitis
Vaginitis/balanoposthitis
Lower urinary tract infections

*Adapted from *Veterinary Guide to Odor and Disease, The Oral Cavity and Dermatology*, Veterinary Learning Systems, 1997.

Malodorous Pets with Skin Disease

Without a doubt, most obviously odorous animals will fall into this group. For the vast majority of patients, the *key sorting aspect* of this group is an otherwise healthy pet with a history of skin disease, blatantly obvious skin disease, skin disease found during the examination, or a combination of

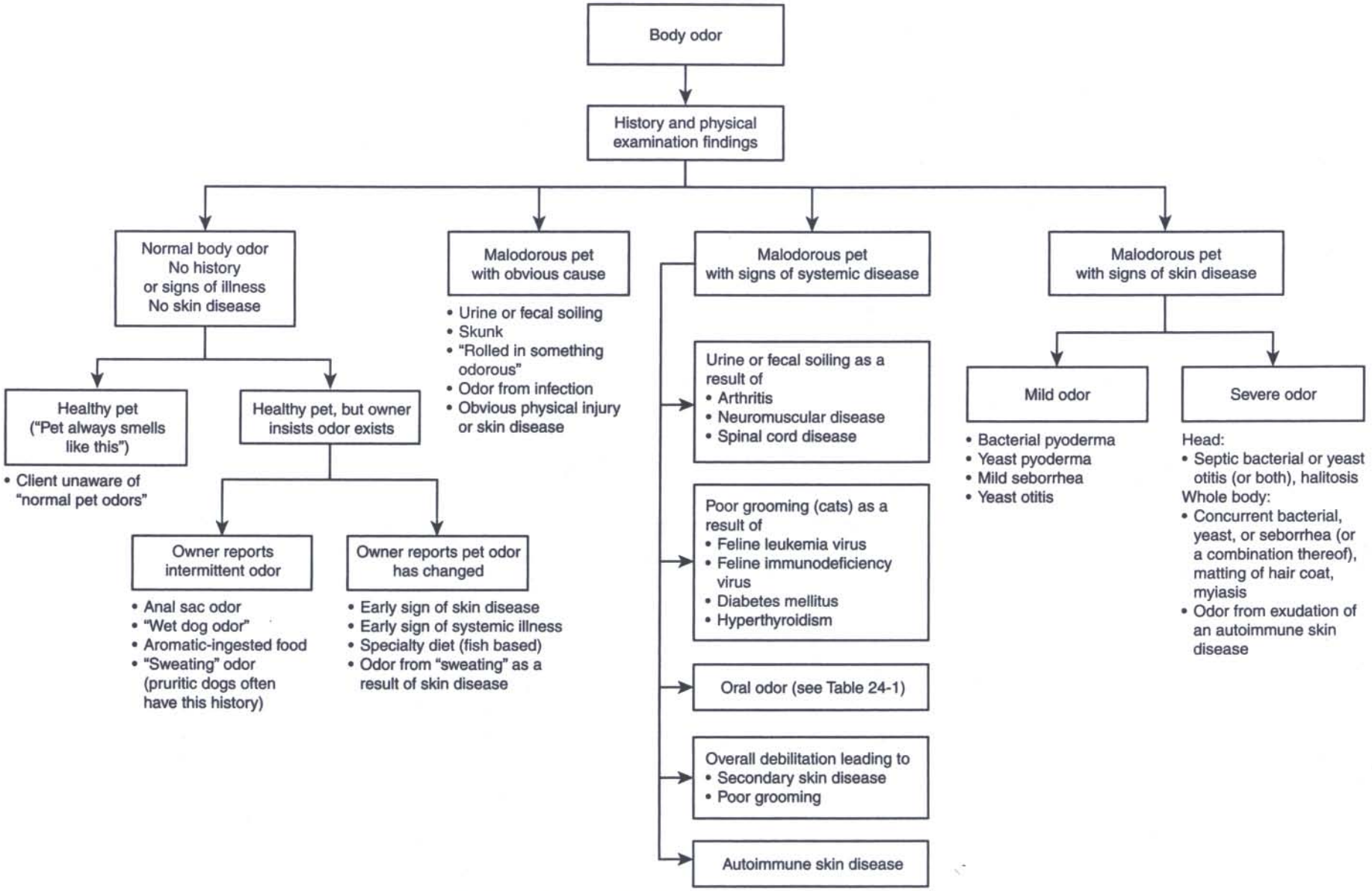


Figure 24-1 Algorithm for presenting complaint of body odor.

Box • 24-2

General Recommendations for Control of Odor

Normal Pets without Skin Disease
- Client education for the owner.
- Keep the haircoat short; no feathering haircuts.
- Clip hair from inner pinnae.
- Avoid cloth dog collars that can become impregnated with the pet's body odor.
- Bathe pet in a veterinary hypoallergenic shampoo only as often as to keep odor free.
- Dry pet after exposure to rain or after swimming to avoid wet-dog smell.
- Use veterinary coat deodorizers only.

Skunk Odor
- Liberal application of "Skunk Off"
- Keep pet dry to prevent reemergence of skunk odor (it may take several weeks for the odor to dissipate completely).

Urine, Fecal Matter, and Odors Associated with "Rolled in Something Dead"
- Clip any mats from haircoat.
- Bathe pet in grooming or flea shampoo first to remove gross debris, and rinse well.
- Bathe a second time in a degreasing shampoo such as benzoyl peroxide; odors are often held in skin and hair lipids.

Pets with Odor and Skin Disease
- Complete appropriate diagnostics, and begin appropriate systemic therapy.
- Administer appropriate sedation, analgesia, or anesthesia, if needed.
- Clean or flush ears as needed.
- Grooming recommendations:
  - —Clip haircoat from inner ear pinnae and around ears, if necessary.
  - —Clip hair mats and areas of lip fold pyoderma.
  - —Clip haircoat of medium- or long-haired dogs.
- Bathing recommendations:
  - —Always prebathe pet with grooming or flea shampoo to remove gross debris before using a medicated shampoo; rinse well (this step facilitates efficacy of medicated-shampoo product).
- Bathe pet in antimicrobials or antiseborrheic shampoo (it may work best if the client alternates between two shampoos).
- Severely odorous pets should be bathed daily until client deems pet acceptable.
- Most pets require two to three baths per week during medical treatment.
- Warnings:
  - —Some shampoos are irritating; do not use if pet seems uncomfortable after use.
  - —If haircoat becomes excessively dry, decrease frequency of bathing.
  - —Dogs with primary seborrhea will require aggressive bathing for life to control disease and odor.

these factors. When working with these patients, the clinician should remember several key points:
- The most common causes of body or ear odor is almost always some combination of bacterial pyoderma, *Malassezia* pyoderma, and seborrhea (usually oily).
- Many of these patients are severely pruritic. The pruritus is most likely caused by a combination of the microbial infections, inflammatory degradation products of oily seborrhea, the presence of an underlying pruritic disease (e.g., atopy), or a combination of these factors.
- The duration of the skin problem, presence or absence of underlying primary seborrhea, and severity of the skin infections (superficial or deep) mostly determine the severity of the odor. Other factors such as length of the haircoat, presence or absence of hair mats, and exposure to moisture can also affect the severity of the odor.
- The odor will most likely resolve with appropriate systemic and topical treatment of the superficial microbial infections and seborrhea; it may or may not return. This depends on whether the underlying trigger of microbial infections is still present, whether the patient has a previously undiagnosed primary disorder of keratinization, and whether the pruritus has resolved. If not, the return of the body odor is almost guaranteed because it will trigger secondary microbial infections and seborrhea.
- Recurrent otic or skin odor always means an underlying skin disease is present. Whether or not diagnostics beyond skin scrapings, flea combing, skin and ear cytology, and possibly a fungal culture are indicated in malodorous pets with skin disease depends on the patient's history and physical examination.

Note: A subgroup of malodorous pets exists with skin disease and signs of systemic illness (e.g., anorexia, persistent or waxing and waning fevers, depression, reluctance to walk, weight loss, dehydration). This triad (odor, skin disease, illness) should alert the clinician to the possibility that the patient has a severe life-threatening condition such as deep pyoderma with or without demodicosis, drug reactions, immune-mediated diseases, deep fungal infections with cutaneous manifestations, or toxic epidermal necrolysis. An immediate aggressive dermatologic evaluation is needed: skin scrapings, bacterial cultures, impression smears of exudate, and skin biopsy, in addition to appropriate medical diagnostics and supportive care pending diagnosis.

CHAPTER 25

Ocular Manifestations of Systemic Disease

David J. Maggs

Clinicians tend to consider the eye and adnexa as unique structures that are dissimilar to nonocular tissues. This can lead to omission of the ophthalmic examination in patients with systemic disease or omission of the general physical examination in patients presented with ophthalmic disease. In fact, the eye is a complex aggregate of tissues with marked anatomical and functional similarities to tissues found in most other organ systems. Viewed in this manner, the eyes provide a unique opportunity for direct observation of tissue types that are otherwise not visible without invasive techniques or special instrumentation.

The major correlations between ocular and nonocular tissues are summarized in Table 25-1. This table identifies ocular tissues that should be examined carefully in animals with systemic disease and nonocular tissues that should be examined in those with ocular disease. For example, in a dog or cat with generalized lymphadenopathy, the conjunctiva, third eyelid gland, and uveal tract should be closely examined because they are also composed of lymphoid tissue. Likewise, a thorough general physical examination of the pet with retinal disease may reveal more widespread vascular, neurologic, or hematologic disease.

The following is a description of specific ocular conditions, arranged by affected ocular tissue, often associated with systemic disease. This chapter highlights the correlation between ocular and systemic tissues. It does not provide an exhaustive description of the diagnostic approach or therapies.

SURFACE OCULAR DISEASE

The eyelids, conjunctiva, cornea, and sclera are intimately related, physiologically and anatomically. They provide a protective surface for the eye, and all three tissues are susceptible to the same insults that cause surface (dermatologic) disease elsewhere. Therefore a thorough dermatologic history and a complete dermatologic examination may be helpful in animals with surface ocular disease. The diagnostic approach to lesions involving eyelids, conjunctiva, or cornea is identical to that used for skin. It includes incisional or excisional biopsy, scrapings, and viral, fungal, chlamydial, and mycoplasmal or bacterial culture.

Ocular surface tissues may also be affected as "innocent bystanders" in more serious orbital disease or intraocular conditions such as uveitis or glaucoma. Retropulsion of the globe and thorough intraocular exam with measurement of intraocular pressure (IOP) will identify such animals.

Table 25-1

Correlations between Ocular and Nonocular Tissues

Tissue Type	Visible Ocular Correlates
Mucous membrane	Conjunctiva
Vascular tissue	Conjunctiva, uvea, retina
Neural tissue	Retina, optic nerve
Lymphoid tissue	Uvea, conjunctiva, third eyelid
Glandular tissue	Meibomian glands, conjunctival goblet cells, third eyelid gland
Connective tissue	Sclera, cornea
Smooth muscle	Iris, upper eyelid (Muller's muscle), third eyelid
Interstitial space	Anterior chamber, subretinal space, vitreous
Hematologic	Conjunctiva, uvea, retina

Eyelids

Although blepharitis may represent more widespread dermatitis, special consideration should be given to unique palpebral anatomy. Meibomian glands are specialized sebaceous glands that can be primarily infected; particularly with *Staphylococcus* and *Demodex* spp. Altered immune responses can exacerbate clinical signs at this site. Immunodeficiency may encourage colonization by organisms such as dermatophytes or *Demodex* spp., whereas an exuberant immunologic response such as hypersensitivity to *Staphylococcus* spp. may cause more severe inflammation. Eyelid margins represent a clearly visible mucocutaneous junction that could be involved in primary immune-mediated dermatitis such as the pemphigoid diseases or systemic lupus erythematosus (SLE). Other immune-mediated diseases such as vasculitis or uveodermatologic syndrome (also known as Vogt-Koyanagi-Harada [VKH] or VKH-like syndrome) may also be more obvious or more severe in periocular skin.

Altered lid position, with or without altered pupil size or globe deviation can also represent central, peripheral, or disseminated neurologic disease, specifically dysfunction of cranial nerve (CN) III or VII or decreased sympathetic tone (Horner's syndrome). Clinical localization of the lesion or lesions is important, particularly for Horner's syndrome—the triad of enophthalmos (with protrusion of the third eyelid), ptosis, and miosis. Because of the circuitous, three-neuron route by which sympathetic neurons course from the hypothalamus to the eye, Horner's syndrome can result from disease involving the brain, spinal cord, brachial plexus, thorax and mediastinum, neck, temporal bone and tympanic bulla, or orbit. Diagnostic procedures should be directed at each specific area to eliminate definitive causes. However, even with intensive diagnostic testing, approximately 50% of cases of Horner's syndrome are idiopathic and usually resolve within 2 months.

Conjunctiva

Conjunctival disease is seen alone, with blepharitis or keratitis, or may reflect inflammation of deeper structures such as the sclera, meibomian glands, orbital contents, third eyelid gland, or intraocular tissues. The rich vascularity of conjunctiva and

its almost transparent epithelium also make it an excellent site for detection of hematologic (cyanosis, anemia, icterus) or vascular disease.

Feline herpesvirus (FHV-1) and *Chlamydophila felis* (formerly *Chlamydia psittaci*) are primary conjunctival pathogens of cats. Although cats undergoing primary FHV-1 exposure generally demonstrate concurrent signs of upper-respiratory infection, cats infected with *C. felis* and those undergoing a recrudescent FHV-1 episode may demonstrate few or mild nonocular clinical signs. Despite an apparent lack of systemic signs, recent evidence confirms that cats harbor and shed *C. felis* from nonocular sites. Studies also suggest that systemic therapy is more effective than topical therapy at decreasing clinical signs and shedding of *C. felis*.

Conjunctivitis in dogs is usually not associated with systemic disease. Ligneous conjunctivitis is an uncommon but important exception. This is a chronic, membranous conjunctivitis in which gross thickening of conjunctiva occurs bilaterally. Younger, female Doberman pinschers may be predisposed. Other mucous membranes may also be involved, and the majority of affected dogs also have evidence of upper-respiratory or urinary tract disease. Histology reveals a characteristic amorphous, eosinophilic hyaline material throughout the subconjunctiva.

Cornea and Sclera

Corneal clarity is important for normal vision. Attentive owners may often note early or subtle corneal pathologic changes. Although altered corneal appearance may represent primary keratitis or intraocular disease (particularly uveitis or glaucoma), corneal opacification that begins at or is most notable at the limbus is often an indicator of systemic disease. For example, lymphosarcoma (LSA) tends to cause a homogenous, creamy-pink discoloration of the peripheral corneal stroma. Corneal lipidosis is an important differential diagnosis in these cases and may occur secondary to any disease causing systemic hyperlipidemia. Hypothyroidism is one of the most common causes; however, hyperadrenocorticism, diabetes mellitus, and familial hypertriglyceridemia should also be considered. Serum triglycerides and cholesterol should both be assessed in animals with corneal lipidosis. Rarely, corneal opacification in dogs or cats will be caused by mucopolysaccharidosis.

Although hyperadrenocorticism and diabetes mellitus are associated with prolonged corneal wound healing, dogs with diabetes mellitus have also recently been shown to have significantly decreased corneal sensitivity relative to normal dogs. This may represent a manifestation of diabetic neuropathy, making dogs less likely to blink and produce reflex tears to protect their corneas. In addition, multiple growth factors are transferred to the cornea by sensory nerves, and these are likely to be reduced in such dogs. This likely contributes to the poor wound healing observed in these pets. Therefore therapy and monitoring of corneal disease, especially ulceration, should be more intense in diabetic dogs.

Keratoconjunctivitis Sicca

Decreased aqueous tear production with subsequent keratoconjunctivitis sicca (KCS) is common in dogs but uncommon in cats. In dogs it is usually caused by idiopathic lymphocytic-plasmacytic dacryoadenitis. Rarely, cats or dogs with KCS have immune-mediated destruction of the salivary glands and associated xerostomia (Sjögren's-like syndrome), sometimes clinically apparent as dysphagia. KCS in association with xeromycteria (dry nose) should prompt investigation of neurogenic KCS caused by damage to afferent or efferent pathways of lacrimal innervation. Lacrimal stimuli are transmitted by CN V, and efferent (parasympathetic) fibers are carried first by CN VII and peripherally by CN V. Because these same neural pathways are involved in the production of moisture for the nasal mucosa, ipsilateral xeromycteria evidenced by a dry crusty nostril may be seen. Diagnostic efforts should be directed at disease processes along the paths of CN V and VII, particularly in the region of the tympanic bullae.

KCS may also occur as a result of drug therapy. Drugs incriminated in decreased tear production include systemically or topically administered atropine, systemically administered sulfa drugs, etodolac, and general anesthesia within the preceding 2 days. Dogs with marginal tear production before administration of these drugs, and those weighing less than 12 kg (in the case of trimethoprim sulfa), appear to be at increased risk of developing KCS. Dose and duration of therapy are less relevant. Restoration of tear production and corneoconjunctival health does not always occur upon discontinuation of the offending drug; therefore Schirmer tear test (STT) results should be monitored before and during therapy.

Finally, KCS may occur as a component of systemic disease but may be overlooked unless a STT test is performed. Systemic infection with canine distemper virus (CDV) or FHV-1 is associated with usually transient KCS. Dysautonomia (Key-Gaskell syndrome) can cause bilateral reduced aqueous tear secretion, nonresponsive dilated pupils, and protrusion of the third eyelids. Associated systemic signs of autonomic dysfunction including urinary and fecal incontinence, bradycardia, hypotension, dysphagia, and dry nose are usually more noticeable than the ocular signs; however, ocular signs may help to confirm the diagnosis. Association between hypothyroidism and KCS has not been substantiated by recent studies.

UVEAL TRACT

Uveal pathology is commonly seen with systemic disease. The uveal tract includes the iris, ciliary body and choroid and is the major vascular supply for the avascular components of the eye (cornea, lens, outer retina). It is composed of a large network of arterioles, venules, and fine capillaries and therefore is a sensitive indicator of vascular or hematologic conditions, such as vasculitis, hypertension, anemia, and hyperviscosity (see Fundus). Loss of vascular integrity may be apparent in the anterior chamber as breakdown of the blood-aqueous barrier. This appears differently, based on the extent of breakdown and the presence or absence of inflammatory mediators within the anterior chamber and surrounding tissues. With minimal breakdown, albumin and other small serum proteins are detectable in the anterior chamber as aqueous flare. The aqueous humor may be thought of as a directly visible area of interstitial space, and if serum contents are seen within this space, the possibility of similar plasma "leakage" in other less visible nonocular interstices should also be considered.

Detection of aqueous flare requires that a beam of light emanating from a bright and focal source be viewed transversely, preferably with some magnification, as it traverses the anterior chamber. This examination should be done with dim ambient light. A slit lamp biomicroscope provides the optimum combination of these conditions; however, a direct ophthalmoscope turned to the smallest spot of light and held within 1 cm of the corneal surface provides a focal light source and can be used in general practice to detect flare. By definition, albumin, and therefore aqueous flare, will be approximately evenly distributed throughout the anterior chamber. Cellular debris (hyphema, dispersed white blood cells [WBCs], or hypopyon) or larger proteins, particularly fibrin in the anterior chamber suggests more major vascular compromise or potent, cytokine-mediated extravasation of cells. These blood constituents are more likely to settle into the ventral anterior chamber. Depressing the pet's nose so that

the eyes are elevated within the orbits will often assist in seeing this region.

Fine uveal capillary beds can act as a biologic "filter" that traps organisms, particularly fungi, or metastatic neoplastic cells. It is frequently involved in systemic infectious disease or as a site of metastatic neoplasia. The uvea also contains the major intraocular lymphoid tissue and is therefore a common site for LSA. It is also frequently involved in specific or nonspecific ocular inflammatory responses (uveitis) that may reflect broader immunopathology such as infectious or neoplastic disease. The list of organisms that have been associated with uveitis is expanding and is somewhat species specific. In cats, feline infectious peritonitis (FIP), feline immunodeficiency virus (FIV) (principally a retinochoroiditis), feline leukemia virus (FeLV) (principally via LSA), *Toxoplasma gondii*, Mycobacteria, and the systemic mycoses (principally a chorioretinitis) have traditionally been associated with uveitis. More recently, intraocular detection of other organisms such as FHV-1, *Bartonella* spp., and some *Ehrlichia* spp. has led to suggestions that these organisms also warrant consideration as causative agents in feline uveitis. Despite this expanding list of differential diagnoses and thorough diagnostic testing (sometimes including enucleation and histopathology), a definitive cause of uveitis is not identified in 50% to 70% of affected cats.

The list of infectious organisms causing uveitis in dogs includes fungal organisms, *Leishmania donovani*, *Ehrlichia platys* or *canis*, *Rickettsia rickettsii*, *Brucella canis*, *Toxoplasma gondii*, Canine adenovirus, and *Leptospira* spp. In addition, dogs appear to be more susceptible to immune-mediated uveitis than cats. One example is lens-induced uveitis, in which lens proteins leak from a cataractous or ruptured lens and overwhelm normal immune tolerance of these proteins. Another example is uveodermatologic (VKH-like) syndrome in which the immunopathology is directed at melanocytes throughout the body. Because of the preponderance and visibility of melanin-containing cells in the uveal tract and skin, clinical manifestations of disease in these two tissues are most dramatic.

It is incorrect to suggest that the clinical appearance of uveitis can be used to determine a definitive cause. However, noting whether the uveal inflammation appears more cellular or granulomatous, blood tinged, or proteinaceous may help prioritize diagnostic efforts (Figure 25-1).

Finally, the iris (anterior uvea) forms the pupil and therefore often provides clinical evidence of neurologic disease. Pupillary abnormalities suggestive of systemic disease include feline "spastic pupil syndrome" in which intermittent periods of anisocoria are seen without obvious iridal or afferent neurologic defects. Most cats are FeLV positive or become so soon after diagnosis but may not have other systemic signs of infection when pupil abnormalities are noted. A virally induced neuropathy of CN III is suspected. Pupilomotor abnormalities with normal vision and without ocular inflammation are also seen with dysautonomia (mydriasis) and Horner's syndrome (miosis).

LENS

The two most common conditions affecting the lens are cataract and lens dislocation (subluxation or luxation). Lens dislocation usually occurs secondary to severe intraocular disease, particularly uveitis, which may be a sign of systemic disease. Although lens dislocation may also occur as a primary event in predisposed dog breeds such as terriers, these pets do not have evidence of the generalized connective tissue disorders seen in some humans.

Although the majority of canine cataracts are hereditary in origin, almost all dogs with diabetes mellitus will develop cataracts within 12 months of diagnosis. By contrast, the most common cause of feline cataracts is uveitis. Cats with diabetes rarely develop cataracts. Other systemic causes of cataracts include altered nutrition (especially orphan animals raised on milk replacement products), hypocalcemia with or without hyperphosphatemia (as seen with hypoparathyroidism), electric shock, lightning strike, and senility.

FUNDUS

The ocular fundus is not a single structure. Rather, it is a collective term describing all structures in the posterior portion of the globe that can be viewed with the ophthalmoscope. Visible structures will vary but may include retinal pigment epithelium (if pigmented), neurosensory retina, optic nerve head, retinal vasculature, sclera, tapetum, or choroid. The fundic examination therefore provides a unique opportunity to directly visualize a large cranial nerve (optic nerve), sensitive neural tissue (retina), large venules and arterioles (retinal vessels), and a massive capillary bed (choroid). For this reason, a fundic examination should be performed in all animals with systemic disease.

The choroid is perhaps the fundic tissue most commonly affected in animals with systemic disease. Because of its position immediately subjacent to the retina and its critical role in retinal nutrition and function, signs of choroidal disease are frequently first noted once they affect the retina. The classic example is retinal detachment, which may be caused by primary retinal disease but frequently reflects choroidal effusion. As a result of these close anatomic and physiological relationships, the terms *chorioretinitis* and *retinochoroiditis* are used to reflect inflammation of these two tissues. The difference between these two terms is subtle, with the intent that the first-mentioned tissue is the one believed to be primarily involved. For example, the systemic mycoses have a predilection for the choroid and so cause a marked chorioetinitis. By contrast, CDV targets neurologic tissue in general and, within the eye, retinal tissue specifically. Insults to the subjacent choroid usually also occur, and the disease is typically referred to as a *retinochoroiditis*.

Optic Nerve and Retina

Although primary dysfunction of the optic nerve or retina occurs, altered appearance of these tissues often represents disease of the adjacent central nervous system (CNS) or subjacent choroid (see Uveal Tract). Optic neuritis and retinitis may therefore reflect more widespread meningoencephalitis or uveitis. Causes include infectious agents (CDV, systemic mycoses, or *Toxoplasma gondii*), immune-mediated diseases such as granulomatous meningoencephalitis, or neoplasia involving the CNS, meninges, orbit, or choroid. Diagnosis frequently involves cerebrospinal fluid (CSF) analysis and advanced imaging. Optic nerve edema without hemorrhage, exudates, or blindness is termed *papilledema* and is seen in association with increased intracranial pressure. Therefore fundic examination is recommended in all animals suspected of having CNS disease, especially when a CSF tap is planned.

Taurine deficiency in cats has been associated with retinal degeneration that begins as a focal rhomboid area of subtle increased granularity of the area centralis, progresses to involve retina on both sides of the optic papilla, and ultimately affects the whole retina. Affected cats should also be screened for dilated cardiomyopathy. This syndrome is sometimes called *feline central retinal degeneration* (FCRD) because abnormal dietary or tissue taurine concentration is not always established.

Sudden acquired retinal degeneration (SARD) describes a rapid onset of complete blindness in middle-aged to older

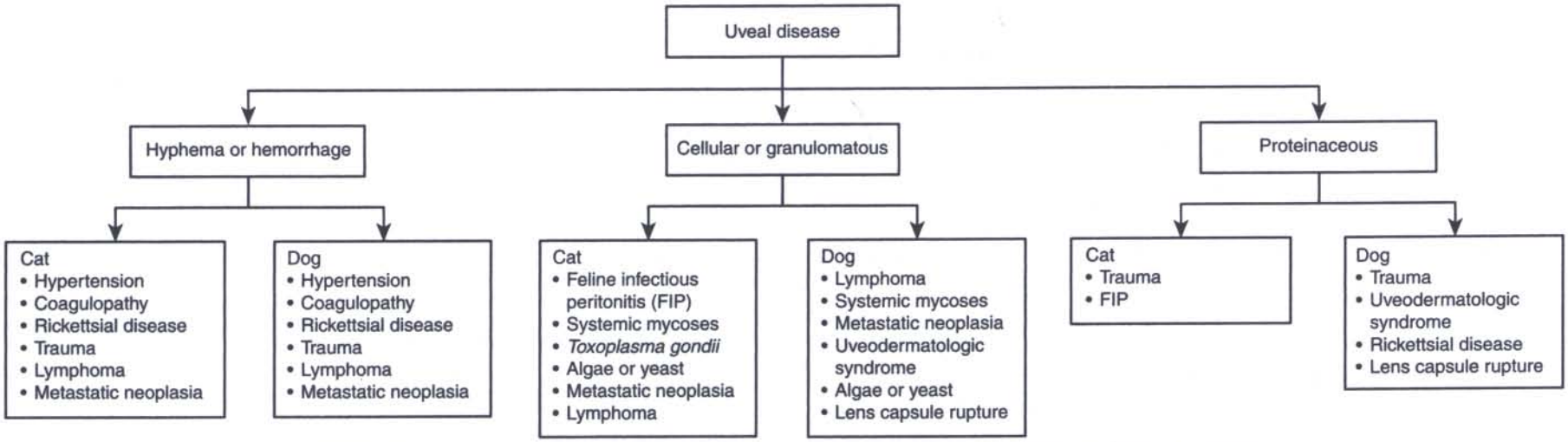


Figure 25-1 The nature of the exudates in patients with uveitis can be used to prioritize differential diagnoses.

dogs with initially normal fundic examination findings. Generalized retinal degeneration becomes clinically evident within 4 to 6 weeks of blindness. Complete and irreversible loss of photoreceptor function takes place without any clinically or histologically detectable inflammation. Female dogs appear overrepresented and many are moderately overweight. Many have a history suggestive of hyperadrenocorticism and some may have clinical signs, blood work, or both that support the diagnosis. The cause of the apparent hyperadrenocorticism is unknown, but unlike the vision loss, systemic signs typically resolve without treatment. This disease must be differentiated from blindness as the result of optic nerve or CNS disease (particularly a functional pituitary tumor with blindness secondary to pressure effects at the optic chiasm). This can be accomplished with advanced imaging under general anesthesia; however, it is completed more simply, safely, and inexpensively by demonstrating an extinguished electroretinogram in the dog with SARD. Sight is never regained; however, owners should be reassured that this is a nonpainful disease that does not involve other ocular tissues.

Vascular and Hematologic Disease

Direct visualization of retinal (and sometimes choroidal) blood vessels permits assessment of many hematologic abnormalities, including anemia (where obvious attenuation or paleness of vessels exists), hyperlipidemia (where retinal vessels take on a creamy orange hue), and hyperviscosity (where increased vessel tortuosity sometimes is noted). Anemia, hyperviscosity, and systemic hypertension also alter tissue perfusion and vessel wall viability and can be associated with segmental vascular constriction and sacculations of retinal vessels (so-called "box-carring"), "sludging," and extravasation of blood or plasma into the choroid, retina, and subretinal space. This is clinically apparent as intraretinal or subretinal edema or hemorrhage or as retinal detachment. Some hypertensive cats also have iridal aneurysms and hyphema. A recent retrospective study of hypertensive cats established that concurrent chronic renal failure, hyperthyroidism, diabetes mellitus, hyperaldosteronism, and cardiac or neurologic abnormalities were common; however, the majority of cats with systemic hypertension are brought to veterinarians after owners observe apparent vision loss.

CHAPTER • 26

Acute Vision Loss in Small Animals

Teresa R. Tucci-Prošek

Vision loss is seldom truly acute; more commonly it is a sudden recognition of blindness in a pet by the owner. Multiple lesions in the visual system and central nervous system (CNS) can result in bilateral blindness. Acute vision loss is more apparent to the owner compared with progressive vision loss. Gradual vision loss enables the dog or cat to acclimate and memorize its surroundings. Many times the owner may not realize their pet is blind until an abrupt change takes place in the pet's environment, such as rearranging the furniture or moving the pet to another location. The goal of this chapter is to provide the proper guidelines for a comprehensive ophthalmologic examination, which enables the veterinarian to accurately assess acute vision loss in a dog or cat. (Please see Figure 26-1 in the e-dition.)

ABNORMALITIES RESULTING IN BLINDNESS

Blindness is a bilateral functional complete loss of vision to which attributing causes are numerous. Three categories are listed in the initial approach to locate a lesion that has caused blindness:

1. Lesions interfering with formation of an image onto the retina
2. Lesions preventing transmission of an image (peripheral → central)
3. Lesions inhibiting image interpretation (central)

Lesions limiting the formation of the image onto the retina are caused by the absence of a normally clear ocular media (cornea, aqueous humor, lens, and vitreous humor). Disruption of this media results in varying degrees of blindness (Boxes 26-1 and 26-2). Lesions affecting the retina and its ability to transmit

Box • 26-1

Ocular Media Abnormalities Causing Blindness

Cornea
- Edema (glaucoma, endothelial dystrophy, immune-mediated keratitis such as keratouveitis caused by canine adenovirus-1, neurotropic keratitis, trauma)
- Cellular infiltrate (bacterial, fungal, viral)
- Vascular invasion (exposure keratitis)
- Fibrosis (scar formation)
- Dystrophies (lipid, genetic)

Aqueous Humor
- Fivrin (anterior uveitis—numerous causes)
- Hyphema (trauma, neoplasia, blood-clotting deficiencies)

Lens
- Cataracts (genetic, nutritional, metabolic/diabetic, toxic, traumatic)

Vitreal Humor
- Hemorrhage (trauma, systemic hypertension, retinal detachment, neoplasia, clotting deficiency)
- Hyalitis (numerous infectious diseases such as feline infectious peritonitis [FIP], penetrating injury causing cellular infiltrate)

Box • 26-2

Retinal Lesions Causing Blindness

Retinopathies
- Glaucoma
- Sudden acquired retinal degeneration syndrome (SARD)
- Progressive retinal atrophy (rod-cone dysplasia, rod dysplasia, progressive rod-cone degeneration)
- Central progressive retinal atrophy
- Feline central retinal degeneration
- Toxicity (fluoroquinolone administration in cats)

Retinal Detachment Syndromes
- Exudative/transudative retinal detachment (systemic hypertension, mycoses, viral, bacterial, rickettsial)
- Neoplasia
- Retinal dysplasia
- Hereditary/congenital (collie eye anomaly)

Box • 26-4

Abnormalities Resulting in Failure to Interpret the Visual Message

- Viral (canine distemper virus and feline infectious peritonitis [FIP])
- Canine distemper virus and FIP
- Granulomatous meningoencephalitis (GME)
- Systemic mycoses
- Trauma
- Heatstroke
- Hypoxia
- Hydrocephalus
- Hepatoencephalopathy
- Neoplasia
- Storage diseases
- Postictal
- Meningitis

images to the brain or visual pathway (optic nerve, optic chiasm, optic tract, lateral geniculate nuclei [LGN] and optic radiations) are listed (Box 26-3). Central blindness, also known as *cortical blindness*, results when interpretation of an image is absent (Box 26-4).

VISUAL ASSESSMENT

Obtaining a complete and proper history is an essential component of completing an ophthalmologic examination. Discerning information, such as previous developmental, hereditary, traumatic, or systemic disease problems, should assist in accurate diagnosis of the dog or cat's acute blindness. In addition, a history of prior neurologic disturbances or drug usage will many times confuse lesion localization of visual deficits. A unique feature of the eye is that its structures can be directly observed and interpreted without clinical pathology or invasive tests. Orderly sequence of examination is essential for a thorough, detailed analysis of the ocular structures and is typically performed by examining the superficial structures and then proceeding to deeper structures. Characterization of blindness will assist in lesion localization. For example, day blindness with good night vision (hemeralopia) could be an indication of the pet having cataracts. In dim light the pupil dilates, allowing sight around the cataract. Good day vision with poor night vision (nyctalopia) may be an indication of progressive retinal atrophy (PRA). Blindness with no cause (amaurosis) or mechanical blindness (exophthalmia, facial nerve paralysis, elevated third eyelid [Horner's syndrome]) will give the examiner an area of focus when deciphering the clinical findings.

Box • 26-3

Abnormalities Resulting in Failure to Transmit the Visual Message

Viral Diseases
- Canine distemper
- Feline infectious peritonitis (FIP)

Systemic and Ocular Mycoses
- Blastomycosis, cryptococcosis, histoplasmosis, and coccidiodmycosis
- Neoplasia
- Tramautic avulsion of optic nerves
- Granulomatous meningoencephalitis (GME)
- Hydrocephalus
- Optic nerve hypoplaysia
- Immune-mediated optic neuritis

Motion Detection

Evaluation of motion detection in animals is done by tossing an object (cotton balls) across the animal's field of view and monitoring the response, such as a head or eye movement following the object. The presence of tactile hairs, especially in cats, makes it important not to touch or create air currents or sound if stimulation of these hairs would create a similar response.

Obstacle Course

Creating an obstacle course in an exam room will allow the examiner to determine if the dog or cat is able to navigate an unknown environment. Any large solid object can be used (chairs, wastebasket, or cones). It is important to perform this test in both bright and dim light and to perform several trials. Neurologic deficits or animals who are unwilling to walk are not good candidates for this test. The animal should be able to walk through the course and avoid walking into the obstacles. If the dog or cat is unable to visualize objects and hesitates or bumps into them, that animal is likely blind.

Menace Response

Before testing the menace response, a palpebral reflex should be elicited to assess if the dog or cat is capable of blinking (intact facial nerve CN VII and eyelid function). Severe buphthalmia, exophthalmia, or blepharospasm will prevent blinking and obtund the menace testing. A menace response is elicited by waving a hand or an object toward the animal's head and eyes. The normal response is an avoidance motion, such as moving the head away from the object or blinking

the eyes. The response is "learned" and therefore not typically present in dogs or cats less than 12 weeks of age. An intact menace response requires an intact visual cortex, whereas a dazzle reflex and corneal reflex are strictly subcortical responses. Dazzle reflex is mediated by reflex centers in the rostral colliculi and can evaluate optic nerve function while not stimulating the trigeminal nerve.

Visual Placing and Postural Reactions

This test is performed by holding the animal cradled in a horizontal position with its front legs free to move and then moving toward the edge of a tabletop. A visual animal will respond by lifting the legs before touching the table. A blind animal will move the legs after they touch the table. Stairs can be used to perform this test on dogs too large to hold.

Pupillary Light Reflex

Pupillary light reflex (PLR) is not a test of vision but rather a starting point in lesion localization. No special equipment is needed for this test. Using a focal light source in a dimly lit room, the examiner can adequately assess the PLR in a dog or cat. Brachycephalic patients such as Boston terriers and pugs can sometimes be more difficult to examine because of their lateral globe position. A nervous animal may require a few minutes for the sympathetic nervous system (SNS) response to lessen. Stimulation of the SNS causes mydriasis, giving the examiner the illusion of absent or diminished PLR. Before testing the PLR, the examiner should ensure that the pupils are equal size in both dim and ambient light. Unequal pupil size (anisocoria) is usually pathologic in small animals.

The PLR pathway requires normal optic nerve function, optic chiasm, optic tracts, pretectal and accessory oculomotor nuclei (Edinger-Westphal), oculomotor nerves (parasympathetic portion), and functional iridal muscles (iridal sphincter mm). The retinas are also required for the PLR pathway, although there can be marked retinal pathology and a PLR may still be present. Iris atrophy, synechia, and opacification of the cornea or anterior chamber are additional complications that can diminish the PLR or prevent observation of the pupil. In this situation the lesion may or may not be localized in the globe.

SPECIAL DIAGNOSTIC TESTS

Electroretinography (ERG) is a highly sensitive test interpreted by specialists to evaluate the function of the photoreceptors (rods and cones) using light stimulation. The ERG is beneficial in dogs and cats with acute vision loss when ophthalmoscopic examination proves normal because of its ability to differentiate between photoreceptor disease verses optic nerve or CNS lesions.

Ocular ultrasonography is a useful tool in diagnosis of intraocular or retrobulbar lesions when opacification of the ocular media such as corneal edema, cataracts, or severe enophthalmos is present.

Computed tomography (CT) and magnetic resonance imaging (MRI) scans are excellent diagnostic imaging tools used to localize lesions in animals with acute vision loss. When other tests are unremarkable, they suggest a retrobulbar, optic nerve, or central lesion.

Urogenital

CHAPTER 27

Vaginal-Vulvar and Preputial Discharge

Claudia J. Baldwin

VAGINAL-VULVAR DISCHARGE

When veterinarians examine a female animal with genital discharge, it is usually a vulvar discharge, composed of fluid, cells, and/or tissue, that originates from the uterus, vagina, urinary tract, vestibule, or vulva. Such discharges may occur in both intact and neutered females. Other sources or causes that need to be considered, because their manifestations may present as a vaginal-vulvar discharge, are sex hormone-producing ovarian disorders (neoplasia or remnant), generalized mucosal disease, exudative perivulvar dermatitis, and bleeding diathesis arising from disorders of blood coagulation.

Normal physiologic vaginal-vulvar discharges, which originate from the uterus, are expected in the intact bitch and queen during the reproductive cycle. During proestrus, the bitch produces a serosanguineous discharge of varying volume. During estrus, the discharge becomes less bloody and usually is straw colored. During early diestrus, the discharge is scant and, if present, is mucoid to dark red. The queen does not normally exhibit appreciable discharge. During late gestation, both the queen and the bitch may display a mucoid discharge. At parturition, both produce a clear to green-black discharge that signifies amniotic fluid and separation of placentas, respectively. Normal lochia is red/green/brown; it diminishes to undetectable levels by 3 weeks post gestation in the bitch but may not be appreciable in the queen. The etiology of a *pathologic vaginal-vulvar discharge* (Table 27-1) can be considered using the DAMNITT diagnostic method. This broad scheme allows the clinician to consider the origin and potential causes of discharge in both intact and ovariohysterectomized (OHE) females. (*D* stands for degenerative or developmental, *A* stands for allergic or autoimmune, *M* for metabolic, *N* for neoplastic or nutritional, *I* for iatrogenic, idiopathic, or inflammatory [infectious or immune related], *T* for toxic or traumatic.)

Table • 27-1

Source and Etiology of Pathologic Vaginal-Vulvar Discharges

	SOURCE		ETIOLOGY	
ORGAN OR DISORDER	DEVELOPMENTAL/ DEGENERATIVE ORIGIN	NEOPLASTIC	INFLAMMATORY/ INFECTIOUS OR IATROGENIC	TRAUMATIC/TOXIC
Uterus/stump	Healing failure post-OHE, SIPS	Various	CEH/pyometra, metritis,	Parturient
Vagina	Vaginal bands/septa	Various	Primary and secondary	Breeding, postpartum, FB
Urinary tract	Ectopic ureter, sphincter laxity Vaginal abnormality	TCC	Cystitis/urethritis Iatrogenic	Calculi
Vestibule	Vulvovestibular stricture	Various	Primary or secondary	Breeding, postpartum, FB
Vulva	Ventral displacement/ agenesis Infantile/intersex	Various	Clitoral enlargement	FB
Generalized mucosal disease			Immune mediated Infectious	Irritant
Ovarian disorders	Cystic disease/remnant	E2-secreting tumor	Ovarian remnant	
Perivulvar dermatitis			Pyoderma	Irritant
Bleeding diathesis	Inherited deficiency		Iatrogenic platelet dysfunction	Vit K antagonism

OHE, Ovariohysterectomy; *CEH*, cystic endometrial hyperplasia; *SIPS*, subinvolution of placental sites (etiology is nondegeneration of trophoblastic cells); *FB*, foreign body; *TCC*, transitional cell carcinoma; *E2*, estradiol; *Vit*, vitamin.

History

The history is important in determining the age, breed, and reproductive status of the female. Information on the date of the OHE or the last estrus, pregnancy, or parturition may assist the clinician in choosing diagnostics. When there is a question as to whether an OHE has been performed, the clinician should inspect the skin for a surgical incision line.

The history may include a continuous or intermittent discharge, licking, and scooting. Developmental or inherited conditions likely would manifest in a younger female, whereas neoplastic disease would be more common in an older female. Clinical signs of systemic illness (e.g., fever, anorexia) would be expected with inflammatory, infectious, disseminated neoplastic, traumatic, or toxic disorders. A drug administration history is important.

Physical Examination

A complete physical examination should be performed, including abdominal palpation to detect organomegaly (uterine or bladder) or discomfort. Inspection of the vulva and perineal region may reveal edema, often associated with estradiol influence, inflammation, or trauma; primary or secondary dermatitis; or anatomic abnormalities (e.g., enlarged clitoris, infantile vulva, or ventral vulvar displacement). A rectal examination in bitches allows palpation of the cranial vestibule, the urethra, and a variable portion of the vagina.

Cytology

Further reproductive evaluation should include collection of discharge from the vestibule with a cotton swab (or in a container if copious). Cytologic evaluation is important to characterize the discharge further. Typically, large amounts of *clear* discharge are relatively acellular and most often of urinary bladder origin. Analysis of fluid to determine compatibility with urine (chemical and microscopic) is indicated, as is comparison of results with those from a voided sample or one obtained by cystocentesis. A *mucoid* discharge displays few cells cytologically, usually healthy appearing neutrophils. With *mucopurulent to purulent* discharges, neutrophil numbers have increased and an increasing number of cells have degenerated. *Serosanguineous to sanguinous* discharges contain red blood cells with either healthy appearing neutrophils or degenerate neutrophils, indicating inflammation. Discharges that are *greenish-black or a mixture of red, green, and brown* derive this coloration from red blood cell breakdown pigment and tissue particles when associated with abortion.

Vaginal-Vulvar Examination

Once fluid has been collected, a *digital vaginal examination* is indicated. Examination may not be possible without sedation in a juvenile small breed dog or in a cat or if pain or discomfort is present. The digital examination should be performed before vaginoscopy, because structural abnormalities can easily be "passed by" if the clinician is relying only on what is seen.

Digital examination allows evaluation of the vulva, vestibule, urethral papilla, vaginovestibular region, and possibly the vagina. Normal anestrous or OHE females have narrowing at the vulvovestibular junction and also at the vaginovestibular junction (the *cingulum*). Abnormal findings such as circumferential strictures or vaginal septa or bands (commonly at the cingulum) or narrowing of the lumen and altered mucosal texture should be noted, as should straining or discomfort. Digital examination may elucidate the cause of the discharge.

Vaginoscopy can be performed in many dogs without sedation. A rigid pediatric proctoscope can be used in medium to large dogs. Other instruments (e.g., a rigid endoscope) allow visualization in cats and smaller dogs. Insufflation and adequate

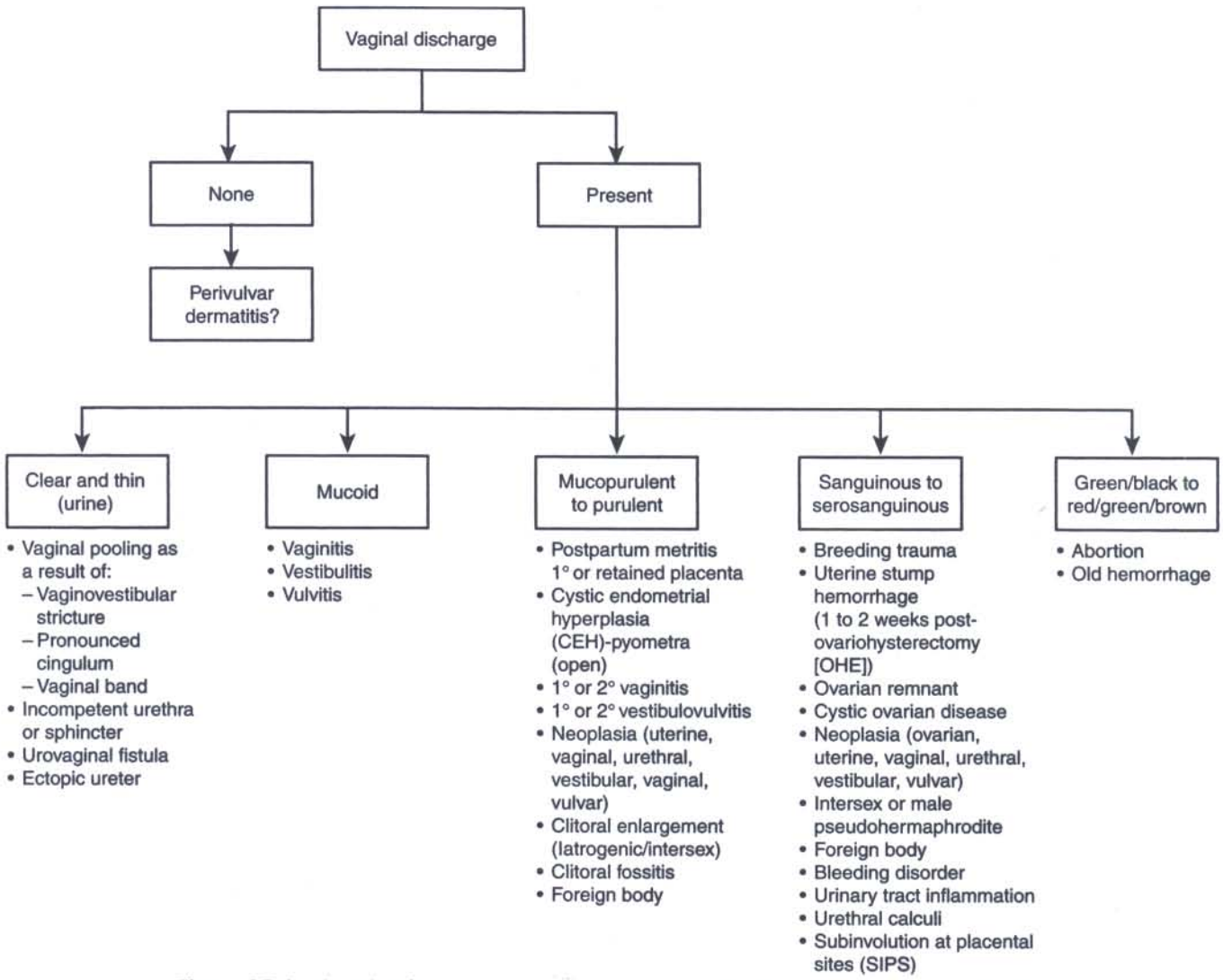


Figure 27-1 Algorithm for assessment of pathologic vaginal-vulvar discharge based on character of discharge and digital examination.

lighting are essential. Shorter instruments with a light source can be used to examine the vestibule, clitoris, and fossa.

With the information gained from these examinations, the clinician may approach the problem with more clarity (Figure 27-1). (See Artificial Insemination and Vaginoscopy and Vaginal Disorders for further detail on these procedures.)

Other diagnostic testing may be indicated. If the dog or cat has signs of systemic illness, a *complete blood count (CBC), serum biochemistry,* and *urinalysis* should be performed. If the abdomen is painful, the uterus enlarged, and/or the discharge is characterized as purulent, a pyometra should be considered and cystocentesis should be avoided to prevent contamination of the abdomen. *Bacterial culture* of the discharge (collected with a guarded or sheathed culturette to avoid contamination) is indicated for a systemically ill animal or if an infectious process is suspected. Susceptibility testing of the cultured organisms is indicated to determine the appropriate therapy. *Imaging of the abdomen and urogenital system* by means of plain and contrast radiology (i.e., vaginogram, vagino-urethrogram), as well as ultrasound, may be indicated.

Assessment of *reproductive hormonal status* is important when evaluating both intact and OHE females. Increased estradiol concentrations and vaginal cytology suggestive of estradiol influence (keratinization of vaginal cells) is consistent with normal proestrus or estrus, follicular cysts, ovarian secreting neoplasia, or ovarian remnant, although estradiol concentrations may fluctuate. *Stimulation tests* using human chorionic gonadotropin or gonadotropin-releasing hormone, which induce ovulation with resultant increases in the progesterone concentration, may be diagnostic for follicular cysts or ovarian remnant (see the section on Ovarian and Estrous Cycle Abnormalities). Measurement of serum progesterone for evidence of the luteal phase of the reproductive cycle may also be helpful with suspected cystic endometrial hyperplasia (CEH)/pyometra in both intact and OHE females, because the majority of females with this disorder have an elevated progesterone concentration or have received exogenous progestational therapy (see the section on Cystic Endometrial Hyperplasia and Pyometra).

Histology of masses found in the reproductive tract can further characterize them and allow prognostication. *Coagulation system testing* should be considered in a female with a serosanguineous to sanguinous discharge. Mucosal hemorrhage is characteristic of a primary system (platelet and vascular) defect but may also be associated with a coagulation factor

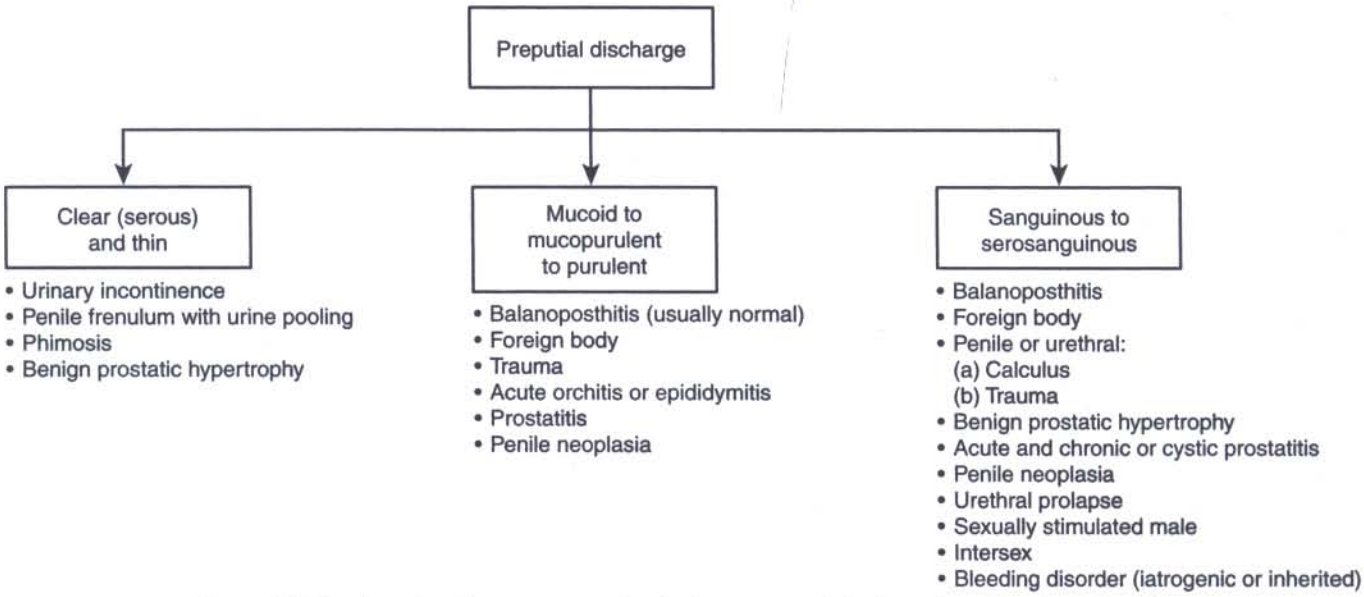


Figure 27-2 Algorithm for assessment of pathologic preputial discharge based on character of discharge and examination.

abnormality. Iatrogenic, inherited, and acquired disorders should be considered.

At times no cause may be apparent for a vaginal-vulvar discharge. Common causes of chronic vaginitis include morphologic abnormalities of the reproductive or urinary tract, resulting in urinary incontinence or pooling. Juvenile vaginitis, seen in the prepubertal bitch, is almost always self-limiting. Vaginitis in the queen is unusual. (See Vaginal Disorders.)

PREPUTIAL DISCHARGE

Preputial discharges are composed of fluid and cells that originate from the urinary bladder, prostate gland, testes and epididymis, urethra, and mucosa of the penis and penile sheath. Discharges may be present in both intact and neutered males, and they are much more common in the dog than in the cat. Other causes that should be considered are sex hormone–induced conditions (e.g., hermaphroditism), generalized mucosal disease, or bleeding diathesis caused by disorders of blood coagulation.

Normal discharge in the male is typified as a small amount of grayish-white to yellow material that may be seen at the preputial orifice as moist or dried exudate. It may be difficult to determine, upon inspection of the preputial orifice and surrounding skin and haircoat, whether the volume present is normal. Careful examination of the genitalia is indicated. *Abnormal discharge* in the male may be investigated by means of the source of origin and the gross appearance of the discharge. Abnormal discharge may be characterized grossly as clear or serous, mucoid to mucopurulent to purulent, and sanguinous or serosanguineous (see the section Cytology, above, for the cytologic characteristics).

History

It is important to determine the age, breed, and reproductive status of the animal. It also should be ascertained whether the male has been castrated and if so, whether one or both testes were removed. Reproductive activity may be important. The duration and historical character of the discharge should also be noted. The presence of systemic signs that precede or are associated with discharge would be expected with inflammatory or infectious disease, neoplasia, and traumatic or toxic causes.

Physical Examination

A complete physical examination should be performed, with particular attention given to the scrotum, testes (if present), and prepuce. Edema of the scrotum or enlargement or asymmetry of testicular or epididymal tissues is important. The prostate gland can be evaluated by simultaneous abdominal and rectal palpation for size, symmetry, and pain. The size of the urinary bladder can also be evaluated by abdominal palpation. The prepuce and penis should be palpated, and the prepuce then should be retracted, caudal to the bulbus glandis, to allow visual inspection of the entire penis. Digital and visual inspection of the preputial space (using a blunt instrument) may be indicated.

Other Diagnostic Testing

Based on the appearance of the discharge, the historical information, and the physical examination findings, a list of differential diagnoses can be generated (Figure 27-2). Further evaluation might include a CBC, *serum biochemical profile*, and *urinalysis*, as well as *imaging* of the testicles, prostate, or urinary bladder by means of ultrasound or radiology. Evaluation of testicular or prostatic secretions may be possible through *semen collection* or *prostatic massage*. Additional diagnostics may include *bacterial culture with susceptibility determination, fine needle aspiration, or biopsy*. (See Cystocentesis; Bladder, Urethral, Vaginal, Prostatic Mass Aspiration/Biopsy; and Urethral Catheterization and Cystoscopy.) *Coagulation system testing* should be considered for a male with a serosanguineous to sanguinous discharge. Mucosal hemorrhage is characteristic of a primary system defect but may also be associated with a coagulation factor abnormality; iatrogenic, inherited, and acquired disorders should be considered.

The above evaluation may well lead to a definitive diagnosis. In the absence of definite findings, the male should be re-evaluated at a later date. Comparison of subsequent findings with the original data may lead to a definitive diagnosis or management plan.

CHAPTER 28

Polyuria and Polydipsia

Edward C. Feldman

Concerns about a pet's atypical or unusual urination habits are a common reason for owners to seek veterinary assistance. For example, a dog or cat may urinate excessive volumes, urinate more frequently than "normal," appear to be incontinent, urinate for an unusually long time, or urinate in atypical or unacceptable locations. Some owners seek veterinary care because they think their pet is drinking too much water, but this is a less common concern than those previously mentioned.

PHYSIOLOGY OF WATER METABOLISM

Water consumption and urine production are controlled by complex interactions between plasma osmolality, fluid volume in the vascular compartment, the thirst center, the kidneys, the pituitary gland, and the hypothalamus. Dysfunction in any of these can result in the clinical signs of polyuria (PU) and polydipsia (PD). Vasopressin (antidiuretic hormone [ADH]) plays a key role in the control of renal water resorption, urine production, urine concentration, and water balance. In the presence of ADH and dehydration, the average healthy dog or cat has the capacity to produce urine with an osmolality well above 2000 mOsm/kg. If a dog or cat is chronically deficient in ADH or is chronically unable to respond to ADH at the renal tubular level, the urine may be as dilute as 20 mOsm/kg.

Plasma osmolality and its principal determinant, the plasma sodium concentration, normally are maintained within remarkably narrow ranges. This stability is achieved through the adjustment of total body water concentrations to maintain balance with the plasma sodium concentration. Water balance is controlled by an integrated system that involves precise regulation of water intake via thirst mechanisms and control of renal water loss via ADH secretion and action. Water is continuously lost through the urine, respiratory tract, and feces. Lost water is replaced by that consumed. The urine concentrating capacity can reduce but not eliminate water loss.

ADH, a nonapeptide, is synthesized in the hypothalamus and secreted from the posterior pituitary gland. The primary sites of ADH activity are epithelial cells in the renal distal tubules and collecting ducts. Here, ADH acts to increase the hydro-osmotic permeability of these cells. The fluid in the tubular lumen normally is dilute, and the fluid in the interstitial space, through which the tubules traverse, is concentrated. Therefore, if water is allowed to diffuse passively along concentration gradients, it flows from the lumen of the nephron in which the fluid is dilute into the hypertonic milieu that normally exists in the interstitial space of the renal medulla. If ADH is present, the volume of fluid in the nephron decreases, the osmolality of that fluid increases, and water is conserved. Thus the "normal" animal has the capacity to secrete ADH in response to appropriate stimuli (increasing plasma osmolality, decreasing plasma volume) and the ability to respond to ADH at the level of the renal tubules and collecting ducts. In the absence of ADH (central diabetes insipidus) or if renal tubular cells are resistant to the action of ADH (nephrogenic diabetes insipidus), the cells lining this portion of the nephron are resistant to diffusion of both water and solutes. Hence, the hypotonic filtrate formed in the more proximal portion of the nephron passes unmodified through the distal tubule and collecting duct. This *water diuresis* is associated with large volumes of urine that has a low osmolality.

It should be noted that 85% to 90% of the fluid filtered by the glomerulus is reabsorbed isosmotically with sodium and glucose in the proximal portion of the nephron. Sodium then is selectively reabsorbed from the remaining fluid, making the fluid in the distal nephron hypotonic. However, if a poorly reabsorbed solute, such as urea or glucose, is present in excess in the glomerular filtrate, fluid resorption from the proximal tubule is impaired. Because of this physiologic process, an abnormally increased volume of fluid reaches the distal nephron and can overwhelm its capacity to reabsorb water. Consequently, urine volume increases despite the presence of ADH. This type of polyuria is called *solute diuresis.*

DIAGNOSTIC APPROACH TO POLYURIA, POLYDIPSIA, AND OTHER ABNORMALITIES IN URINATION

The First Step: Collecting the Urine

It may be difficult for a veterinary hospital staff member to distinguish "inappropriate" urination (frequency with or without straining or hematuria) from polyuria at the time an owner phones the hospital to make an appointment. Therefore, it is strongly recommended that all cat and dog owners with any "chief complaint" that resembles those mentioned here, be encouraged to catch a urine sample from their pet (Figure 28-1). That urine (even if only a few drops) should be collected in a clean container with a lid and brought with the pet at the time of initial evaluation. Owners of medium-to-large breed dogs rarely have difficulty collecting urine in a small relatively flat container if they approach their pet slowly and discreetly. Owners of small dogs, especially female dogs, may find success in collecting urine if the container lid is used for collection. Owners of cats can try placing plastic wrap on top of their cats' litter and collecting urine after the cat uses the litter box. Alternatively, owners can replace absorbable litter with non-absorbable litter (using any type of gravel, such as that used in an aquarium). In this situation, the urine can simply be poured into a container.

The Next Step: Evaluating the Urine

When the owner arrives at the veterinary hospital, the urine they collected can be evaluated prior to their pet being examined. The urine specific gravity should be noted and a "dip stick" test completed. Urine is usually considered normally "concentrated" if the specific gravity is 1.025 to 1.035 or greater. Since the owner has collected the urine sample from the pet while that animal was in its home environment, problems in interpretation associated with water being withheld prior to an

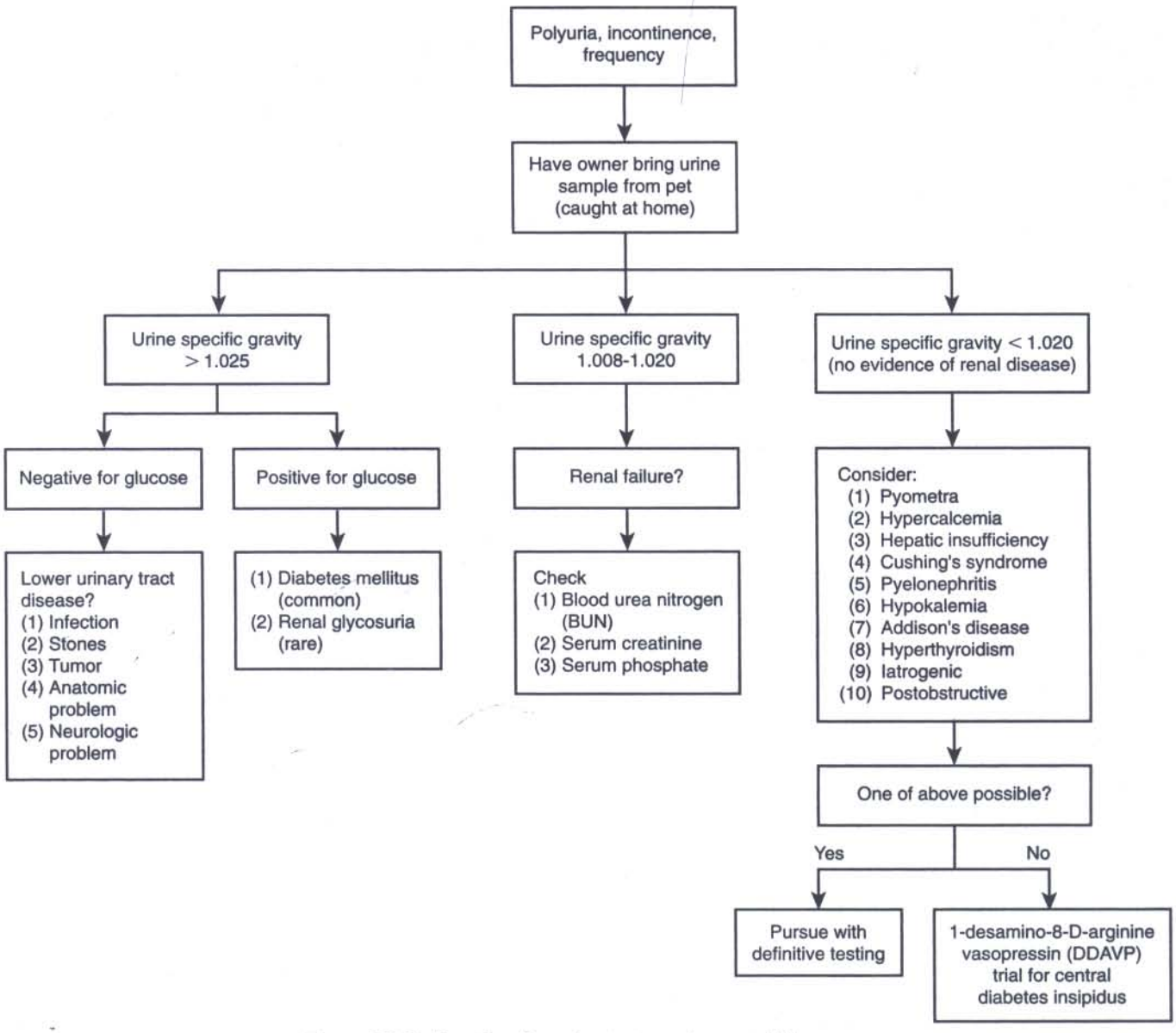


Figure 28-1 Algorithm for polyuria, incontinence and frequency.

automobile trip or a pet not consuming typical amounts of water due to nervousness or fear are not encountered. The truly polyuric dog or cat will almost always have dilute urine (specific gravity <1.012), "relatively" dilute urine (specific gravity >1.012 but <1.022), or it will have glucose in the urine.

Concentrated Urine without Glucose

If the urine bought to the hospital by the owners is concentrated (specific gravity >1.025 to >1.035) and it has no glucose, it is likely that the animal has a lower urinary tract condition. In this situation the veterinarian must consider the possibility of urinary tract infection, bladder calculi, bladder mass, anatomic or neurologic problems that may explain the owner's observations. Appropriate testing for these conditions (culture, abdominal imaging, etc.) can be recommended if the history and physical examination support such an approach.

Concentrated Urine with Glucose

Most dogs and cats with diabetes mellitus are first examined after an owner has observed polyuria. These animals frequently also have polydipsia, polyphagia, and weight loss. Less commonly, a diabetic dog is brought in for veterinary examination after an owner notes that it has become acutely blind due to cataract formation. A dog or cat also may be brought in for treatment of vomiting, diarrhea, anorexia, listlessness, or other systemic signs secondary to developing diabetic ketoacidosis. Regardless, almost all diabetic dogs and cats have a urine specific gravity of 1.025 to 1.045 and glycosuria. The diagnosis of diabetes mellitus can be strongly suspected simply by noting a positive reaction in the glucose reagent portion of the urine test strip within seconds of removing the strip from the urine. Thus diabetes mellitus can be diagnosed in dogs and cats before the pet is ever examined by the veterinarian. This diagnosis can be confirmed by the finding of hyperglycemia. In cats, stress may result in glycosuria; also, two uncommon causes of hyperglycemia and glycosuria are Cushing's syndrome and acromegaly. In the rare case in which the blood glucose concentration is within reference limits, the veterinarian should consider the possibility of renal glycosuria, a congenital renal tubular defect in the basenji and Norwegian elkhound. Renal glycosuria, however, can occur in any dog or cat.

Isosthenuric Urine (Urine Specific Gravity of 1.008 to 1.012): Chronic Renal Failure

The term *isosthenuria* usually implies that the urine specific gravity or osmolality is the same as that of serum or plasma. Using this criterion, urine with a specific gravity of 1.008 to 1.012 is *isosthenuric*. However, for clinical purposes, it is important to remember that a dehydrated animal typically has a plasma osmolality greater than normal due to loss of water and abnormal retention of solutes (e.g., urea). In this setting, urine with a specific gravity of 1.013 to 1.020 may be "isosthenuric" despite being greater than the classic 1.008 to 1.012. In other words, what happens if a cat or dog is examined and is thought to be 3% to 10% dehydrated? If the animal has a normal hypothalamus, pituitary, and kidneys, it should have responded to this degree of water loss by secreting maximum amounts of ADH (it has been demonstrated repeatedly that a 3% to 5% decrease in body weight due to water loss is associated with this response). The urine of such an animal, therefore, should reflect maximum release of ADH, and the specific gravity should be well in excess of 1.035. If the dog or cat has a urine specific gravity of 1.018, for example, it should not be considered to have responded appropriately to the dehydration.

The primary concern a veterinarian should have when an animal has polyuria and a urine specific gravity within the isosthenuric range is renal insufficiency or failure. In chronic renal failure, the number of functioning nephrons progressively decreases. A compensatory increase in the glomerular filtration rate by surviving nephrons occurs, and a commensurate increase in fluid volume is presented to the distal renal tubules. The increase in the tubular flow rate causes less urea and sodium to be reabsorbed. The result is an osmotic diuresis, which may be exaggerated by a reduction in the renal medullary concentration gradient. For an animal with this type of urine specific gravity, a serum chemistry evaluation is the first step toward determining the presence or absence of renal disease as the cause of the polyuria. Specifically, the blood urea nitrogen (BUN), serum creatinine, and serum phosphate concentrations should indicate whether the pet has renal disease.

Urine Specific Gravity <1.020: Pyometra

It has been stated that any ill, intact female dog or cat should be considered a candidate for having pyometra until proven otherwise. This is an appropriate approach because of the serious nature of uterine infection. Animals with pyometra can quickly deteriorate as a result of overwhelming sepsis. Dogs and cats that may have pyometra typically have a history of being in estrus 2 to 10 weeks previously, and most have a purulent vaginal discharge. For any animal in which pyometra is suspected, a complete blood count (CBC) should be done to assess for evidence of systemic infection; abdominal radiographs or ultrasound scans also should be obtained and examined for uterine enlargement. Dogs and cats with pyometra may develop polyuria and dilute urine because of the effects of endotoxin from *Escherichia coli*, the bacteria most commonly associated with pyometra. Because this endotoxin interferes with the action of ADH at the level of the renal tubules, these animals have a reversible form of nephrogenic diabetes insipidus.

Urine Specific Gravity <1.020: Hypercalcemia

Hypercalcemia has several common causes. Some, but not all, of the conditions associated with this biochemical abnormality are lymphosarcoma, chronic renal failure, hypoadrenocorticism, primary hyperparathyroidism, vitamin D toxicosis, granulomatous disease (histoplasmosis, blastomycosis), multiple myeloma, and apocrine gland carcinomas of the anal sac. Therefore, if a dog or cat has a urine specific gravity of less than 1.020, it would be appropriate to obtain a serum biochemistry profile to assess the serum calcium concentration. If the serum calcium concentration is abnormally increased, tests needed to rule in or rule out the various causes of hypercalcemia can be considered. An increased serum calcium concentration may interfere with the action of ADH at the renal tubular level, causing a reversible form of acquired nephrogenic diabetes insipidus. This is the most likely explanation for the polyuria and secondary polydipsia noted in hypercalcemic animals. Other possible explanations for this polyuria are damage to ADH receptors in the renal tubules, inactivation of adenyl cyclase, or decreased transport of sodium and chloride into the renal medullary interstitium.

Urine Specific Gravity <1.020: Hepatic Insufficiency

Although the condition is not extremely common, some dogs with severe hepatic insufficiency also have an inability to concentrate their urine. One possible owner concern, therefore, would be polyuria. In these dogs, a decrease in one or more of the following "liver function" tests usually is seen on routine serum biochemical profiles: albumin, BUN, cholesterol, or glucose. In addition, an afflicted dog may have microhepatica or a liver that appears otherwise abnormal on radiography or ultrasonography. A dog with some or many of these abnormalities could be further assessed with pre- and post-prandial bile acid, a radio-labeled liver scan, or hepatic biopsy. There are several explanations for the polyuria and dilute urine. Although not well understood, one plausible explanation is loss of renal medullary hypertonicity secondary to impaired BUN production. BUN is an important component of the renal medullary concentration gradient. Decreases in this gradient result in polyuria with compensatory polydipsia. Other potential explanations are hypokalemia and impaired metabolism of cortisol.

Urine Specific Gravity <1.020: Canine Cushing's Syndrome

Polyuria is an extremely common clinical sign in dogs with canine Cushing's syndrome (CCS) (excess cortisol concentrations do not commonly cause polyuria in cats). The urine specific gravity in at least 75% of dogs with iatrogenic or naturally occurring CCS is less than 1.020 and can be as low as 1.001. The cause of this polyuria remains obscure, although most of these dogs appear to have secondary and reversible ADH deficiency (central diabetes insipidus). Dogs with CCS typically have additional clinical signs, such as polydipsia, polyphagia, panting, muscle weakness, alopecia, pot belly, and thin skin. Routine laboratory abnormalities commonly include increases in serum alkaline phosphatase and alanine amino transferase activities, increased serum cholesterol concentration, and a decreased or low-normal BUN. Confirmation requires appropriate pituitary-adrenocortical function tests.

Urine Specific Gravity <1.020: Pyelonephritis

Infection and inflammation of the renal pelvis can destroy the countercurrent mechanism in the renal medulla. This results in isosthenuria, polyuria, secondary polydipsia and, eventually, renal failure. A dog or cat with bacterial pyelonephritis may have nonspecific signs of lethargy, anorexia, and fever. Neutrophilic leukocytosis may be noted on the CBC. Urinalysis may reveal white blood cells, casts, bacteria, and red cells. Recurrent urinary tract infection may increase suspicion of pyelonephritis. Urine cultures should be performed on cystocentesis samples, but these may or may not be positive for bacteria. Abdominal ultrasonography or urography usually is required to confirm this diagnosis.

Urine Specific Gravity <1.020: Hypokalemia

Hypokalemia is thought to interfere with the action of ADH in the renal tubules, creating a reversible form of nephrogenic diabetes insipidus. This electrolyte disturbance is more common in cats than in dogs, more commonly causes muscle weakness than polyuria, and usually occurs secondary to other disorders (see Chapter 65).

Urine Specific Gravity <1.020: Hypoadrenocorticism (Addison's Disease)

Most dogs with Addison's disease are young to middle-aged females. Despite normal kidney function and severe hypovolemia, animals in an Addisonian crisis frequently have a urine specific gravity of less than 1.030 due to the hyponatremia caused by mineralocorticoid deficiency. Hyponatremia reduces the renal medullary concentration gradient, impairing the ability to produce concentrated urine. Although "relatively" dilute urine is typical of addisonian dogs and cats, signs of polyuria or polydipsia are quickly overshadowed by the more worrisome and obvious signs of vomiting, diarrhea, listlessness, weakness, anorexia and weight loss. The combination of signalment and findings of hyperkalemia and hyponatremia should raise suspicion of Addison's disease. Confirmation requires a finding of an abnormally suppressed plasma cortisol concentration after administration of ACTH.

Urine Specific Gravity <1.020: Hyperthyroidism

Polyuria and polydipsia are common in hyperthyroid cats and dogs. Although the exact mechanism of the polyuria is unclear, it is likely that increases in renal blood flow cause a decrease in renal medullary concentration. This impairs water resorption from the distal nephron. Concurrent renal insufficiency may also contribute to these signs. The tentative diagnosis of hyperthyroidism is based on palpation of a thyroid nodule or mass. Confirmation requires a finding of abnormally increased serum total or free thyroxine concentrations.

Urine Specific Gravity <1.020: Iatrogenic

Several drugs may cause polydipsia and polyuria, including some that are commonly used, such as glucocorticoids, diuretics, and anticonvulsants.

Urine Specific Gravity <1.020: Postobstructive Diuresis

Postobstructive diuresis is most often encountered after a urethral obstruction has been relieved in cats, but it may occur in dogs. These animals often show dramatic increases in BUN secondary to the obstruction, which accounts for a marked osmotic diuresis after the obstruction has been relieved.

CENTRAL DIABETES INSIPIDUS, NEPHROGENIC DIABETES INSIPIDUS, AND PSYCHOGENIC (PRIMARY) POLYDIPSIA

It should be emphasized that most dogs and cats with polyuria and polydipsia have one of the conditions described in the previous sections of this chapter. Most causes of polydipsia and polyuria can be identified from the signalment, history, physical examination, urinalysis (especially if the urine is caught by the owner before leaving the home environment), CBC, and serum biochemistry profile. *Primary nephrogenic diabetes insipidus (NDI)* is an extremely rare condition. However, secondary and often reversible NDI accounts for the polyuria in many of the conditions previously discussed. Both *central diabetes insipidus (CDI)* and *psychogenic (primary) polydipsia (PP)* are quite uncommon (although CDI is much more common than PP). If an animal has dilute urine and does not appear to have any of the previously discussed conditions, it is appropriate to assume that the animal does not have primary NDI, but it may have CDI or PP.

The veterinarian then can ask the following question: Does this animal drink a lot because it urinates a lot (CDI), or does it urinate a lot because it drinks a lot (PP)? If CDI is present, the serum osmolality should be high-normal or increased. If PP is present, the serum osmolality should be low-normal or decreased. Thus the serum osmolality becomes a reasonable, cost-effective, and simple test to run. Because the veterinarian has reached a point where it is likely that one of these two conditions may exist and because CDI is much more common than PP, trial therapy at home is recommended using oral DDAVP (synthetic ADH, which is commercially available as 0.1 or 0.2 mg tablets). The dose is empirical. It is recommended that a 20 kg dog be given 0.1 mg three times a day for about 7 days and that a 40 kg dog be given 0.2 mg three times a day for about 7 days. The dosage for dogs and cats weighing more or less than this can be so-adjusted. The response in dogs or cats with CDI is quick and obvious. Owners can collect urine on a daily basis during the trial to substantiate their clinical impressions regarding response. If the pet responds, CDI (Cushing's syndrome remains a possibility) is diagnosed, and dose of DDAVP can be slowly tapered to determine the minimum required for long-term treatment. The use of nasal drops placed in the eyes is no longer recommended. The water deprivation test is considered dangerous and is never warranted.

CHAPTER 29

Micturition Disorders

Mary Anna Labato

Micturition is a two-stage process involving the passive storage and the active voiding of urine. Processes that interfere with the storage and voiding of urine are termed *micturition disorders*. Micturition disorders may lead to unresponsive urinary tract infection, resulting in an ascending pyelonephritis and ultimately renal disease. Neurogenic disorders, typically functional obstructions, include lower motor neuron disorder, or atonic bladder, with overflow incontinence; upper motor neuron disorder, or automatic bladder; detrusor-urethral dyssynergia, and dysautonomia. Non-neurogenic disorders, typically mechanical obstructions, include such processes as infection, inflammation, calculi, and neoplasia.

ANATOMY AND PHYSIOLOGY OF THE URINARY BLADDER

The body of the bladder is composed of smooth muscle, which is referred to as the *detrusor*. The *outlet conduit* consists of the trigone and proximal urethra. The smooth muscle fibers

of the detrusor continue into the proximal urethra, forming a functional internal urethral sphincter. The distal urethra is composed of striated skeletal muscle and functions as an external sphincter. During the storage phase of micturition, the bladder functions as a low-resistance, high-capacity vessel. The urethra functions as a high-resistance barrier. The reverse is true during the voiding phase, at which time the bladder acts as a muscular pump and the urethra as a low-resistance vessel.

NERVOUS CONTROL OF MICTURITION

Nervous control of the bladder and urethra is a combination of autonomic and somatic interactions. Parasympathetic innervation is supplied to the detrusor by the pelvic nerve, which arises from sacral spinal cord segments S1 to S3. Sympathetic innervation is supplied via the hypogastric nerve, which is composed of preganglionic fibers that exit the lumbar spinal cord (L1 to L4 in dogs and L2 to L5 in cats) and synapses in the caudal mesenteric ganglion. Sympathetic innervation, which is supplied both to the detrusor and the urethral smooth muscles, characterizes the storage phase of micturition. Alpha-adrenergic fibers synapse in smooth muscles in both the trigone and proximal urethra. Stimulation results in contraction of these muscles and forms a functional internal urethral sphincter. Beta-adrenergic fibers synapse in the detrusor muscle; stimulation results in relaxation. Somatic innervation is supplied via the pudendal nerve, which arises from sacral spinal cord segments S1 to S3 and provides stimulation to the striated urethral musculature. For voluntary control of micturition to occur, the actions of the cerebral cortex, pons, and reticulospinal tract must be integrated. A second pathway, from the cerebral cortex to the sacral nuclei, coordinates voluntary sphincter control.

HISTORY AND DIAGNOSIS

When an animal is presented for a urine retention problem, it is of utmost importance to obtain a complete history, including reproductive status; age at neutering; age at the onset of the problem; previous medical problems, especially those involving the urogenital system; previous history of trauma; and an accurate description of the abnormality (Figure 29-1). If the animal is having difficulty urinating, two other questions are important: How frequent is urination? Is there stranguria, and if so, is any urine being passed?

A *complete physical and neurologic examination* should be performed, with particular attention paid to the urogenital system. The bladder should be palpated carefully before and immediately after voiding to evaluate the extent of distension, tone, and the ease with which the bladder may be expressed manually. Lower motor neuron lesions generally are associated with easy manual expression and reduced sphincter tone. Upper motor neuron lesions generally are associated with difficult manual expression and increased sphincter tone. In the neurologic examination, the innervation of the urogenital system should be evaluated. The perineal reflex evaluates the pudendal nerve. Pricking or pinching the skin of the perineum results in contraction of the anal sphincter. The bulbospongiosus reflex evaluates the integrity of both the pudendal nerve and the sacral spinal segments. Squeezing the distal portion of the penis or the edges of the vulva causes the anal sphincter to contract.

A *rectal examination* should be done to evaluate the prostate gland, pelvic diaphragm, and anal tone. The veterinarian should try to observe the animal urinating to verify the micturition abnormality. Also, the residual urine volume should be measured. The animal is allowed to void until urine is no longer passed, the bladder is catheterized, and the volume of any remaining urine is measured. In a normal animal, the residual volume should not exceed 0.4 mL/kg. Catheterization of the bladder also assesses the patency of the urethra.

The *minimum database* should include a *complete blood count (CBC), serum biochemical profile,* and *urinalysis and culture.* In most cases the CBC and chemistry profile are within normal limits, unless a post renal azotemia has developed from an obstructive process. The urinalysis may reflect evidence of infection, inflammation, or neoplasia or a combination of these.

Survey and *specialized radiographic studies* may be useful. Survey radiographs should be checked for any obvious abnormalities in the bladder, urethra, pelvis, or spine. Contrast radiographic studies (intravenous urography, retrograde urethrocystography, vaginourethrography) are evaluated for bladder wall thickening, calculi, prostatic enlargement, urethral strictures, and skeletal abnormalities in the pelvis. An abdominal ultrasound examination may be useful for evaluating bladder wall thickness, the prostate, and the sublumbar lymph nodes and for checking for calculi or masses. A myelogram may be indicated to evaluate for spinal cord compression, as with cauda equina syndrome, or intervertebral disk disease. Magnetic resonance imaging may be indicated to evaluate for diseases of the spinal cord and vertebrae.

Urodynamic studies to evaluate micturition disorders routinely consist of a cystometrogram and urethral pressure profile; electromyography also may be a part of the study. The cystometrogram is a pressure-volume recording that measures bladder tone and volume, threshold volume and pressure, maximum contraction pressure, and the detrusor reflex. The urethral pressure profile measures intraurethral resistance and identifies and localizes areas of increased or decreased resistance. Electromyography can evaluate coordination of muscular activity between the detrusor and the urethral sphincter. Electromyography usually is performed on the anal sphincter; however, with specialized catheters that incorporate electrodes, it also can be performed directly on the urethral sphincter.

CAUSES OF MICTURITION DISORDERS

Micturition disorders have a number of causes, which may be categorized as *neurogenic* or *non-neurogenic.*

Neurogenic Causes

The four types of neurogenic disorders are lower motor neuron disorder, upper motor neuron disorder, detrusor-urethral dyssynergia, and dysautonomia.

Lower Motor Neuron Disorder (Detrusor Areflexia with Sphincter Areflexia)

Lower motor neuron disorder, or *atonic bladder,* results from lesions involving the sacral spinal cord segments or pelvic nerve, including intervertebral disk disease, cauda equina syndrome, sacroiliac luxations, sacrococcygeal fracture/separation, and tumors (e.g., spinal lymphoma). This type of disorder causes both detrusor and sphincter areflexia. Dribbling of urine with the bladder remaining full often is referred to as *overflow incontinence.* The bladder typically is large, distended, and easily expressed. The incontinence is continuous, and a loss of perineal, bulbospongiosus, and detrusor reflexes is noted.

Treatment involves manual expression of the bladder three or four times daily. Long-term therapy for this disorder has not been successful. Complications include urine scalding, decubital ulcers, and recurrent urinary tract infections. Bethanechol, a parasympathomimetic, may be administered to increase detrusor contractions.

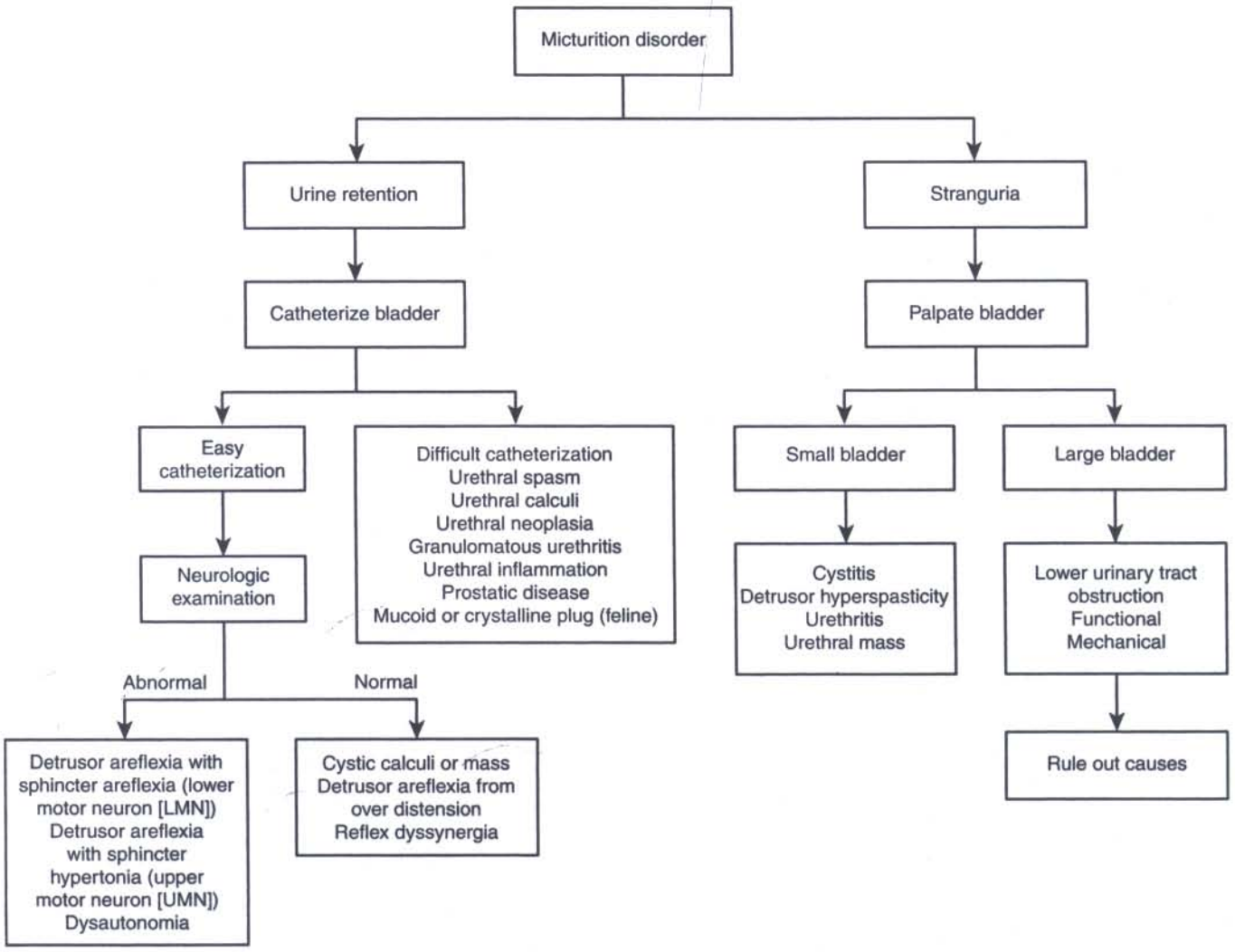


Figure 29-1 Algorithm for diagnostic approach to micturition disorders. *LMN*, Lower motor neuron; *UMN*, upper motor neuron.

Upper Motor Neuron Disorder (Detrusor Areflexia with Sphincter Hypertonus)

Upper motor neuron disorder, or *automatic bladder*, results from a lesion involving the spinal cord above the sacral spinal cord segments, such as intervertebral disk disease, tumor, or trauma. This disorder causes incomplete reflex detrusor contraction and spasticity of the urethral sphincter, the result being incomplete emptying of the bladder. The bladder is large, turgid, and initially extremely difficult to express. The animal has a history of inability to urinate, and concomitant hindquarter paresis or paralysis frequently is seen.

Voluntary control is lost, and manual expression is difficult if not impossible. After a period of days to weeks, the spinal reflexes resume. Involuntary micturition is initiated when the threshold capacity of the bladder is reached (automatic bladder). Initially it is difficult to express the bladder manually. Because of the risk of bladder rupture, this maneuver should not be attempted until manual evacuation of the bladder is tolerable. Instead, the patient should be catheterized aseptically at least three times daily to empty the bladder completely. An indwelling catheter should not be used because of the risk of urinary tract infection. Frequent urinalyses with culture and sensitivity should be performed.

Concurrent administration of antibacterial agents may be indicated, especially with long-term intermittent catheterization. Baclofen, a skeletal muscle relaxant, decreases muscle tone by exerting a depressive effect on the central nervous system. It inhibits medullary interneurons and spinal reflexes, and it decreases spasticity by reducing the activity of gamma efferent neurons.

Detrusor-Urethral Dyssynergia

In detrusor-urethral dyssynergia, initiation of the detrusor reflex that results in voiding is followed by involuntary contraction of the urethral sphincter. The term *detrusor-urethral dyssynergia* refers to involuntary contraction of the external urethral sphincter in the distal urethra (detrusor-striated sphincter dyssynergia) or contraction of smooth muscle in the bladder neck and proximal urethra (detrusor-smooth sphincter dyssynergia) during detrusor contraction. The condition is caused by lesions or partial lesions (masses, degeneration) of the reticulospinal tract. Increased sympathetic activity of both the smooth and striated urethral musculatures may arise from a lesion cranial to or involving the caudal mesenteric ganglion. Treatment involves decreasing sympathetic tone or the use of muscle relaxants (Table 29-1).

Table • 29-1

Pharmacologic Agents Used in the Treatment of Micturition Disorders

AGENT	ACTION	DOSAGE	ADVERSE EFFECTS	CONTRAINDICATIONS
Baclofen	Skeletal muscle relaxant	*Dog:* 1–2 mg/kg PO q8h *Cat:* Not recommended	Weakness, pruritus, GI upset	
Bethanechol	Parasympathomimetic effect	*Dog:* 5–25 mg PO q8h *Cat:* 2.5–10 mg PO q8h	Vomiting, anorexia, cramping, ptyalism	Urethral obstruction, GI disease, hyperthyroidism
Dantrolene	Skeletal muscle relaxant	*Dog:* 1–5 mg/kg PO q8-12h *Cat:* 0.5–2 mg/kg PO q8h	Weakness, GI upset, sedation, hepatotoxicity	Cardiopulmonary disease
Diazepam	A benzodiazepine; skeletal muscle relaxant	*Dog:* 2–10 mg/dog PO q8h *Cat:* 1–2.5 mg/cat PO q8h	Sedation, polyphagia, paradoxic excitement, hepatotoxicity	Hepatic disease, pregnancy
Phenoxybenzamine	An alpha antagonist; urethral smooth muscle relaxant	*Dog:* 0.25 mg/kg PO q12-24h *or* 2.5–20 mg/dog PO q12-24h *Cat:* 1.25–7.5 mg/cat PO q12-24h	Hypotension, GI upset, tachycardia	Cardiac disease, glaucoma, diabetes mellitus, renal failure
Prazosin	Same as phenoxybenzamine	*Dog:* 1 mg/15 kg PO q8h *Cat:* 0.5 mg/cat PO q12-24h	As for phenoxybenzamine	As for phenoxybenzamine
Terazosin	Same as phenoxybenzamine	*Dog:* 0.5–5 mg/dog PO q12-24h *Cat:* Not established	As for phenoxybenzamine	As for phenoxybenzamine

GI, Gastrointestinal.

Alpha-adrenergic blocking agents (e.g., phenoxybenzamine, prazosin, and terazosin) can be used to decrease internal sphincter resistance. In addition to its alpha-1 antagonism in urethral smooth muscle, prazosin can cause a centrally mediated decrease in somatic input to the external urethral sphincter. Skeletal muscle relaxants (e.g., baclofen, diazepam, and dantrolene) can be used to decrease external sphincter resistance.

Dysautonomia

Dysautonomia is a result of dysfunction of the autonomous nervous system. The cause is unknown. It is a rare disease seen mostly in cats in Great Britain, but it has been recognized in dogs and cats worldwide. The clinical signs are acute in onset and involve many autonomic abnormalities. Urine dribbling and dysuria often are presenting clinical signs due to an atonic bladder. Treatment options include administration of bethanechol and frequent bladder emptying by means of catheterization or manual expression.

Non-Neurogenic Causes of Micturition Disorders

As mentioned previously, non-neurogenic disorders, which typically involve mechanical obstructions, include such processes as infection, inflammation, calculi, and neoplasia.

Detrusor Atony from Overdistention

Detrusor atony from overdistention results from a mechanical or functional outflow obstruction that causes the tight junctions of the detrusor muscle to separate. Subsequent contractions of the detrusor muscle are weak and ineffectual. A functional outflow obstruction may have a neurogenic component. It usually is the result of excessive sympathetic stimulation to the urethra, which effects an increase in urethral tone. Common examples of mechanical obstruction are urethral obstruction (especially in cats from mucoid or crystalline plugs), cystic and urethral calculi, neoplasia of the trigone or urethra, severe urethritis, stricture of the urethra, and prostatic disease.

As a result of a functional or mechanical obstruction, urine volume increases until the intravesicular pressure can overcome the urethral resistance. Once the urethral pressure has been overcome, dribbling of urine occurs because of ineffectual detrusor contractions.

With detrusor atony from overdistention, the animal has a history of continuous incontinence and urine outflow obstruction. Abdominal palpation reveals a large, flaccid bladder. Neurologic examination reveals intact perineal and bulbospongiosus reflexes, yet the detrusor reflex is weak or absent. There is a large residual urine volume. Urodynamic studies may help rule out a neurogenic component.

Detrusor atony from overdistention is the one disorder in which indwelling urinary catheterization for up to 7 to 14 days is indicated, because the bladder must be kept as small as possible to re-establish tight junction connections in the detrusor muscle. It is imperative that the obstruction be removed or the primary cause resolved. Occasionally anti-inflammatory therapy is indicated. Frequent urinalyses should be performed, and the appropriate antibiotics, based on susceptibility results, should be given. The cholinergic drug bethanechol has been used successfully to stimulate detrusor contractions in both neurogenic and non-neurogenic atonic bladders. It also is effective for postobstructive atony; however, care must be taken to ensure urethral patency. When the overdistention is caused by increased urethral resistance, an alpha-adrenergic blocker is given before the administration of bethanechol.

OUTCOME

The prognosis for return to normal function depends on the underlying cause of the micturition disorder. The prognosis is good for acute mechanical obstruction associated with resolving obstructive or irritative disease, acute reversible neurologic lesions, and detrusor atony from overdistention. The prognosis is less favorable for chronic detrusor atony or idiopathic functional obstructive disorders. A complete return to normal voiding may not occur, and long-term treatment may be necessary.

CHAPTER 30

Urinary Incontinence

S. Dru Forrester

Urinary incontinence is the inability to voluntarily control the passage of urine through the urethra. *Enuresis* is urinary incontinence that occurs during sleep; it is a common finding in dogs with urethral incompetence. Dogs and cats with urinary incontinence may also have *nocturia* (excessive urination at night), although this probably is more likely in pets with *polyuria* (increased urine volume). *Dysuria* (painful or difficult urination) most often is characterized by *pollakiuria* (increased frequency of urination attempts) or *stranguria* (straining to urinate); however, it may be associated with incontinence caused by increased urgency to urinate.

PHYSIOLOGY OF MICTURITION

Control of micturition is centered in the lumbosacral spinal cord and is modified by higher neurologic structures. Sympathetic input originates from lumbar spinal cord segments and projects to beta-adrenergic receptors in the urinary bladder and alpha-adrenergic receptors in the urinary bladder neck and internal urethral sphincter. Parasympathetic input is derived from sacral spinal cord segments and travels through the pelvic nerve to cholinergic receptors in the urinary bladder. The pudendal nerve originates from sacral spinal cord sements and provides somatic input to the external urethral sphincter.

Urine storage is maintained primarily by sympathetic activity, whereas voiding is initiated and maintained by parasympathetic input. Sympathetic input stimulates beta-adrenergic receptors in the urinary bladder, causing detrusor relaxation. Sympathetic input also stimulates alpha-adrenergic receptors in the urethra, causing contraction of the internal urethral sphincter. Voluntary contraction of the external urethral sphincter contributes to increased outlet resistance, which helps maintain continence. Filling of the urinary bladder stimulates stretch receptors, which send impulses through the pelvic nerve and spinal pathways to the brain stem and cerebral cortex. Parasympathetic impulses are transmitted from the micturition center through spinal pathways and the pelvic nerve to stimulate cholinergic receptors and initiate detrusor contraction. During detrusor contraction, concomitant inhibition of sympathetic and somatic input to the urethra allows urethral opening. In normal animals, complete voiding occurs, and the urinary bladder returns to a relaxed state.

CAUSES OF URINARY INCONTINENCE

Neurogenic Disorders

Any neurologic lesion that affects the micturition reflex may cause abnormal micturition. Incontinence is most likely to occur with lower motor neuron disorders (i.e., S1 to S3 segments or peripheral nerves), such as congenital malformation of the sacrum in Manx cats, sacral fractures, trauma affecting the pelvic nerve, and lumbosacral disease (e.g., rupture of an intervertebral disk, neoplasia, and stenosis). Upper motor neuron disorders (e.g., lesions cranial to S1) usually are characterized by urinary retention; however, if the urinary bladder is overdistended, urine may leak through the urethra once intravesicular pressure exceeds outlet resistance, causing overflow incontinence.

Non-Neurogenic Disorders

Incontinence may be associated with functional or anatomic disorders of the urethra or urinary bladder. Urethral incompetence is a functional disorder associated with incontinence; it occurs most often in neutered dogs but has also been observed in dogs with ectopic ureters and cats with feline leukemia virus infection. A less common functional cause of incontinence is detrusor instability, a disorder characterized by failure of the urinary bladder to relax during the storage phase. Anatomic abnormalities such as ectopic ureters, patent urachus, and vaginal stricture also may cause incontinence. Lower urinary tract disorders (e.g., urinary tract infection, urolithiasis) most often cause pollakiuria; however, incontinence may occur secondary to an increased urge to urinate. Animals with partial urinary outlet obstruction (e.g., small uroliths) may have incomplete voiding and a distended urinary bladder, but they also may have periods of paradoxical incontinence as urine escapes past the obstructive lesion.

DIAGNOSTIC EVALUATION

In the evaluation of dogs and cats with abnormal micturition, it is helpful to determine whether failure of urine storage or of voiding (or both) is present. Urinary incontinence is the hallmark of urine storage disorders; however, some animals with primary urine retention may also have incontinence. In addition to the information gained from the signalment, history, and physical examination, it is helpful to determine whether neurologic deficits, which may be a cause of incontinence, are a factor (Figure 30-1). Additional diagnostic tests (e.g., imaging studies) may be needed to identify the underlying cause and to help determine the appropriate treatment.

Signalment

Congenital disorders (e.g., ectopic ureters) are more common in younger animals, whereas acquired diseases (e.g., hormone-responsive incontinence) are more likely in older dogs and cats. Ectopic ureters occur most frequently in female, large breed dogs. Hormone-responsive incontinence is most common in neutered female dogs that weigh more than 20 kg.

History

Owners should be asked about previous urogenital tract problems in their pets, including trauma or surgery. Dogs and cats with ectopic ureters usually have incontinence from birth, whereas hormone-responsive incontinence often occurs in dogs several months to years after neutering. Animals with urethral incompetence often dribble urine while sleeping or lying down. If polyuria exists, it may worsen clinical signs in dogs predisposed to incontinence. It should be determined whether the incontinence is intermittent or continuous. Continuous incontinence occurs with bilateral ectopic ureters and severe urethral incompetence; intermittent incontinence may be observed with mild to moderate urethral incompetence, unilateral ectopic ureters, and disorders that cause paradoxical incontinence. The presence of dysuria, stranguria, or pollakiuria suggests lower urinary tract disorders (e.g., urinary tract infection, urolithiasis), which may cause urge incontinence.

A description of the pet's urination should be obtained from the owner; if this is not possible, the veterinarian should observe the animal urinate. The ability to voluntarily initiate and maintain urination until voiding is complete indicates normal detrusor reflex activity. Absence of this ability occurs with neurogenic diseases. Animals with urethral incompetence and those with anatomic abnormalities (e.g., ectopic ureters) can initiate and maintain urination.

Physical Examination

A thorough physical examination should be completed before the urogenital tract is examined. The urinary bladder should be palpated to detect masses and to determine whether it is full or empty, spastic or flaccid, and easy or difficult to express. Upper motor neuron disorders are associated with a firm, distended urinary bladder that is difficult to express. However, if urinary retention is prolonged, the urinary bladder may become overdistended and flaccid. Lower motor neuron diseases result in a flaccid, distended urinary bladder that is easily expressed. After the animal has voided, the bladder should be palpated again to allow estimation of the residual urine volume, which should be less than 0.4 mL/kg in normal animals. A rectal examination is indicated for evaluation of the caudal urinary bladder, urethra, and prostate gland. Vaginal palpation should be done in female dogs to detect strictures and urethral masses. The perineal area should be inspected for anatomic abnormalities and evidence of urine staining or scalding, which may occur with incontinence.

Neurologic Examination

A neurologic examination should be completed to detect deficits caused by neurogenic disorders. A decrease in or the absence of anal tone, perineal sensation, and the bulbospongiosus reflex are consistent with lower motor neuron disease. Pain on palpation over the lumbosacral area or when the tail is lifted and decreased tail tone occur in patients with lumbosacral disease. Animals with intervertebral disk disease may have ataxia, proprioceptive deficits in the rear limbs, and/or pain on palpation of the vertebral column.

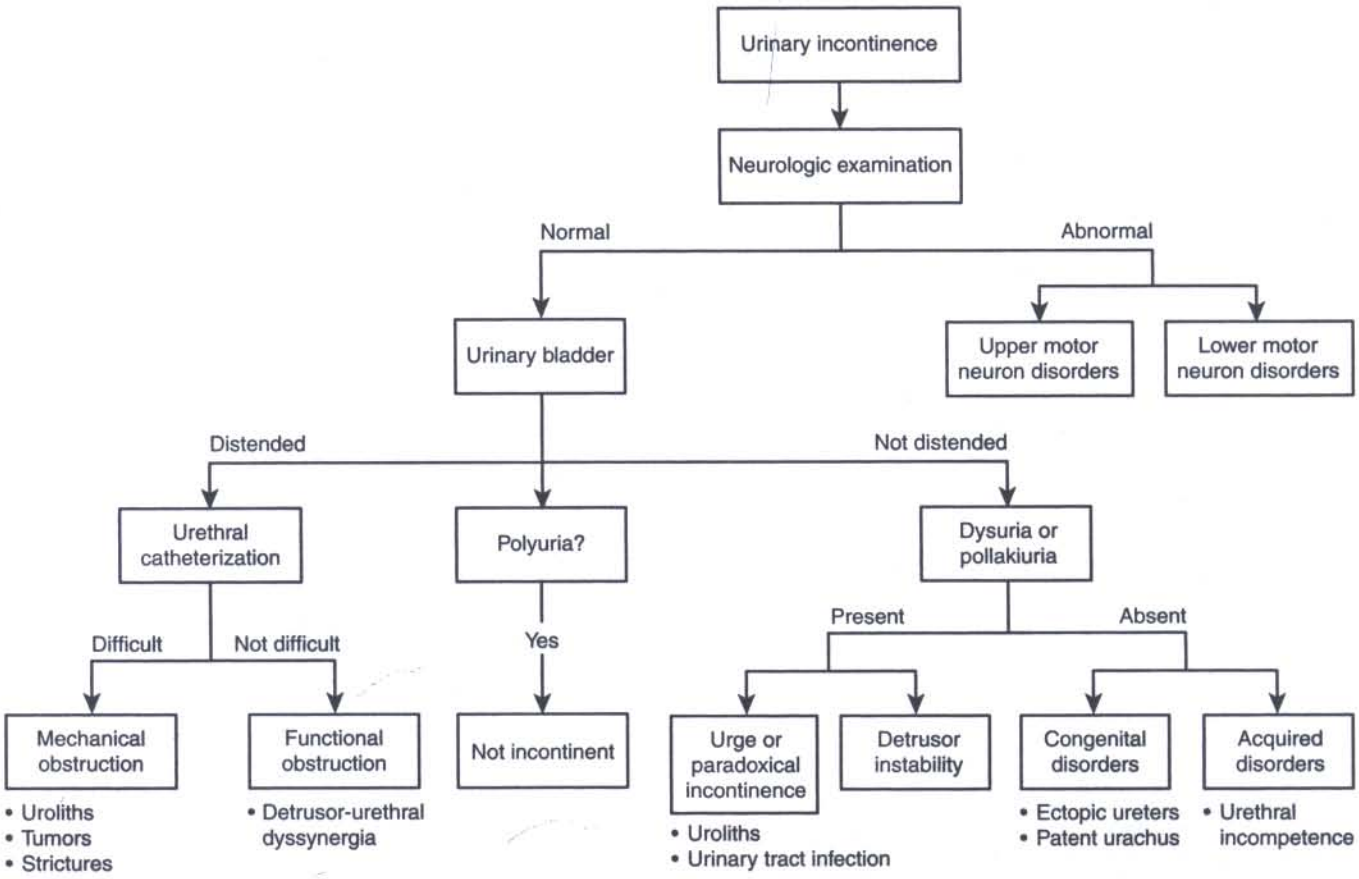


Figure 30-1 Algorithm for diagnosis and treatment of urinary incontinence.

Laboratory Tests

A urinalysis should be done and urine should be collected for culture in all animals with incontinence; other tests, such as serum chemistries, are indicated when systemic signs of illness are present (e.g., inappetence, vomiting, polyuria, polydipsia). Cystocentesis is the preferred method of collecting urine. The presence of pyuria is consistent with urinary tract inflammation, which may cause urge incontinence. Hematuria may be the predominant finding in feline lower urinary tract disease and in animals with urinary tract neoplasia. Bacteriuria found in urine collected by cystocentesis is highly suggestive of urinary tract infection. Although urinary tract infection may cause urge incontinence, it also may occur secondary to abnormal host defenses in animals with incontinence.

Diagnostic Imaging

Radiography and ultrasonography are helpful when anatomic or structural abnormalities are suspected to be the cause of incontinence. Abdominal radiographs provide information about the size and location of the urinary bladder and also help identify radiopaque uroliths and prostatomegaly. Ultrasonography is helpful for identifying structural abnormalities of the urogenital tract. If the results of noninvasive imaging are normal, contrast studies should be considered. Cystourethrography and vaginography are indicated for identifying abnormalities of the lower urinary tract and vagina, respectively. Excretory urography may be helpful for detecting ectopic ureters. In animals with neurogenic disorders, additional imaging studies (e.g., spinal films, myelography, computed tomography) may be indicated.

Endoscopy

Endoscopy of the lower urogenital tract may be helpful in female dogs suspected of having congenital or anatomic abnormalities. Vaginal strictures should be identified through digital examination of the vaginal vault, and urethral masses can be identified by vaginoscopy. Cystoscopy may be used to evaluate the flow of urine through the ureteral openings into the urinary bladder in normal dogs; the absence of urine flow through one or both ureteral openings is consistent with ectopic ureters.

Urodynamic Tests

Urodynamic studies measure pressure, volume, and flow in the urinary bladder and urethra. Because specialized equipment is needed, these tests generally are available at referral centers. In most cases, urodynamic testing is not needed; however, it may be helpful when the diagnosis is uncertain or when the response to treatment is inadequate.

OUTCOME

The outcome depends in part on the underlying cause of the urinary incontinence. The outcome in dogs and cats with structural abnormalities that can be corrected is good to excellent. Surgical correction of ectopic ureters may be successful; however, incontinence may persist due to concomitant urethral incompetence in these animals. Dogs with hormone-responsive incontinence respond well to treatment but may have periods of worsening signs that require adjustments in dosage.

CHAPTER • 31

Discolored Urine

Joseph W. Bartges

NORMAL URINE

Normal urine is typically transparent and yellow or amber upon visual inspection. Two pigments impart the yellow coloration: urochrome and urobilin. Urochrome is a sulfur-containing oxidation product of the colorless urochromogen. Urobilin is a degradation product of hemoglobin. Because the 24-hour urinary excretion of urochrome is relatively constant, highly concentrated urine is amber, whereas dilute urine may be transparent or light yellow. The intensity of the color is partly related to the volume of urine collected and the concentration of urine produced; therefore color should be evaluated in the context of the urine specific gravity. Care must be taken not to overinterpret the significance of urine color as part of a complete urinalysis. Significant disease may exist when urine is normal in color. Abnormal urine color may be caused by the presence of several endogenous or exogenous pigments. Although the abnormal color indicates a problem, it provides relatively nonspecific information. Causes of abnormal coloration should be investigated with appropriate laboratory tests and examination of urine sediment. Detection of abnormal urine color should prompt questions related to diet, administration of medication, environment, and collection technique. A knowledge of urine color may also be important in interpreting colorimetric test results, because the color may induce interference with the test.

DISCOLORED URINE

Urine color that is anything other than yellow or amber is abnormal. Discolored urine has many potential causes (Table 31-1). The most common abnormal urine color in dogs and cats is red, brown, or black, which may be caused by

Table • 31-1

Potential Causes of Discolored Urine

URINE COLOR	CAUSES
Yellow or amber	Urochromes, urobilin
Deep yellow	Highly concentrated urine, quinacrine,* nitrofurantoin,* phenacetin,* riboflavin (large quantities),* phenolsulfonphthalein (acidic urine)*
Blue	Methylene blue, indigo carmine and indigo blue dye,* indicans,* *Pseudomonas* infection,* water-soluble chlorophyll,* rhubarb,* toluidine blue,* triamterene,* amitriptyline,* anthraquinone,* blue food dye*
Green	Methylene blue, dithiazanine, urate crystalluria, indigo blue,* Evan's blue,* bilirubin, biliverdin, riboflavin,* thymol,* phenol,* triamterene,* amitriptyline,* anthraquinone,* green food dye*
Red, pink, red-brown, red-orange, or orange	Hematuria, hemoglobinuria, myoglobinuria, porphyrinuria, Congo red, phenolsulfonphthalein (after alkalinization), neoprontosil, warfarin (orange),* food pigments (rhubarb, beets, blackberries),* carbon tetrachloride,* phenazopyridine, phenothiazine,* diphenylhydantoin,* bromsulphalein (after alkalinization), chronic heavy metal poisoning (lead, mercury),* rifampin,* emodin,* phenindione,* eosin,* rifabutin,* acetazolamide,* red food dye*
Orange-yellow	Highly concentrated urine, excess urobilin, bilirubin, phenazopyridine, sulfasalazine,* fluorescein sodium,* flutamide,* quinacrine,* phenacetin,* 2,4-d,* acetazolamide,* orange food dye*
Yellow-brown or green-brown	Bile pigments
Brown to black (brown or red-brown when viewed in bright light in a thin layer)	Melanin, methemoglobin, myoglobin, bile pigments, thymol,* phenolic compounds,* nitrofurantoin,* nitrites,* naphthalene,* chlorinated hydrocarbons,* aniline dyes,* homogentisic acid*
Brown	Methemoglobin, melanin, sulfasalazine,* nitrofurantoin,* phenacetin,* naphthalene,* sulfonamides,* bismuth,* mercury,* feces (rectal-urinary fistula), fava beans,* rhubarb,* sorbitol,* metronidazole,* methocarbamol,* anthracin cathartics,* clofazimine,* primaquine,* chloroquine,* furazolidone,* copper toxicity
Colorless	Very dilute urine (diuretics, diabetes mellitus, diabetes insipidus, glucocorticoid excess, fluid therapy, overhydration)
Milky white	Lipid, pyuria, crystals

*Only observed in human beings.

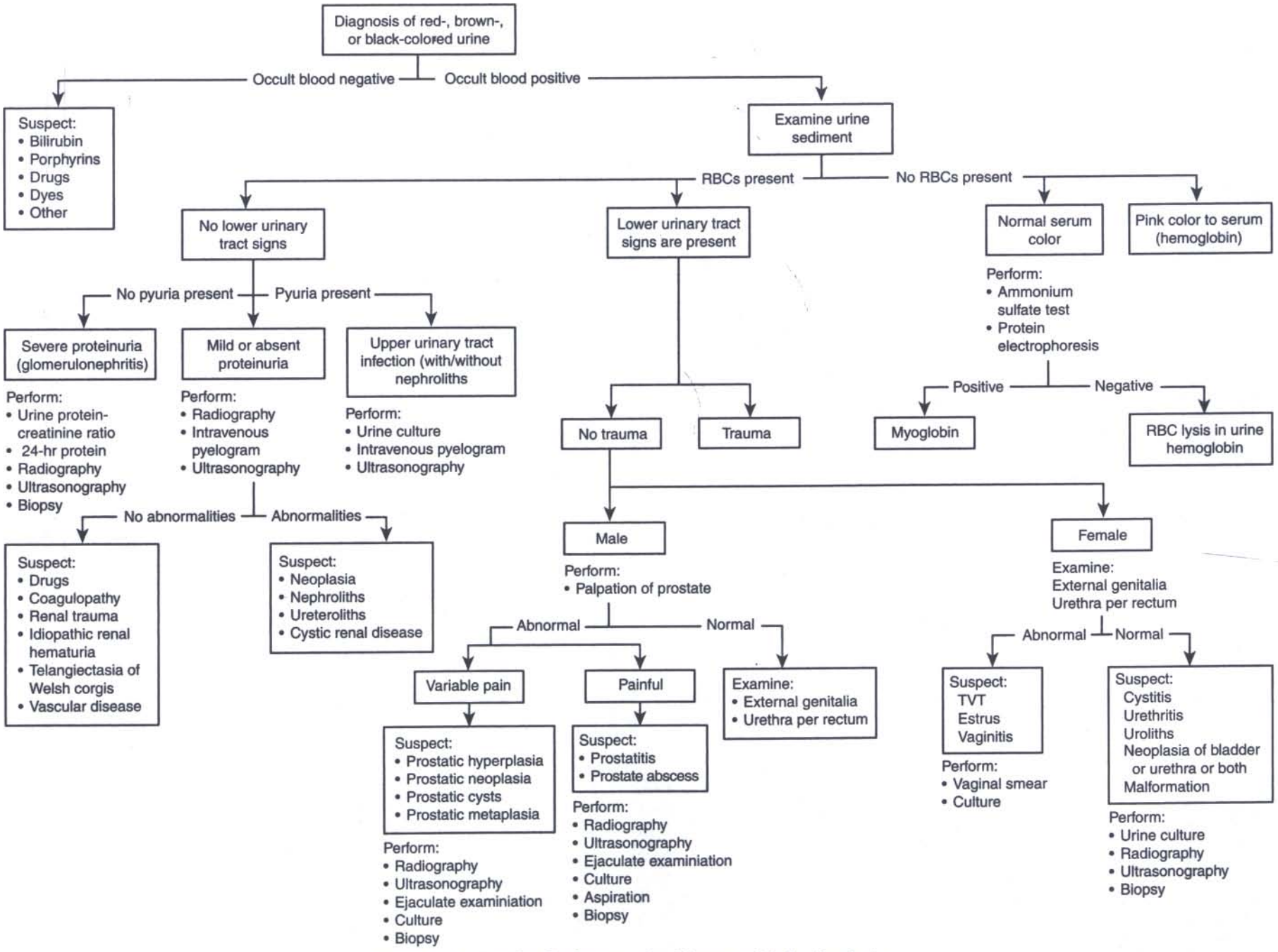


Figure 31-1 Algorithm for diagnosis of red, brown, or black colored urine.

hematuria, hemoglobinuria, myoglobinuria, and bilirubinuria (Figure 31-1).

Pale Yellow Urine

Urine that is pale yellow or clear may be normal or indicative of a polyuric state. Urine may be appropriately dilute if associated with recent consumption or administration of fluids, consumption of a diet containing low amounts of protein or high amounts of sodium chloride, glucocorticoid excess, or administration of diuretics. Urine concentration would be considered inappropriate if it were dilute in the presence of dehydration. Diseases that may be associated with persistently dilute urine include renal failure, diabetes insipidus, hyperadrenocorticism, hypoadrenocorticism, hypercalcemia, diabetes mellitus, and hyperthyroidism. If the urine is pale yellow or clear, the urine specific gravity often is less than 1.015. A simple test of whether polyuria is persistent is to determine the urine specific gravity of a sample collected in the morning. Other tests should include serum biochemical analysis and a complete urinalysis. Additional testing may include measurement of the serum thyroxine concentration, adrenal function testing, or monitoring of the urine specific gravity after several days of vasopressin administration.

Red, Brown, or Black Urine

Urine that is red, brown, or black suggests the presence of blood, hemoglobin, myoglobin, or bilirubin (see Figure 31-1). A positive occult blood reaction is obtained when urine contains any of these substances. Discoloration of urine may also result in false-positive reactions on other urine dipstick test pads. Analysis of urine sediment reveals the presence of red blood cells if the discoloration is due to hematuria. If no red blood cells are present on microscopic examination of the urine sediment, hemoglobin, myoglobin, or bilirubin should be suspected. Examination of plasma color may help differentiate these. If the discoloration of the urine is due to myoglobin, the plasma is clear, because myoglobin in plasma is not bound significantly to a carrying protein and the result is filtration and excretion of myoglobin. Pink coloration of the plasma is suggestive of hemoglobin. A yellow plasma color is suggestive of bilirubin; the serum bilirubin concentration should also be increased. Myoglobinuria is indicative of muscle damage, and serum creatine kinase activity often is increased in this setting. Hemoglobinemia is indicative of intravascular hemolysis resulting from immune-mediated, parasite-mediated, or drug-mediated destruction of red blood cells. Hyperbilirubinemia may result from liver disease, posthepatic obstruction, or hemolysis.

Milky White Urine

A milky white color may be due to the presence of white blood cells (pyuria), lipid, or crystals in the urine. The more concentrated the urine sample is, the more opaque it may appear. The presence of pyuria secondary to a bacterial urinary tract infection is the most common cause of milky white urine; however, pyuria may occur as a result of inflammation and may not be associated with an infection. Lipiduria may be observed in healthy animals but is frequently observed in cats with hepatic lipidosis. Crystalluria, if heavy and present in a concentrated urine sample, may also result in milky white urine. Microscopic examination of the urine sediment aids differentiation of these causes.

CHAPTER 32

Proteinuria

Gregory F. Grauer

Normal canine and feline urine contains only a small amount of protein. The permselectivity of the glomerular capillary wall hinders filtration of most plasma proteins, primarily on the basis of weight and, to a lesser extent, charge. Proteins with a molecular weight greater than 60,000 to 65,000 daltons are not usually filtered because of their size. Negatively charged proteins of glomerular capillary walls further restrict the filtration of other negatively charged proteins, such as albumin. Smaller molecular weight proteins, as well as the positively charged proteins that are filtered, are largely resorbed from the glomerular filtrate by proximal tubular epithelial cells. Resorbed proteins may be catabolized by the epithelial cells or returned to the circulation. Protein resorption by tubular epithelial cells has a transport maximum and, if that maximum is exceeded, proteinuria may result.

Another source of urine protein is the secretion of enzymes, mucoproteins, and immunoglobulins by renal tubular and lower urinary and genital tract epithelial cells. These secreted proteins may account for as much as 50% of the protein typically present in urine.

When examining a dog or cat with proteinuria, it is important that the veterinarian try to identify the source of the urine protein. Proteinuria may be caused by physiologic or pathologic conditions (Table 32-1). Physiologic or benign proteinuria often is transient and abates when the underlying cause is corrected. Strenuous exercise, seizures, fever, exposure to extreme heat or cold, and stress are examples of conditions that may cause physiologic proteinuria. The process by which physiologic proteinuria occurs is not completely understood; however, relative renal vasoconstriction, ischemia, and congestion likely are involved. Decreased physical activity may also influence urine protein excretion in dogs; one study demonstrated that dogs confined to cages had a higher urine protein loss than dogs with a normal level of activity.

Pathologic proteinuria may be caused by urinary or nonurinary abnormalities. "Nonurinary" disorders associated with proteinuria often involve excessive production of small molecular weight proteins, which are freely filtered by the glomerulus and which subsequently overwhelm the resorptive capacity of the proximal tubule. Examples of this excessive

Table • 32-1

Diagnostic Criteria for Different Types of Proteinuria

TYPE AND POSSIBLE CAUSES OF PROTEINURIA	DIAGNOSTIC TESTS/SIGNS
Physiologic/Benign Proteinuria	
Change in exercise level, seizure activity, fever, exposure to temperature extremes, stress	• UP/C usually <0.5 • Compatible history • Intermittent/transient proteinuria
Pathologic Proteinuria	
Nonurinary	• UP/C not indicated
Congestive heart failure	• History/PE/thoracic radiographs/echocardiogram
Hemoglobinuria/myoglobinuria	• Urine remains red after centrifugation
Paraproteinuria	• Serum/urine electrophoresis
Genital tract inflammation/hemorrhage	• PE/imaging/urine sediment changes
Urinary—nonrenal	
Lower urinary tract inflammation (e.g., bacterial cystitis, cystoliths, polyps, neoplasia)	• UP/C not indicated • History/PE • Urine sediment changes • Imaging • Urine culture
Urinary—renal	
Renal parenchymal inflammation (e.g., pyelonephritis, renoliths, neoplasia)	• UP/C not indicated • Urine sediment changes • Imaging
Tubular proteinuria	• UP/C usually 0.5-1.0 • Can be associated with normoglycemic glucosuria and excessive urinary loss of electrolytes
Glomerular proteinuria	• Persistent UP/C ≥1.0 • Inactive urine sediment except for possible hyaline casts

PE, Physical examination; *UP/C*, urine protein/creatinine ratio.

production include the production of immunoglobulin light chains (Bence-Jones proteins) by neoplastic plasma cells or the release of hemoglobin and myoglobin from damaged red blood cells and muscle tissue. Hemoglobin and myoglobin in plasma are bound by haptoglobulin, and glomerular filtration of these proteins does not occur until the binding capacity of haptoglobulins has been exceeded. Renal vascular congestion secondary to heart failure may also result in pathologic nonurinary proteinuria, as can genital tract inflammation (e.g., prostatitis or metritis).

"Urinary" proteinuria may arise from renal or nonrenal sources. Nonrenal proteinuria most frequently is associated with lower urinary tract inflammation or hemorrhage. Changes in the urine sediment often suggest the underlying cause (e.g., urolithiasis, neoplasia, trauma, or bacterial cystitis). Glomerular lesions are the most common causes of renal proteinuria. Glomerulonephritis and amyloidosis alter the selective permeability of the glomerular capillaries and frequently result in proteinuria greater than 40 mg/kg/24 hours or urine protein/creatinine ratios greater than 2.0. Persistent proteinuria of this magnitude with a normal urine sediment or a urine sediment that contains hyaline casts is suggestive of glomerular disease. In addition to glomerular disease, renal proteinuria may be caused by inflammatory or infiltrative disorders of the kidney (e.g., neoplasia or pyelonephritis) or by tubular abnormalities that result in decreased resorption of filtered protein (e.g., Fanconi syndrome) (see Table 32-1).

Proteinuria is routinely detected by semiquantitative methods, including the dipstick colorimetric test and the sulfosalicylic turbidimetric test. The dipstick test is inexpensive and easy to use; amino groups of proteins bind to the indicator incorporated in the filter paper on the dipstick and cause a color change. The color change is graded by subjective comparison to a standard. The dipstick test is most sensitive to albumin, inasmuch as albumin has more free amino groups compared with globulins or Bence-Jones proteins. False-positive results are common and may be seen with alkaline urine or urine that has been contaminated with quaternary ammonium compounds, or with excessive urine contact time, which causes the citrate buffer to leach out of the filter paper pad. False-negative results may occur with Bence-Jones proteinuria or dilute or acidic urine. The sensitivity of the dipstick test is approximately ≥30 mg/dL.

The sulfosalicylic acid test can be performed by mixing equal amounts of urine and 5% sulfosalicylic acid. The turbidity that results from the acid precipitation of protein is graded on a scale of 0 to 4+. The advantages of this test, compared with the dipstick test, are increased sensitivity and the ability to detect proteins other than albumin (e.g., Bence-Jones proteins). False-positive results are rare but may be obtained if urine contains radiographic contrast agents, penicillin, cephalothin, cephalodine, sulfisoxazole, or thymol preservatives. The protein content may be overestimated with the sulfosalicylic acid test if uncentrifuged urine or turbid urine is analyzed. False-negative results may be obtained with

highly alkaline or dilute urine. Similar to the dipstick test, the varying degrees of turbidity are not standardized, and variability in results may be seen among laboratories. The sensitivity for this test is approximately ≥ 5 mg/dL.

Proteinuria detected by these semiquantitative methods should always be interpreted in light of the urine specific gravity (USG) and urine sediment findings. Significant proteinuria may be overlooked if the urine is dilute and voluminous. Conversely, a protein reaction of trace or 1+ may be normal in concentrated urine. For example, a 2+ proteinuria with a 1.010 USG suggests much greater urine protein loss on a 24-hour basis than does a 2+ proteinuria with a 1.040 USG. In addition, the urine protein concentration is frequently increased in dogs or cats with urinary tract inflammation and/or hemorrhage. Proteinuria, therefore, should also be assessed in relation to changes in the urine sediment that are compatible with inflammation or hemorrhage (e.g., bacteria and increased numbers of white and red blood cells and epithelial cells in the urine sediment).

Recently an enzyme-linked immunosorbent assay (ELISA) for detecting low levels of albumin in canine and feline urine *(microalbuminuria)* has become commercially available (E.R.D.-Screen, Heska Corp., Fort Collins, CO). Microalbuminuria usually is defined as a urine albumin concentration between 1.0 and 30 mg/dL. These concentrations are too small to be detected routinely by standard dipstick screening tests. It is interesting to note that microalbuminuria has been shown to be an accurate predictor of subsequent renal disease in human beings secondary both to systemic hypertension and to diabetes mellitus and that it has also been observed in human beings with systemic diseases associated with glomerulopathy. Studies in dogs have shown the prevalence of microalbuminuria in apparently healthy dogs to be 19% and in dogs brought to veterinarians because of illness to be 36%. In addition, high prevalence rates of microalbuminuria have been reported in soft-coated wheaten terriers (SCWT) and SCWT/crosses (76%); in dogs experimentally infected with heartworm disease (100%); and male dogs with X-linked hereditary nephropathy (97%). Each of these models is associated with glomerulopathy, and in all three studies microalbuminuria, when it occurred, appeared to be progressive and preceded the onset of overt proteinuria. These results suggest the utility and importance of microalbuminuria as an early marker of renal disease in the dog.

Prerenal (physiologic and pathologic-nonurinary), postrenal (pathologic urinary-nonrenal), and inflammatory renal proteinuria usually can be identified on the basis of the history, physical examination, and urine sediment changes (see Table 32-1). Renal proteinuria caused by abnormal tubular resorption may be accompanied by glucosuria and excessive urinary loss of electrolytes, which helps differentiate tubular proteinuria from glomerular proteinuria. Identification of the source of the proteinuria is important, because quantitation of glomerular proteinuria can be a helpful prognostic tool, although it is not useful in patients with prerenal or postrenal proteinuria.

When glomerular proteinuria is suspected, urine protein excretion should be quantitated. Quantitation of renal proteinuria aids evaluation of the severity of renal lesions, as well as the response to treatment or the progression of disease. The trichloroacetic acid-N-Ponceau S, Coomassie brilliant blue, or benzethonium chloride tests are the methods most commonly used to quantify urine protein and are available at referral centers and reference laboratories. Collection of urine for 24 hours and measurement of urine protein excretion in milligrams per kilogram per 24 hours has been the time-honored method of quantitating proteinuria, because errors caused by variation in urine volume are minimized by 24-hour collection. However, such collections require the use of a metabolism cage, an indwelling urinary catheter, or repeated urinary catheterization, all of which make the procedure cumbersome and expensive. In addition, incomplete collection of all urine produced over the 24-hour period results in errors. Alternatively, the urine protein concentration (in milligrams per deciliter [mg/dL]) in a single, random urine sample may be divided by the urine creatinine concentration (also in mg/dL). This ratio negates the effect of urine volume on the urine protein concentration.

Calculation of the urine protein/creatinine ratio from canine and feline urine samples has been shown to accurately reflect the amount of protein excreted in the urine over a 24-hour period. This test has greatly facilitated the diagnosis of glomerulonephritis in small animals. Most studies suggest that normal urine protein excretion in dogs and cats is less than 10 to 20 mg/kg/24 hours. A regression line equation allows the urine protein/creatinine ratio, when multiplied by approximately 20, to be converted to milligrams of protein per kilogram per 24 hours. A urine protein/creatinine ratio of less than 0.5 to 1.0 is usually considered normal in dogs and cats. A complete urinalysis should always be obtained before or along with the urine protein/creatinine ratio, because hematuria or pyuria may indicate significant nonglomerular proteinuria. If evidence of inflammation is present (e.g., pyuria, bacteriuria), the protein determination should be repeated after successful treatment of the inflammatory disorder. The urine protein/creatinine ratio cannot be used to differentiate glomerular proteinuria from proteinuria associated with lower urinary tract inflammation or hemorrhage.

Urine and serum protein electrophoresis may be helpful both in identifying the source of the proteinuria and in establishing a prognosis. Proteinuria associated with hemorrhage into the urinary tract has an electrophoretic pattern similar to that of the serum. Early glomerular damage usually results principally in albuminuria; however, with progression of the glomerular disease, an increasing amount of globulin may be lost as well. Marked hypoalbuminemia and increased concentrations of larger molecular weight proteins in the serum suggest severe glomerular proteinuria and are often associated with nephrotic syndrome.

The consequences of glomerular proteinuria may include loss of plasma oncotic pressure, sodium retention, formation of edema and/or ascites, hypercoagulability, muscle wasting, and weight loss. With progressive renal disease and nephron loss, proteinuria tends to diminish as the number of affected glomeruli decrease. However, the remaining viable nephrons that have undergone compensatory hypertrophy exhibit intraglomerular hypertension and hyperfiltration. Protein loss remains increased in these individual nephrons. Evidence is accumulating in many species, including the dog and cat, that proteinuria can contribute to progressive nephron loss through tubulointerstitial damage and exacerbation of glomerular lesions.

Gastrointestinal

CHAPTER 33

Anorexia

John P. Hoover
William E. Monroe

In general, a good appetite for food is associated with health, whereas *anorexia*, or loss of appetite, is associated with illness. Reduced food consumption is a common manifestation of disease. When accompanied by observable weight loss, anorexia often prompts pet owners to seek veterinary attention. Anorexia may be the result of decreased appetite (true anorexia) or may occur secondary to other factors that do not affect appetite *(pseudoanorexia)*. Anorexia can range from partial to complete and can reflect the severity or cause of disease.

PATHOPHYSIOLOGY

Appetite was once simplistically thought to be controlled by a "hunger" or "feeding center" in the lateral (hypothalamic) nuclei (LHN) as modulated or inhibited by a "satiety center" in the ventromedial nuclei (VMN) of the hypothalamus. Chemical mediators produced by vagal or sympathetic stimulation of central and peripheral receptors provide LHN and VMN input that alters appetite. *Satiety* is associated with the absence of hunger during the absorptive phase after food ingestion, when metabolic fuels are supplied by nutrients assimilated from the gastrointestinal tract. *Hunger* is associated with the postabsorptive phase before food ingestion when energy must be derived from mobilization of stored nutrients such as glycogen, triglycerides, and proteins to provide glucose, fatty acids, and amino acids. Current evidence suggests that in addition to the LHN and VMN, the amygdala, the solitary nuclei, arcuate nuclei, paraventricular nuclei (PVN), and suprachiasmic nuclei, the anterior piriform cortex, and the telencephalon play important roles in facilitating or inhibiting appetite by means of a plethora of peripheral and central neurochemical mediators or transmitters.

HISTORICAL FINDINGS

Environmental or psychologic factors that an owner may not perceive as significant (e.g., fear, dominance) may lead to pseudoanorexia. The addition of animals that are threatening or aggressive may interfere with eating. A new baby or other individuals who make an animal feel threatened or ignored, or a change of housing, may also affect appetite. Changing the diet to one that is less palatable may lead to anorexia or a reduced appetite.

Animals that lack a sense of smell *(anosmia)* may have difficulty finding their food, and animals with severe nasal disease, especially cats, may find food unpalatable. Pets with lingual, pharyngeal, or esophageal dysfunction or those with neurologic disorders that affect swallowing (e.g., trigeminal neuritis) may show interest in food but may drop it and be unable to eat. Others with painful retrobulbar abscesses, masticatory myositis, mandibular fractures, temporomandibular joint disease, maxillary or nasal fractures or masses, severe periodontal or dental disease, or oral foreign bodies may attempt to eat only to stop, cry out, and drop food. Some may show no interest in eating. There may be a history of trauma, feeding of bones, or chewing on sticks or other potential sources of self-trauma. Animals with respiratory disease and marked dyspnea or orthopnea may be unable or unwilling to eat or drink due to compromise in breathing during prehension and deglutition.

The historical findings in animals that do not eat because of systemic disease are variable and depend on the disease present. In general, animals that are anorectic because of systemic disease have no interest in food. Pain, lameness, motor dysfunction, urination abnormalities, vomiting, diarrhea, coughing, and dyspnea all may be signs of disease that leads to anorexia. Animals with neurologic disease that results in decreased eating because of reduced cerebral arousal may have a history of behavioral changes or stupor.

Medications also may cause partial or complete anorexia through direct effects on appetite centers. Chemotherapeutic agents may inhibit appetite by inducing nausea. Opioid peptides inhibit the orexigenic network and suppress appetite. Supplying glucose, fatty acids, and amino acids by intravenous infusion may promote satiety and decrease hunger similar to that seen after eating, in the absorptive state.

PHYSICAL FINDINGS

Animals that are anorectic because of psychologic causes, such as environmental stress or unpalatable diet, usually are normal on physical examination. Bite or fight wounds may be present in pets that are not eating because of the presence of another dominant animal or excessive competition. The veterinarian can determine if an animal is having trouble finding food because of a poor sense of smell by blindfolding the pet and placing aromatic food near its nose. If the animal shows no sniffing behavior, it may not be able to smell. Observing the animal walk around the examination room where other animals have been may also reveal whether it has a sense of smell, because most pets exhibit sniffing behavior in these circumstances.

An animal that is unable to eat because of pain or dysfunction of the oral area may resist or cry out when the mouth is opened for examination. Skull fractures, soft tissue trauma, neoplasia, craniomandibular arthritis or osteoarthropathy, masticatory myositides, and retrobulbar masses all may be

associated with pain when attempts are made to open the mouth. Asymmetry of the face, mandible, nose, mouth, or skull may be apparent. Evidence of dental disease may be noted, such as severe calculus, loose or broken teeth, pain, or exudation when applying pressure to or tapping on the teeth. Ulcers, wounds, stomatitis, gingivitis, masses, or foreign bodies such as sticks, rocks, or bones may be noted when the mouth and pharynx are examined. If nasal disease is the cause of poor appetite, nasal swelling, epistaxis, mucopurulent discharge, masses, or ulceration of the mucocutaneous junctions of the nares may be seen. Exophthalmos often is noted with retrobulbar abscesses or tumors and masticatory myositides. Trigeminal neuritis or trauma to the jaw may be associated with a dropped jaw and inability to eat.

Physical examination abnormalities associated with systemic diseases that cause anorexia are as varied as the potential causes of disease. Fever, pallor, jaundice, ocular abnormalities, abdominal pain, abnormally small or large organ size, abdominal distention from fluid accumulation, spinal or limb pain, masses or swellings, cardiac murmurs, dyspnea with muffled heart and lung sounds, and adventitial breath sounds all are signs of diseases that can lead to anorexia.

DIAGNOSTIC PLAN

A thorough history is the essential diagnostic tool for psychologic or iatrogenic causes of anorexia. A thorough physical examination, in conjunction with the history, is essential to help determine physiologic causes of anorexia (Figure 33-1). Pets that are anorectic, particularly those that seem interested in food but are unable or refuse to eat, should receive a thorough oral, dental, and cranial examination. If the dog or cat is uncooperative, sedation or anesthesia may be necessary. In addition to the more routine physical examination procedures, the spine should be carefully palpated for pain (e.g., discospondylitis), and a careful rectal examination should be performed in all dogs to determine prostate size (in males), to detect pelvic masses, or to assess for unsuspected abnormalities, such as hematochezia or perineal hernias. When respiratory distress due to pleural space disease is present, thoracocentesis can provide symptomatic relief, and fluid analysis may prove diagnostic. A fundic examination after pupil dilatation should be included in the examination, because systemic diseases such as feline infectious peritonitis, lymphoma, deep mycoses, toxoplasmosis, and rickettsial infections may have characteristic ocular changes.

For pets without a history that supports a psychologic cause for anorexia and that also have no physical examination abnormalities to indicate a physiologic cause, a minimum data base should be compiled that includes a complete blood count, serum chemistry profile, urinalysis with microscopic examination of the sediment, a heartworm test in dogs, and feline leukemia virus and immunodeficiency virus serology in cats. These tests may suggest inflammatory, degenerative, endocrine, metabolic, neoplastic, or toxic disorders that can lead to anorexia. If systemic disease appears to be the probable cause of anorexia, further diagnostic testing should be directed toward abnormalities identified by the history, physical examination, and minimum data base. For cases in which no historical, physical, or data base abnormalities can be found, thoracic and abdominal radiographs or ultrasonography may reveal evidence of occult disorders, such as thoracic masses, gastrointestinal foreign bodies or masses, or pericardial, pleural, or abdominal fluid. When these procedures reveal no abnormalities, gastrointestinal endoscopy, contrast radiographic studies, or a computed tomography (CT) scan may be indicated to rule out the possibility of neoplasia or other infiltrative diseases. Multiple joint centesis may also be indicated to rule out the possibility of polyarthritis.

GOALS OF TREATMENT

The first goal of therapy for anorexia should be to correct any underlying causes, such as oropharyngeal or systemic inflammatory disease. Although definitive treatment requires a definitive diagnosis, animals that have been anorectic for longer than 3 to 5 days should receive nutritional support through enteral or parenteral feeding (see Chapters 92 and 161) until the definitive diagnosis can be made.

Appetite stimulation by drug therapy focuses on agents that affect central nervous system serotonin and dopamine receptors. Benzodiazepines and the serotonin antagonist cyproheptadine induce hunger and inhibit physiologic satiety. Megestrol acetate may stimulate appetite by central inhibition of anorexigenic hormones, such as corticotrophin-releasing hormone, as in human cancer patients. The efficacy of gastrokinetic agents in stimulating appetite in anorectic animals hasn't been established, but metoclopramide, cisapride, and the peripheral dopamine D2 receptor antagonist domperidone have yielded positive results in some human beings.

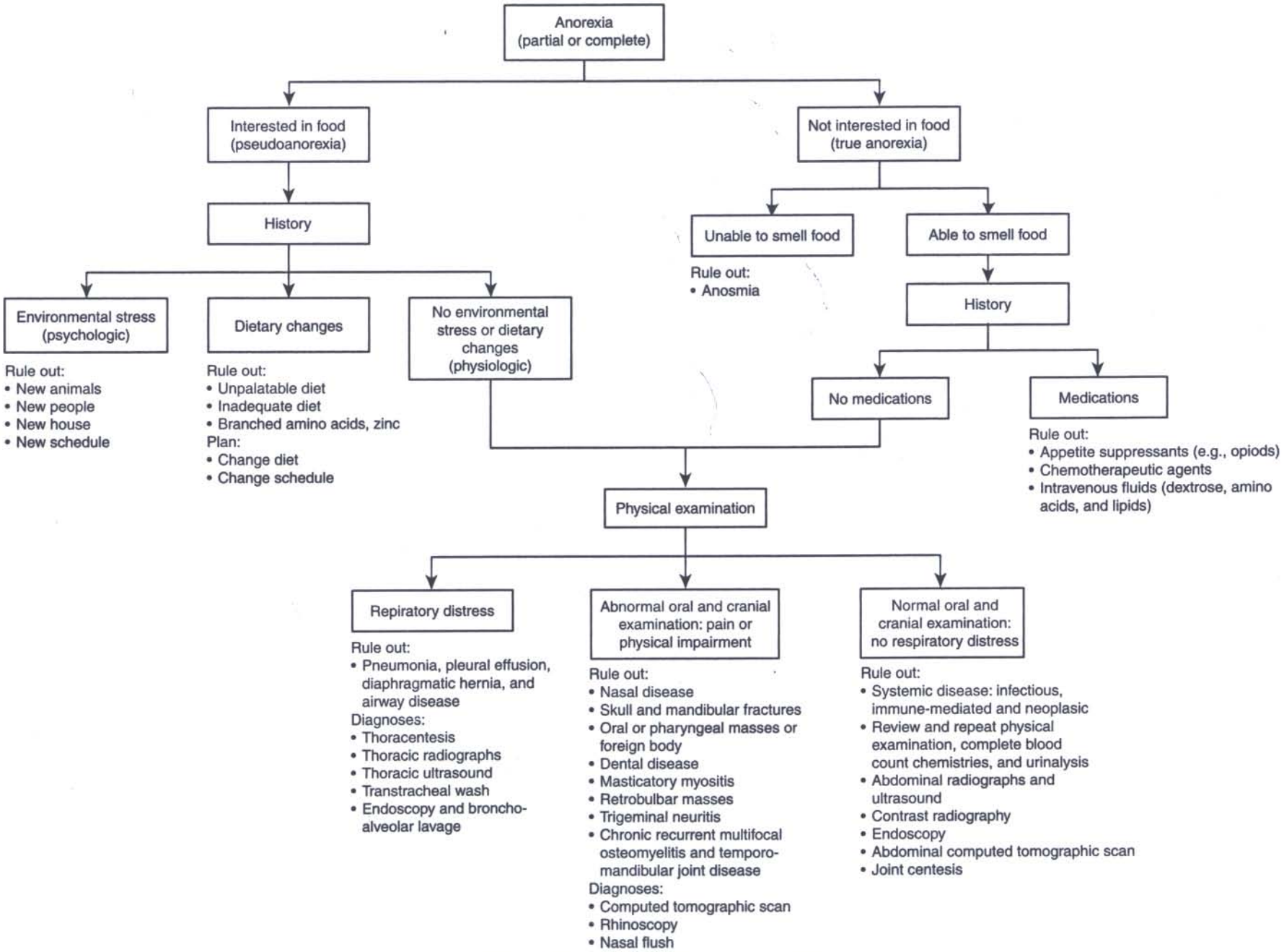


Figure 33-1 Algorithm for evaluation of anorexia.

CHAPTER 34

Polyphagia

Ellen N. Behrend

Polyphagia is the consumption of food in excess of normal caloric intake. Hunger and satiety and, consequently, feeding behavior are primarily controlled by certain regions in the central nervous system (CNS), but many factors affect the function of these areas. Thus polyphagia can be classified as *primary* (i.e., a CNS abnormality) or *secondary* (i.e., a systemic problem affecting the CNS). Secondary polyphagia is by far more common and usually is accompanied by clinical signs of the underlying disease. Determining whether weight gain or loss has occurred should be the first step in formulating a list of differential diagnoses and a diagnostic plan.

PHYSIOLOGY

Food intake is controlled by a variety of factors, including gastrointestinal, environmental, and CNS phenomena. The CNS, mainly the hypothalamus, controls eating behavior. The lateral hypothalamic nuclei represent the "feeding center"; their stimulation causes an animal to eat, and their destruction results in severe, fatal anorexia. Conversely, the ventromedial nuclei are the "satiety center," because their stimulation causes a refusal to eat even highly appetizing food, and their ablation leads to polyphagia and obesity. The feeding center is constantly active unless inhibited by the satiety center (e.g., postprandially). Lesions of the amygdala or paraventricular nuclei also can increase feeding behavior.

Gastrointestinal components that affect feeding include gastric distention, the rate of gastric emptying, the release of gastric hormones, and absorption of nutrients, such as fatty acids, glucose, and amino acids. The gut hormones can act locally on the gastrointestinal tract and centrally on the CNS. Insulin, glucagon, and cholecystokinin secreted in response to a meal decrease feeding signals from the CNS. Leptin, a polypeptide released from adipose tissue, may also help to create a sense of satiety. Decreased serum concentrations of glucose, amino acids, or lipid metabolites cause hunger by stimulating neural centers so as to re-establish normal levels. Feeding behavior also can be incited by increased nutrient utilization (i.e., an elevated metabolic rate).

Normal control of feeding, therefore, is complex and works to maintain energy stores and body weight through an interplay of central and peripheral inputs. Pathologic conditions that affect the CNS can increase feeding behavior even in the presence of normal energy stores *(primary polyphagia)*. *Secondary polyphagia* exists when feeding behavior is stimulated by non-neural factors and can be caused by an increased metabolic rate or decreased nutrient supply (Box 34-1). An augmented metabolic rate can be physiologic (e.g., pregnancy) or pathologic (e.g., hyperthyroidism) in origin. Diabetes mellitus is an unusual case of decreased nutrient supply. Due to an inability to respond to or a lack of insulin, the body does not recognize glucose and reacts to a perceived hypoglycemia. Certain diseases (e.g., hyperadrenocorticism and liver disease) lead to polyphagia by unknown mechanisms. Secondary polyphagia can also be caused by certain drugs.

HISTORY

Any change in body weight is an important differentiating feature of the various causes of polyphagia (Figure 34-1). Primary or drug-induced polyphagia typically results in weight gain, because nutrients are adequate and feeding is inappropriately increased. Pathologic secondary polyphagia is more commonly associated with weight loss, because the nutrient supply usually does not meet physiologic demands. However, some causes, such as acromegaly, hypoglycemia caused by an insulinoma, sudden acquired retinal degeneration syndrome (SARDS), and hyperadrenocorticism (HAC), lead to weight gain. Physiologic polyphagia can result in weight gain (e.g., pregnancy, growth) or maintenance of weight (e.g., lactation, cold environment, increased exercise). An animal with HAC or in the early stages of any of these states, however, may show no weight change.

Certain causes of polyphagia may be diagnosed on the basis of the history. The possibility of exposure to a cold environment, increased exercise and, for intact females, pregnancy and lactation should be ascertained. Polyphagia is commonly associated with anticonvulsant and glucocorticoid therapy but has been observed with other medications as well (see Table 34-1). Psychogenic polyphagia has been noted after introduction of a more palatable diet or in response to a stressful event, most commonly introduction of a new pet into the household. Feeding of a low-calorie diet may also be diagnosed on the basis of a complete dietary history.

An animal with primary polyphagia caused by destruction of the satiety center may have a history of trauma or clinical signs associated with CNS disease. Depending on the extent of a hypothalamic lesion, upper motor neuron signs may be seen in all four limbs or unilaterally. A midbrain lesion often leads to incessant pacing, circling, and blindness; polyuria/polydipsia may also be present. Disorders caused by diffuse or multifocal CNS disease will have other clinical signs as well, depending on the areas affected.

Perturbation of hypothalamic control of the pituitary can lead to reproductive, thyroidal, and adrenal hypofunction and associated clinical signs. Hypothyroidism secondary to pituitary dysfunction is clinically identical to primary thyroidal failure. If adrenal insufficiency occurs secondary to a lack of adrenocorticotropic hormone (ACTH), vague, nonspecific signs of lethargy and gastrointestinal disease usually are seen. Serum electrolyte concentrations (e.g., sodium and potassium) are normal because aldosterone secretion is not affected by pituitary disease. This type of hypoadrenocorticism is referred to as *atypical*.

Historical findings associated with secondary polyphagia can be highly varied. Animals with diabetes mellitus,

Box • 34-1

Differential Diagnoses of Polyphagia

Primary Polyphagia
Destruction of satiety center
- Trauma
- Mass lesion (e.g., neoplasia)
- Infection

Psychogenic causes
- Stress
- Introduction of a more palatable diet

Drug-Induced Polyphagia
Glucocorticoids
Anticonvulsants
Antihistamines
Progestins
Benzodiazepines
Amitraz
Cyproheptadine

Reported Specific Disorders Associated with Polyphagia
Feline infectious peritonitis
Lymphocytic cholangitis (feline)
Spongiform encephalopathy (feline)
Foreign body encephalitis (feline)

Secondary Polyphagia
Physiologic increase in metabolic rate
- Cold temperature
- Lactation
- Pregnancy
- Growth
- Increased exercise

Pathologic increase in metabolic rate
- Hyperthyroidism
- Acromegaly

Decreased energy supply
- Diabetes mellitus
- Malassimilation syndromes
  - Pancreatic exocrine insufficiency
  - Infiltrative bowel disease
  - Parasites
  - Lymphangiectasia
- Decreased intake
  - Megaesophagus (congenital)
  - Low-calorie diet
  - Hypoglycemia
- Unknown
  - Hyperadrenocorticism
  - Portasystemic shunt/hepatoencephalopathy
  - Sudden acquired retinal degeneration (SARDS)

acromegaly, HAC, SARDS, and hyperthyroidism usually are polyuric and polydipsic. Feline acromegaly is seen in middle-aged to older males, and naturally occurring canine acromegaly is seen almost exclusively in intact bitches. In dogs of either sex, progestin administration can lead to acromegaly, and use of this medication should be historically evident. Owners may note inspiratory stridor or a change in body conformation, such as increased interdental spaces, skin folds, or head size in acromegalic animals. It should also be noted that progestin administration to dogs and cats can increase appetite without causing acromegaly. A multitude of historical details can be associated with HAC, including abdominal enlargement, persistent panting, failure to regrow hair after clipping, lethargy, and muscle weakness. Animals with SARDS typically have the presenting complaint of sudden-onset blindness. Hyperthyroidism commonly leads to increased activity but can be associated with depression and lethargy. Gastrointestinal signs (e.g., vomiting and diarrhea) may also be present.

Hypoglycemia has a number of causes. Of these, insulinoma is the most likely to lead to polyphagia, but other neoplasias and insulin overdose may also do so. Hypoglycemic patients may exhibit weakness, trembling, ataxia, disorientation and, possibly, grand mal seizures. Malassimilation can be caused by a number of problems such as pancreatic exocrine insufficiency (PEI), infiltrative bowel disease, parasites, and lymphangiectasia. Malassimilation syndromes and PEI generally cause large-volume, malodorous, soft stools. PEI is more common in younger dogs (i.e., those less than 2 years of age), and the German shepherd breed shows a predisposition for this disorder. In older dogs and cats, PEI is rare but, if seen, is most commonly associated with chronic pancreatitis. The category of infiltrative disease encompasses processes such as inflammatory bowel disease, neoplasia, and infections such as histoplasmosis. Historical details vary according to the underlying disease.

Acquired esophageal disease often leads to anorexia, but animals with congenital megaesophagus may be polyphagic and typically have a history of regurgitation. Although anorexia is more common in animals with a portacaval shunt, polyphagia has been reported in approximately 10% of cases. Depression, vomiting, weight loss, polydipsia, and neurologic signs may also be noted. Polyphagia has been reported rarely in cases of hepatoencephalopathy; other clinical findings are the result of hepatic failure and may be similar to those in an animal with a portasystemic shunt.

PHYSICAL EXAMINATION

Physical examination findings in polyphagic animals vary, depending on the underlying disease. With primary polyphagia, neurologic abnormalities such as ataxia and proprioceptive deficits may be present. A complete neurologic and fundic examination should be performed. With acute causes of central blindness, however, the fundus appears normal.

If unclear from the history, pregnancy potentially can be diagnosed by abdominal palpation and lactation by inspection of the mammae. Approximately 80% of cats with hyperthyroidism have a palpable thyroid nodule, and approximately 50% have tachycardia or a gallop rhythm. Hyperthyroidism is rare in dogs, and a cervical mass usually is palpable. Hyperadrenocorticism can have a variety of physical examination findings, including abdominal and hepatic enlargement, muscle wasting, bilaterally symmetric alopecia, cutaneous hyperpigmentation, areas of poor hair regrowth or calcinosis cutis. Even when not noted by an owner, the physical changes associated with acromegaly can be documented on physical examination; a degenerative polyarthropathy may also be present.

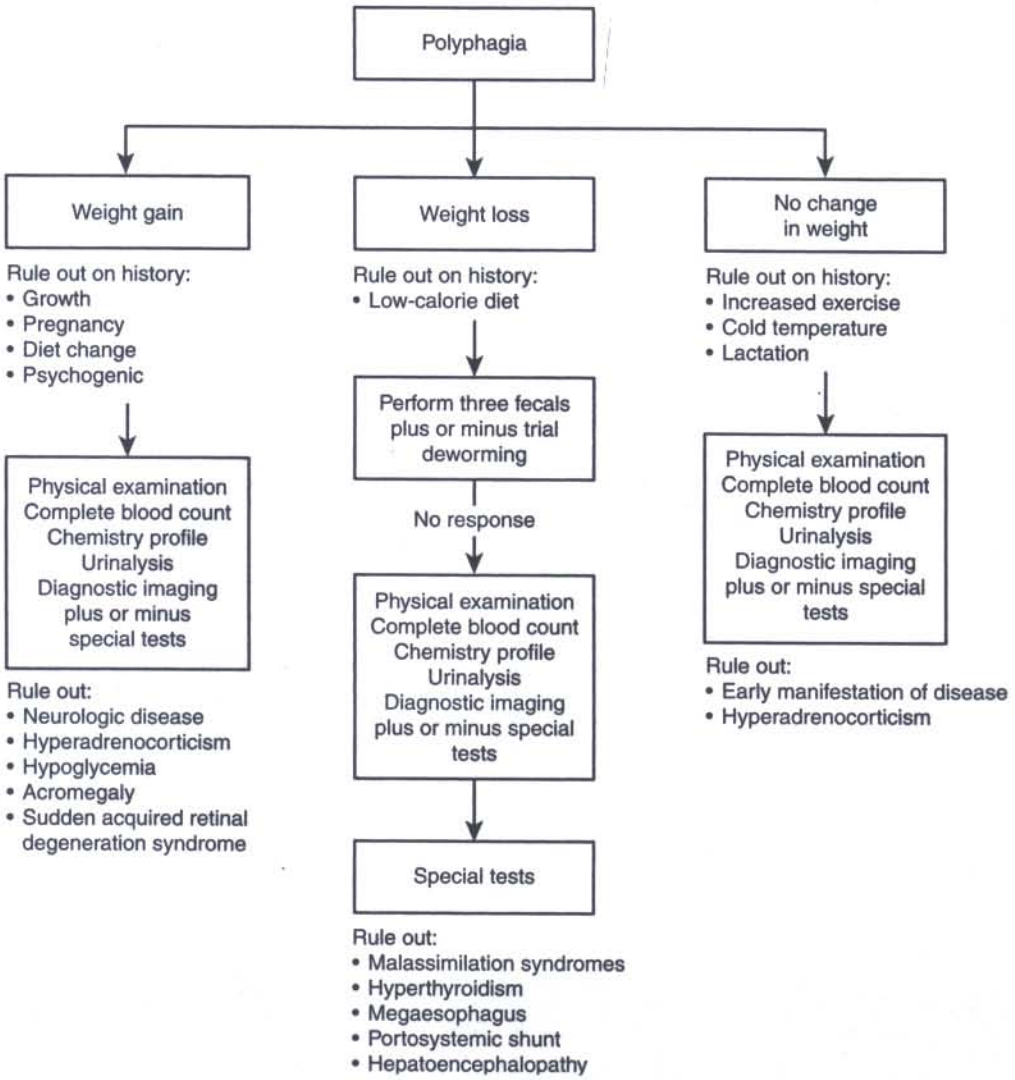


Figure 34-1 Algorithm for diagnostic approach to polyphagia.

Examination findings in a dog with SARDS may be unremarkable, because in the early stages of the disease, the retinas appear normal on fundic examination. Dogs or cats with PEI, an insulinoma, megaesophagus, hepatoencephalopathy, a portasystemic shunt, or a malassimilation syndrome may have no abnormal physical findings other than the associated weight change. In rare cases, polyneuropathies may accompany an insulinoma. Aspiration pneumonia may be present in animals with megaesophagus. Neurologic abnormalities may be detected in an animal with a portasystemic shunt, and ascites is noted in approximately 20% of afflicted dogs. Neurologic findings associated with hepatoencephalopathy may be episodic, and other examination findings vary with the cause of liver disease. Depending on the cause of malassimilation, the intestines may feel thickened. Lymphangiectasia may lead to ascites.

Occasionally, polyphagia may be a clinical sign of a disease with which it is not usually associated. For example, one cat with feline infectious peritonitis (FIP), one with foreign body encephalitis, and one with spongiform encephalopathy have been reported as being polyphagic, as have 18 cats in Great Britain with lymphocytic cholangitis. Other historical and clinical signs are present depending on the cause.

DIAGNOSTIC PLAN

The first step in diagnosis is to ascertain what change has occurred, if any, in the animal's weight (see Figure 34-1). After as many differential diagnoses as possible have been ruled out on the basis of the history, further testing is warranted. In all cases a minimum data base (MDB), including a serum biochemistry profile, complete blood count (CBC), and urinalysis, should be submitted.

For dogs and cats with weight gain, pregnancy must be ruled out. To diagnose primary polyphagia, a complete neurologic examination should be performed, any abnormalities localized, and appropriate tests obtained. A cerebrospinal fluid analysis or diagnostic imaging, such as radiography, computed tomography (CT), or magnetic resonance imaging (MRI), may be necessary.

Hypoglycemia caused by an insulinoma usually can be diagnosed by measuring paired blood glucose and insulin serum concentrations when the animal is hypoglycemic. Rarely, provocative testing may be required (see Chapter 240). The diagnosis of SARDS can be made on the basis of appropriate history, physical examination findings, an MDB that rules out other causes and, if necessary, an electroretinogram (ERG).

Although certain changes in the MDB are typical of hyperadrenocorticism, they do not confirm the diagnosis and further adrenal testing must be performed; an ACTH stimulation test or low-dose dexamethasone suppression test should be performed to confirm the diagnosis (see Chapter 242). Diagnosis of acromegaly can be difficult because of the lack of a commercial assay for growth hormone, but measurement of insulin-like growth factor-I (IGF-I) may be helpful (see Chapter 235). The history, together with conformational changes, can provide evidence of the underlying disease. Acromegalic cats consistently have insulin-resistant diabetes mellitus, and imaging of the pituitary may reveal a tumor.

If weight loss is associated with polyphagia, the MDB should be preceded by three fecal examinations. If the results of these are negative, the MDB does not provide the diagnosis, and the animal is stable, trial therapy with antiparasiticides may be warranted. If deworming does not resolve the problem, additional tests must be done. Hyperthyroidism often can be diagnosed on the basis of a single serum thyroxine measurement; however, other tests, such as measurement of the free thyroxine concentration by equilibrium dialysis, may be required (see Chapter 238).

Malassimilation syndromes cover myriad differential diagnoses (see Table 34-1). Protein-losing enteropathies can be associated with hypoalbuminemia and hypoglobulinemia. Depending on the suspected cause, measurement of serum folate or cobalamin, assessment of fat absorption, abdominal radiography or ultrasonography, and/or biopsy either by endoscopy or exploratory surgery may also be considerations. For verification of PEI, serum trypsin-like immunoreactivity (TLI) should be determined. Thoracic radiographs with a positive contrast esophagram should be used to diagnose megaesophagus; this imaging may also aid in the determination of the cause. Determination of preprandial and postprandial serum bile acid concentrations can document hepatic dysfunction, but a biopsy may be required to document the cause of hepatic failure. Ultrasonography or a radionuclide scan may be used to identify a portacaval shunt.

If the disease is in the early stages, weight change may not yet have occurred, and the list of differentials may be difficult to narrow. However, a good history and physical examination combined with an MDB can eliminate many possibilities. Although animals with HAC may not have a weight change, abdominal enlargement may create the impression of weight gain. All diseases suspected as possible differential diagnoses in this situation should be diagnosed as discussed above.

MANAGEMENT

The management of polyphagia depends on the cause. Physiologic causes of polyphagia are transient. If the condition is drug induced, the polyphagia may be temporary, as is usually seen with anticonvulsants. Psychogenic polyphagia may be corrected by removing the instigating element, if possible, or by behavioral therapy (e.g., paying more attention to the animal). If the polyphagia persists with ongoing drug therapy or if the inciting agent (stress or medication) cannot be removed, food intake should be limited to that necessary to satisfy caloric requirements. Low-calorie, high-fiber foods, such as carrots, can be added to the diet to assuage hunger and prevent obesity. Polyphagia caused by dietary factors can be managed as needed. In cases of SARDS, the polyphagia usually is self-limiting. For all other conditions, appropriate therapy should be initiated to resolve the underlying disease.

CHAPTER 35

Ptyalism

Sandra Manfra Marretta

Ptyalism is the excessive production and secretion of saliva. *Pseudoptyalism* is the drooling or dribbling of saliva because of an inability or reluctance to swallow, which results in an overflow of saliva from the oral cavity.

PATHOPHYSIOLOGY

Saliva is continuously produced by the salivary glands. The production of saliva may be increased by excitation of the salivary nuclei, located in the brain stem, after taste and tactile stimuli are received from the tongue and other areas in the oral cavity. Higher centers in the central nervous system (CNS) may also have an excitatory or inhibitory affect on the salivary nuclei. Increased production of saliva is a normal physiologic occurrence associated with imminent feeding, hyperthermia, and purring in cats.

Oral lesions and central nervous system disorders may stimulate an increase in the production of saliva. Diseases of the pharynx, esophagus, and stomach also may stimulate the production of excessive amounts of saliva. In some cases this excess may be clinically evident not as drooling but as frequent episodes of swallowing.

Anatomic abnormalities of the oral cavity may cause saliva to drip from the mouth even when normal amounts of saliva are produced. Drooling is evident with diseases in which the animal is unable or reluctant to swallow because of pain associated with swallowing.

HISTORICAL FINDINGS AND THEIR MEANINGS

Age and Breed

Young animals with congenital anomalies, including portosystemic shunt and megaesophagus, may hypersalivate. Jaw abnormalities, such as severe retrognathism, may cause excessive drooling. In some giant breed dogs, the shape and size of the lower lip may predispose to drooling. Young animals are

more indiscriminant in their eating habits, which results in a higher incidence of ingestion of foreign bodies, constipation, consumption of caustic materials, and biting on electrical cords.

Diet
High-protein diets can precipitate excessive salivation in animals with a portosystemic shunt. Animals with painful oral lesions may refuse to eat hard food, preferring bland, soft diets.

Eating Behavior
If ptyalism is caused by oral pain, the animal may drop food when attempting to eat or chew on one side.

Anorexia and Weight Loss
When anorexia and severe weight loss accompany ptyalism, the potential for acute or chronic oral lesions, systemic diseases, and gastrointestinal disorders should be considered.

Drugs and Toxins
Various drugs and toxins can cause adverse reactions, including hypersalivation, in animals. Unpleasant-tasting drugs may cause excessive salivation. Administration of higher than normal therapeutic levels of organophosphates may cause cholinergic signs including ptyalism. Overdoses of other drugs that may cause hypersalivation include: pyrethrin and pyrethroid insecticides, D-limonene (citrus oil insecticide), ivermectin, fluids containing a benzoic acid derivative, caffeine, amphetamines, cocaine, and opiates. Toxins that irritate the oral cavity include thallium, metaldehyde, and cresol. The secretions of various toads and newts and the venom of black widow spiders can cause ptyalism. Plants, including *Amanita* mushrooms, nettles, dumb cane, philodendron, dieffenbachia, poinsettia, and Christmas trees, can cause increased salivation. Household cleaning products can irritate the oral mucosa, resulting in hypersalivation.

Anesthesia
A potential complication of anesthesia is reflux esophagitis. Clinical signs, including hypersalivation and regurgitation, may develop 1 to 4 days after anesthetic episodes.

Swallowing Difficulty
Evaluation of dysphagia as a potential cause of excessive drooling can be supported by observing the dog or cat eating and drinking. Pharyngeal lesions, neuromuscular disease, and abnormally large retropharyngeal lymph nodes can cause dysphagia.

Regurgition
Excessive salivation may occur in animals that regurgitate secondary to esophageal disease. In cases of chronic reflux esophagitis, hypersalivation, regurgitation, and vomiting often occur soon after eating. Regurgitation and hypersalivation may also be seen in animals with esophageal foreign bodies or tumors.

Vomiting
Nausea is the first stage in the complex process of vomiting, which may be accompanied by hypersalivation and frequent episodes of swallowing.

Behavioral Changes
Animals with oral pain may show behavioral changes, including depression and/or aggressiveness. These changes may also be associated with hepatic encephalopathy and rabies.

Hepatic Encephalopathy Signs
Animals with CNS signs, behavioral changes, and signs of hepatic failure including anorexia, weight loss, lethargy, polydipsia, polyuria, nausea, ptyalism, vomiting, and diarrhea should be evaluated for hepatic encephalopathy.

Seizures
During a seizure, ptyalism may occur secondary to autonomic discharge, reduced swallowing of saliva, and clonic movements of the jaw.

PHYSICAL FINDINGS AND THEIR INTERPRETATION

Halitosis
Halitosis usually is associated with oral pathology, including periodontal disease, oral ulcers, cheilitis, stomatitis, or neoplasia. Esophageal and gastric disorders less frequently may cause halitosis.

Oral Cavity
Oral Trauma
Animals that are drooling after a traumatic event should be carefully evaluated for oral trauma. Fractured teeth, with pulpal exposure or jaw fractures, cause significant pain and may result in secondary hypersalivation. With bilateral mandibular fractures, the rostral mandible drops and excessive drooling occurs.

Periodontal Disease
Severe periodontal disease may cause significant gingival and oral mucosal inflammation. Severe contact ulcerations may occur on the mucosa in contact with the teeth, causing extreme oral pain and ptyalism.

Stomatitis
Stomatitis, which frequently is associated with ptyalism, has many underlying causes, including local factors, immune-mediated diseases, systemic infections, toxins, and immunologic or nutritional deficiencies.

Oral Masses
Neoplasms, eosinophilic granulomas, and granulomatous lesions may occur in the oral cavity. Ulcerated masses may be painful and cause ptyalism. Caudal oral masses or those that interfere with tongue movement may cause difficulty with swallowing, resulting in excessive drooling.

Glossitis
Lingual ulcers often are painful and may result in hypersalivation. Irritation of the tongue may be caused by chemical or environmental substances, viral infections, metabolic disorders (uremia), immune-mediated diseases, and tumors.

Base of the Tongue
The base of the tongue should be examined thoroughly, with the animal under sedation if necessary, to rule out the presence of a mass or foreign body. Linear foreign bodies may be trapped around the base of the tongue, and penetrating foreign bodies may cause severe inflammatory responses and pain, resulting in hypersalivation.

Faucitis
Severe inflammation and ulceration of the glossopalatine arch occurs primarily in cats. Severe faucitis is painful, and affected cats exhibit severe discomfort when the mouth is fully opened.

Blood-Tinged Saliva
Blood-tinged saliva most frequently is indicative of bleeding from the oral cavity. Less frequently, it may be associated with bleeding from the upper intestinal tract, nasal passages, or lungs.

Mucocutaneous Junction Ulcerations
When ulcerative stomatitis is associated with ulcerations at the mucocutaneous junctions, the possibility of an immune-mediated disease should be considered.

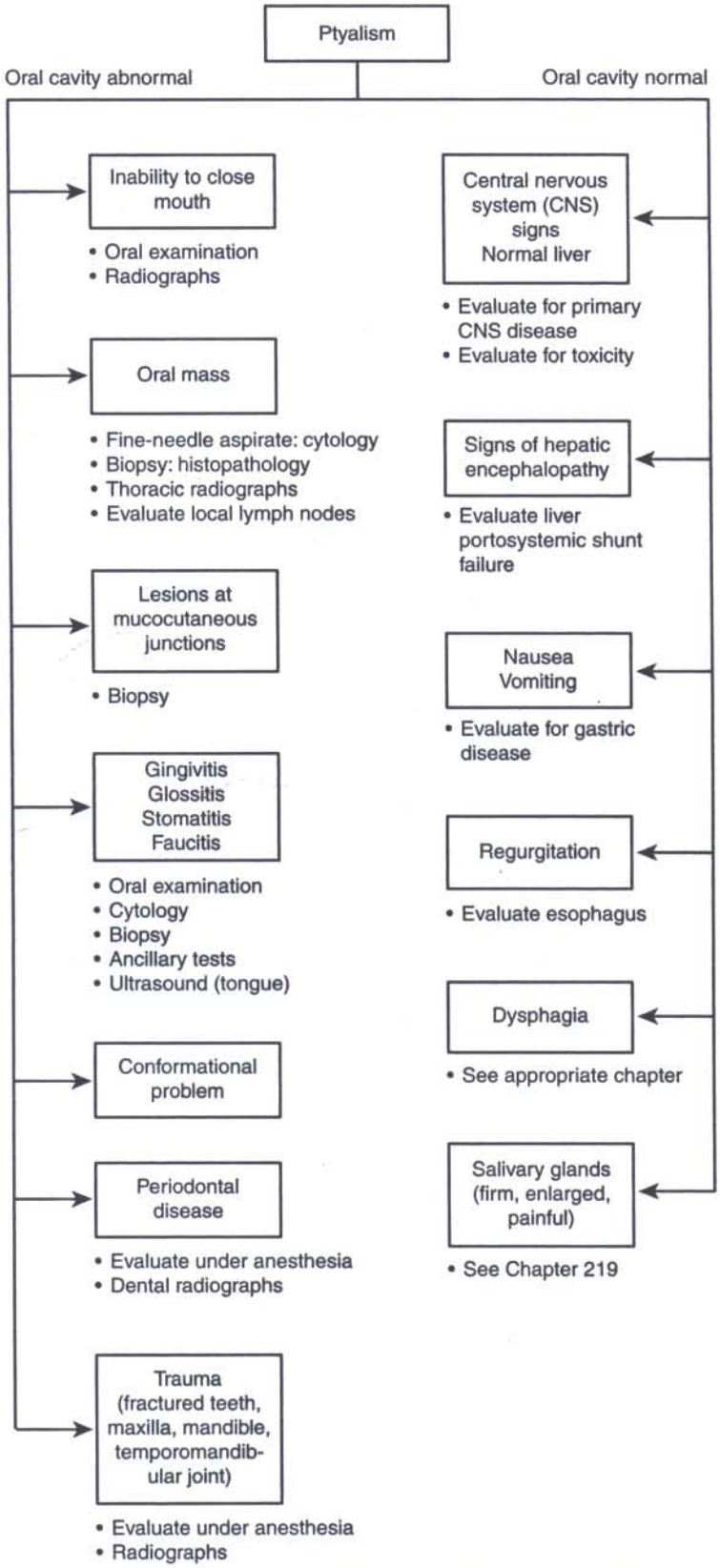


Figure 35-1 Algorithm for differential diagnosis of ptyalism.

Facial Pain
Ptyalism may occur secondary to pain associated with oral or pharyngeal disease, and these patients may resist oral examination.

Dysphagia
Space-occupying lesions and severe inflammatory lesions in the pharyngeal region may cause dysphagia and excessive drooling.

Cranial Nerve Deficits
Lesions of the trigeminal nerve (cranial nerve [CN] V) can cause drooling secondary to an inability to close the mouth. Facial nerve palsy (CN VII) may cause drooling from the affected side because of inability to move the lip. Glossopharyngeal (CN IX), vagus (CN X), and hypoglossal (CN XII) nerve lesions can cause loss of the gag reflex or inability to swallow and secondary drooling.

Dropped Jaw
Trigeminal nerve (CN V) paralysis prevents voluntary closure of the mouth. The differential diagnoses in these cases include idiopathic trigeminal neuritis, bilateral mandibular fractures, and infectious diseases, such as rabies.

Inability to Close Mouth with Assistance
Animals with acute sustained inability to close the mouth, even with assistance, will hypersalivate. Foreign bodies or displaced teeth may interfere with normal occlusion and closure of the mouth. Displacement of the coronoid process lateral to the zygomatic arch or temporomandibular luxations may result in intermittent or sustained locking of the jaw in an open position.

Muscle Atrophy
Muscle atrophy may occur secondary to cranial nerve deficits or muscular disorders, such as myositis, that may result in difficulty swallowing.

Lymph Nodes
Retropharyngeal lymph node enlargement or regional lymphadenopathy may cause dysphagia.

Salivary Glands
Ptyalism rarely may be associated with salivary gland enlargement or necrosis.

DIAGNOSTIC PLAN

A systematic approach is required for diagnosing the underlying cause of ptyalism in animals. The initial plan in all dogs and cats should include a thorough history and physical examination, followed by appropriate diagnostic procedures based on the history and physical findings (Figure 35-1).

CHAPTER 36

Gagging

William Gengler

Gagging is defined as the swallowing-vomiting reflex activity of the elevation of the soft palate followed by a reverse peristalsis of the upper digestive tract. *Swallowing* is the taking in of a substance through the mouth and the pharynx and into the esophagus. It is a combination of a voluntary act and a series of reflex actions. Once begun, the process operates automatically. The swallowing reflex is a rigidly ordered sequence of events that propels food from the mouth to the stomach while concurrently inhibiting breathing and preventing food from entering the trachea.

The nerves involved with swallowing are the sensory and motor branches of the trigeminal nerve (CN V), the hypoglossal nerve (CN XII), the facial nerve (CN VII), and the glossopharyngeal nerve (CN IX). The afferent limb of the swallowing reflex begins with tactile receptors, most notably those near the opening of the pharynx. Sensory impulses from these receptors are transmitted to certain areas in the medulla. The central integrating areas for swallowing lie in the medulla and lower pons, called the *swallowing center.* Motor impulses travel from the swallowing center to the musculature of the pharynx and upper esophagus via various cranial nerves.

The process of swallowing, called *deglutition*, can be divided into three phases in the dog and cat (and also in human beings): (1) the oral (or voluntary) phase, (2) the pharyngeal phase, and (3) the esophageal phase (Figure 36-1). The *oral phase* is initiated by separation of a bolus of food from the mass in the mouth with the tip of the tongue. The bolus is moved in a dorsocaudal direction in the mouth by pressing first with the tip of the tongue and then with the more caudal tongue segment against the hard palate. The bolus is forced into the pharynx, where it stimulates the tactile receptors that initiate the swallowing reflex. In the cat the oral phase is much longer, marked by bolus accumulation in the valleculae.

The *pharyngeal phase* of swallowing occurs in less than 1 second. During this phase, breathing is reflexly inhibited. The soft palate is pulled dorsally and the palatopharyngeal folds move medially, preventing reflux of food into the nasopharynx. The pharyngeal passage narrows, directing the bolus caudally. Concurrently, the vocal cords move medially and the epiglottis covers the opening of the larynx, preventing food from entering the trachea. The cranial esophageal sphincter relaxes to accept the bolus. The dorsal constrictor muscles of the pharynx contract strongly to force the bolus deep into the pharynx. Peristalsis of these muscles initiates the movement of the bolus caudally through the cranial esophageal sphincter into the esophagus.

The *esophageal phase* of swallowing is partly controlled by the swallowing center. The cranial esophageal (pharyngoesophageal) sphincter, or cricopharyngeus muscle, reflexly constricts after the bolus passes caudal to the sphincter, preventing regurgitation of the bolus. A peristaltic wave, which

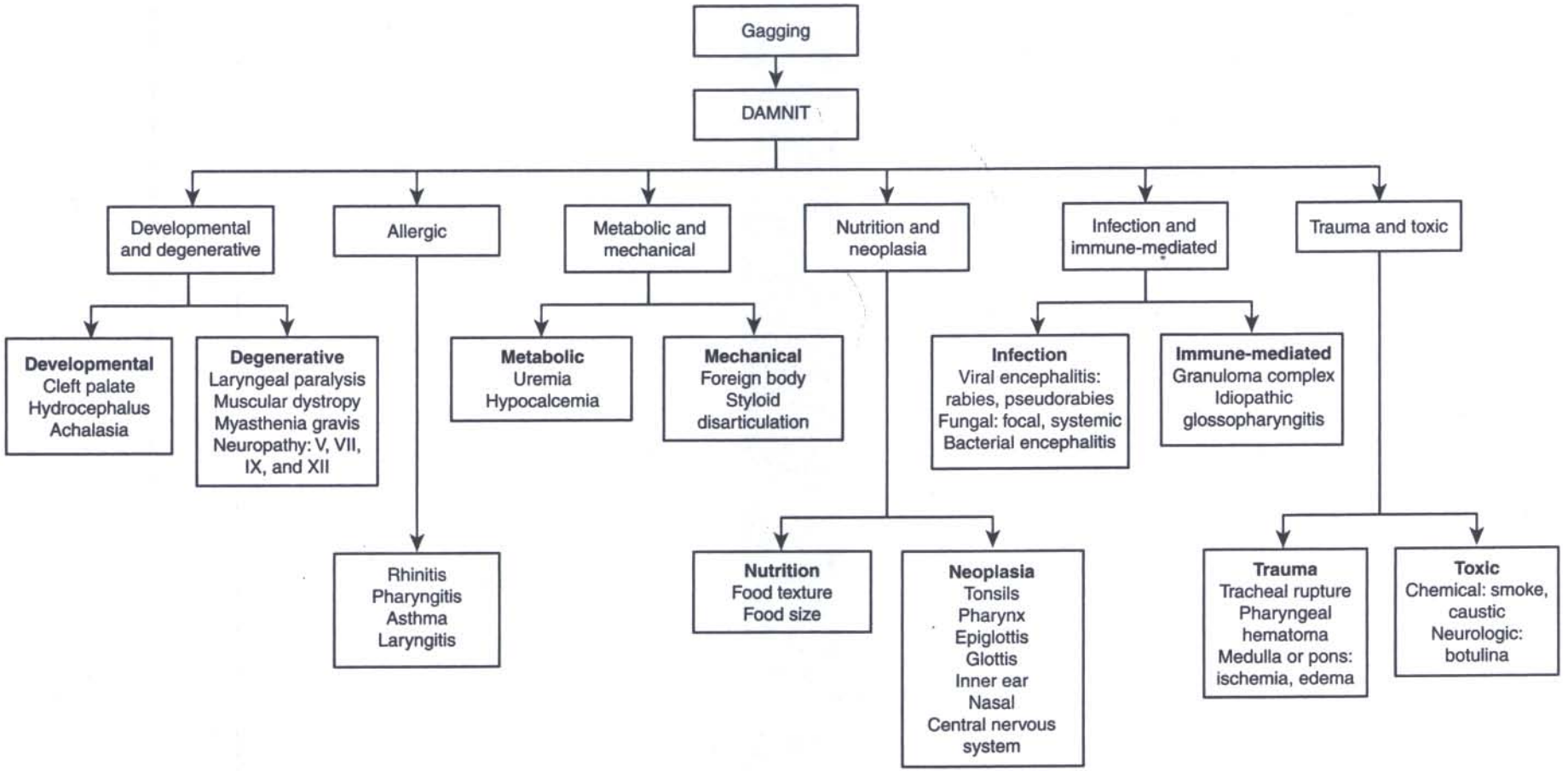


Figure 36-1 Algorithm for gagging.

begins just caudal to the cranial esophageal sphincter, traverses the entire esophagus in approximately 10 seconds. The initial peristaltic wave is termed *primary peristalsis* and is controlled by the swallowing center. If primary peristalsis is insufficient to clear the bolus from the esophagus, distension of the esophagus stimulates *secondary peristalsis,* which is mediated in part by the swallowing reflex and by local stretch receptors.

During primary and secondary peristalsis, the caudal esophageal (gastroesophageal) sphincter relaxes to receive the bolus into the stomach. In human beings and dogs, the cranial one third of the tunica muscularis of the esophagus is composed predominantly of striated muscle, the caudal one third is composed predominantly of smooth muscle, and the middle one third is a mixture of these two muscle types. In the cat, the esophagus changes abruptly from striated to smooth muscle at the heart. Somatic nerve fibers from the vagus nerve (CN X) form motor endplates on striated muscle fibers. Visceral motor nerves are preganglionic parasympathetic fibers that innervate the smooth muscle cells.

Gagging often is associated with retching. *Retching* is an involuntary and ineffectual attempt at vomiting, and the causes of retching are similar to those that cause vomiting. Another physical sign that resembles gagging is *expectoration,* which involves clearing the airway of mucus and discharges without nausea. For cats, expectoration can be a normal means of clearing the airway of hair after grooming.

CHAPTER 37

Dysphagia and Regurgitation

Emilie Fleming

Dysphagia and regurgitation are both manifestations of swallowing disorders. Close attention to the history, clinical signs, and physical examination findings can help localize the disease process responsible (Figures 37-1 and 37-2).

DYSPHAGIA

Dysphagia, defined as difficult or painful swallowing, may be due to pain during the swallowing process, mechanical obstruction of the oral cavity or pharynx, or neuromuscular dysfunction that results in weak or uncoordinated swallowing (Box 37-1). Dysphagia generally is broken down into three types: *oral dysphagia* is difficulty prehending and forming a bolus of food at the base of the tongue; *pharyngeal dysphagia* is a malfunction of the involuntary movement of a food bolus through the oropharynx; and *cricopharyngeal dysphagia* is failure of relaxation *(achalasia)* or closure of the cricopharyngeal sphincter or cricopharyngeal asynchrony (Figure 37-1).

Clinical Signs

Clinical signs vary depending on the location or severity of the swallowing defect. Oral dysphagia is expressed by difficulty prehending food and by modified eating behavior, such as tilting or throwing back the head while eating. With pharyngeal dysphagia, prehension of food generally is more normal, but repeated efforts to swallow often are seen, generally accompanied by flexing and extending of the neck. With cricopharyngeal dysphagia, patients make repeated efforts to swallow and may gag or cough. They also may regurgitate immediately after or during swallowing.

History

Very young affected animals are more likely to suffer from congenital defects. For example, cricopharyngeal achalasia generally is seen at the time of weaning from milk to solid food. Young to middle-aged animals are more prone to ingesting foreign bodies, which may become lodged in the esophagus, or caustic substances. Older dogs, or dogs with chronic signs (e.g., weight loss, reluctance to eat) have an increased likelihood of systemic disease. Acute signs are more consistent with a mechanical obstruction, such as a foreign body, mass, or inflammation. The presence of other cranial nerve signs in conjunction with dysphagia suggests central nervous system (CNS) disease.

Diagnosis

A complete physical examination is essential to enable the clinician to localize the source of the dysphagia. A thorough oral examination, often requiring sedation, is important to evaluate for foreign bodies, masses, stomatitis, and tooth root abscesses. A neurologic examination, including cranial, gait, and peripheral nerves, is essential. It also is important to evaluate the patient as a whole, focusing on body condition, the presence or absence of weight loss, and interest in food. These help narrow down the list of differential diagnoses. Because rabies is a differential diagnosis, caution must be exercised in all cases with any index of suspicion for this disease.

A diagnostic plan begins with survey radiographs of the head, neck, and thorax to evaluate for foreign bodies and evidence of aspiration pneumonia. If other systemic signs are present, a complete blood count, chemistry screen, and urinalysis should be done. If warranted, contrast fluoroscopy motion study or endoscopy can be considered. Also, further blood studies may be indicated to rule out specific disease processes.

Treatment

Treatment of dysphagia involves identification and elimination of the underlying disorder, which may involve medical or surgical treatment. Management with tools such as feeding tubes may be necessary. Treatment of any complications, such as aspiration pneumonia, also is important.

REGURGITATION

Regurgitation is the passive retrograde expulsion of gastric or esophageal contents (Box 37-2). Regurgitation may occur immediately or minutes to hours after eating. The regurgitant

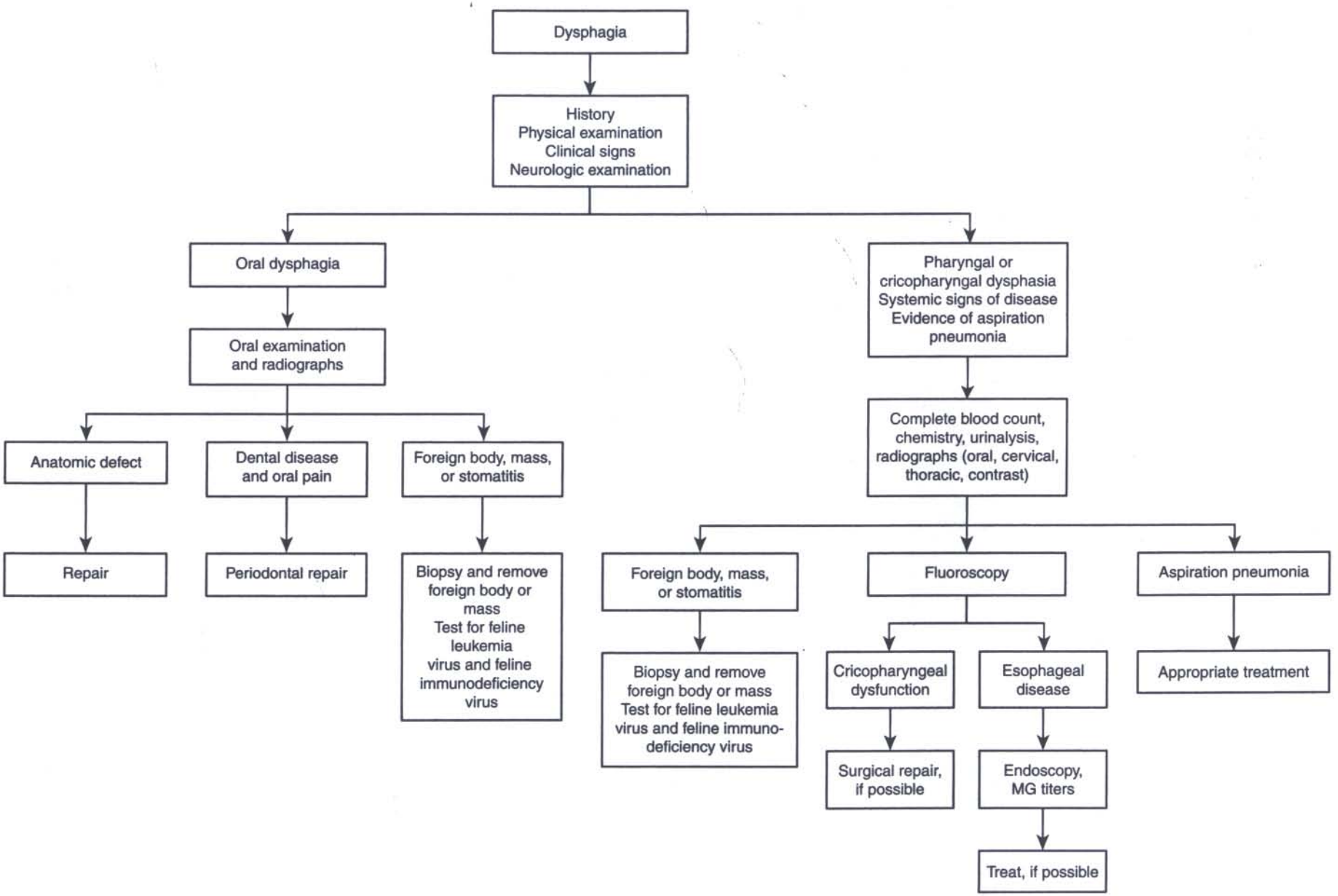


Figure 37-1 Dysphagia.

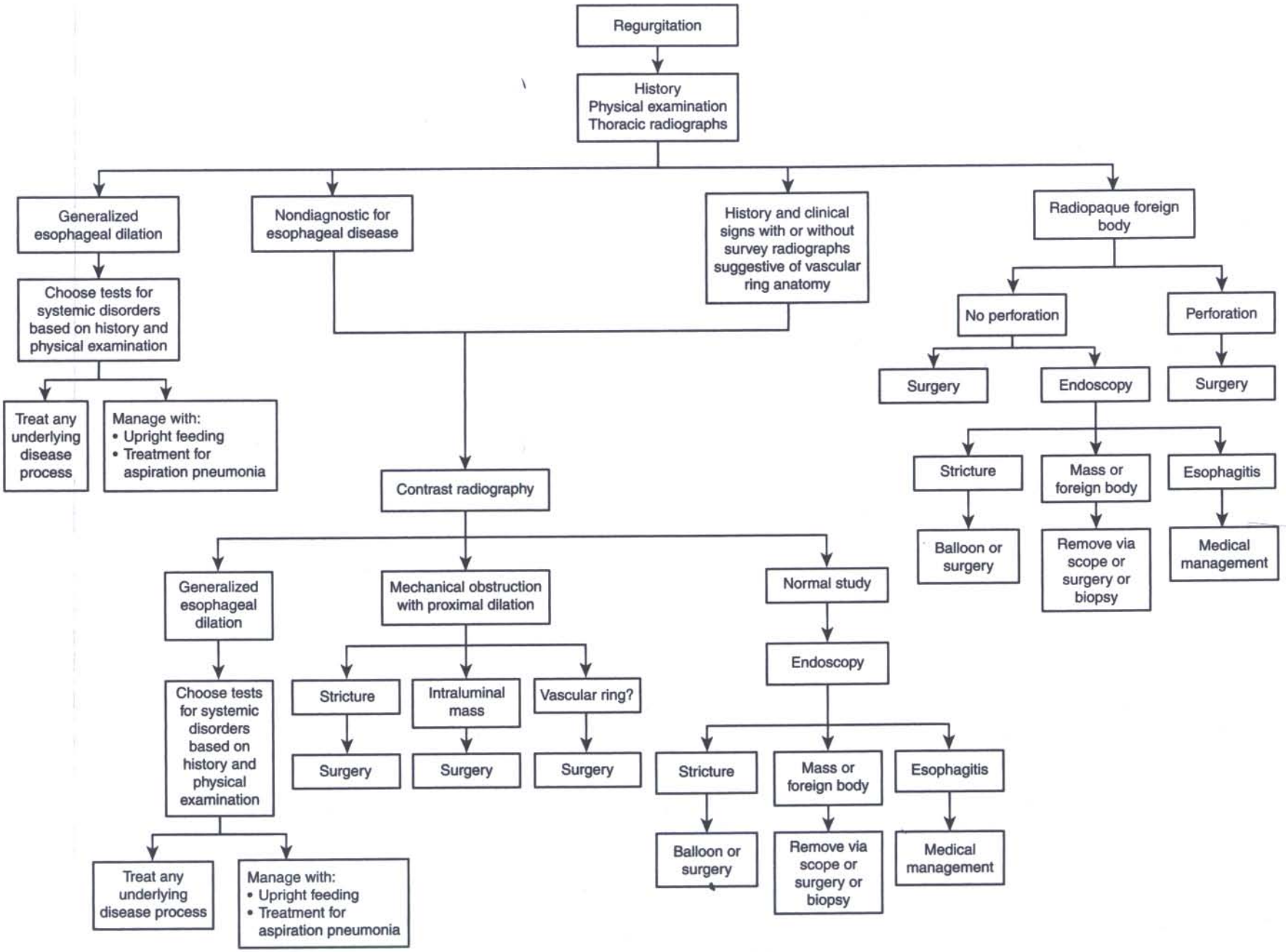


Figure 37-2 Regurgitation.

Box • 37-1

Causes of Dysphagia

Anatomic or Mechanical Lesions
Pharyngeal inflammation (e.g., abscess, inflammatory polyps, oral eosinophilic granulomas)
Foreign body obstruction (oral, pharyngeal, nasopharyngeal, proximal esophagus)
Neoplasia
Retropharyngeal lymphadenomegally
Sialocele
Mandibular fracture
Lingual frenulum disorder
Cricopharyngeal achalasia or asynchrony
TMJ disorder (e.g., luxation, fracture)
Cleft palate
Pharyngeal trauma

Pain
Stomatitis/glossitis/pharyngitis (FIV, FeLV, immune-mediated disease, uremic glossitis, ingestion of a caustic substance)
Tooth-related problems (tooth root abscess, fracture, periodontitis)
Trauma
Electric cord burns
Retrobulbar abscess

Neuromuscular Disorders
Myasthenia gravis (focalized or generalized)
Acute polyradiculitis
Masticatory myositis
Tick paralysis
Botulism
Polymyositis
TMJ disease

Neurologic Disorders
Rabies
Trigeminal paralysis or neuritis
Neuropathies of cranial nerves VII, IX, X, or XII
CNS disease (brain stem lesion)

Box • 37-2

Causes of Regurgitation

Esophageal Disease
Megaesophagus (primary or secondary)
Esophagitis
Mechanical obstruction (foreign body, stricture, vascular ring anomaly)

Alimentary Disorders
Pyloric outflow obstruction
Gastric dilatation volvulus
Hiatal hernia

Neuropathies
Peripheral (polyradiculitis, giant cell axonal neuropathy, polyneuritis, lead poisoning)
Central (distemper, brain stem lesion, neoplasia, trauma)

Neuromuscular Junction Abnormalities
Myasthenia gravis (focalized or generalized)
Botulism
Tetanus
Acetylcholinesterase toxicity

Immune-Mediated Causes
Systemic lupus erythematous
Polymyositis
Dermatomyositis

Endocrine
Hypothyroidism
Hypoadrenocorticism

may be either undigested or digested food or liquid. The first important clinical distinction is to differentiate regurgitation from vomiting. This is done by taking a detailed and careful history, by clinician observation of the patient, or by having the owner videotape the event. Regurgitation is differentiated from vomiting by the lack of forceful abdominal contractions. In addition, the regurgitant should not be yellowish green.

Clinical Signs

Clinical signs may include weight loss accompanied by an increased appetite. Regurgitating animals often present with signs of aspiration pneumonia. Systemic signs of underlying disease processes that can cause regurgitation also may be noted, such as the weakness associated with myasthenia gravis.

Diagnosis

A complete physical examination is essential. A neurologic examination can help reveal a possible neuropathy or neuromuscular dysfunction. Auscultation is important to evaluate for aspiration pneumonia and other respiratory or cardiovascular abnormalities.

Thoracic radiographs should be examined for generalized esophageal dilatation, radiopaque foreign bodies, focal esophageal dilatation or other evidence of vascular ring anomalies, and evidence of aspiration pneumonia. Contrast radiography may be necessary for evaluation of the size and shape of the esophagus and any vascular anomalies. Endoscopy of the esophagus is useful for evaluating for foreign bodies, strictures, or esophagitis. Fluoroscopy can be used to characterize motility during swallowing.

When clinical signs suggest systemic disease or with evidence of megaesophagus, laboratory data are an important tool in ruling out underlying disorders. The initial workup includes a complete blood count, chemistry screen, and urinalysis. Depending on clinical suspicion, a thyroid hormone determination, adrenocorticotropic hormone (ACTH) stimulation test, acetylcholine receptor antibody test, lead level determination, and antinuclear antibody (ANA) test can be considered.

Treatment

Treatment is aimed at any underlying disease process and at complications, such as aspiration pneumonia. Considerable effort can be put into the management of a regurgitating animal. Management of megaesophagus, for example, often includes feeding small, frequent meals from an elevated level.

CHAPTER 38

Vomiting

David C. Twedt

Vomiting is a common clinical sign observed in small animals. It occurs secondary to gastrointestinal and nongastrointestinal disorders.

In its evolution, vomiting began as a rather primitive protective means of removing toxic or noxious ingested substances. Vomiting mechanisms then progressed to prevention of further adsorption of toxin after a toxic substance had entered the bloodstream. A mechanism that stimulates vomiting then evolved so that an animal could feed ingested food from a hunt to an offspring; this reflex is more developed and arises from higher centers in the central nervous system (CNS).

An important fact to remember is that vomiting is a clinical sign, not a disease per se. Clinically, vomiting results from a variety of disorders of the gastrointestinal system, as well as from disorders such as abdominal conditions, systemic or metabolic disease, and drug toxicity. This chapter covers basic pathophysiology, etiologies, and a practical clinical approach to evaluation of a patient with vomiting.

PATHOPHYSIOLOGY

The clinical act of vomiting is divided into three phases: nausea, retching, and vomiting. *Nausea* precedes vomiting and is associated with an episode that defies complete definition in animals. Outward signs of nausea may include depression, shivering, hiding, yawning, and licking of the lips. Increased salivation and swallowing occur; this lubricates the esophagus with bicarbonate-rich saliva that neutralizes gastric acid as it passes through the esophagus. Next, there is a reduction in gastric, lower esophageal sphincter, and esophageal motility, which is followed by increased retrograde motility of the proximal small intestine. *Retching*, the second phase of vomiting, consists of forceful contractions of the abdominal muscles and diaphragm to produce negative intrathoracic pressure and positive intra-abdominal pressure. These pressure changes are associated with movement of gastric contents into the esophagus. *Vomiting*, the third phase, occurs when the gastric contents are forcefully expelled from the mouth by the driving force generated by contraction of the abdominal muscles and diaphragm, which causes intra-thoracic pressure to change from negative during retching to positive during vomiting. As the vomit passes through the pharyngeal cavity, respiration is inhibited and the nasopharynx and glottis close to prevent aspiration.

Vomiting is a complex and poorly understood clinical sign that is best described as a neurologically mediated reflex act initiated by stimulation of the conceptualized *vomiting* or *emetic center* in the medulla oblongata of the brain. Activation of the vomiting center occurs either through a humoral pathway initiated by blood-borne substances or through activation of various neural receptors and the pathways leading to the vomiting center (Figure 38-1). Adjacent to the vomiting center are areas for controlling respiration and salivation, which both are integrated into the vomiting process.

Neural stimulation of the vomiting center arises through either afferent vagal, sympathetic, vestibular, glossopharyngeal, and cerebrocortical pathways. Activation of peripheral receptors found throughout the body can stimulate these neural pathways. Particularly important are receptors located throughout the abdominal viscera. The duodenum contains the highest concentration of these receptors and hence has been referred to as the "organ of nausea." Disease or irritation of the gastrointestinal tract, other abdominal organs, or peritoneum can directly stimulate vomiting through vagal afferent pathways. Receptors found in the kidneys, uterus, and urinary bladder send afferent impulses via sympathetic nerves. Receptors located in the pharynx and tonsilar fossae transmit impulses thorough afferent fibers of the glossopharyngeal nerve. There is evidence that vagal receptors are located in the great vessels in the thorax.

CNS disease may directly stimulate the vomiting center through extension of inflammatory stimuli, hydrocephalus, or

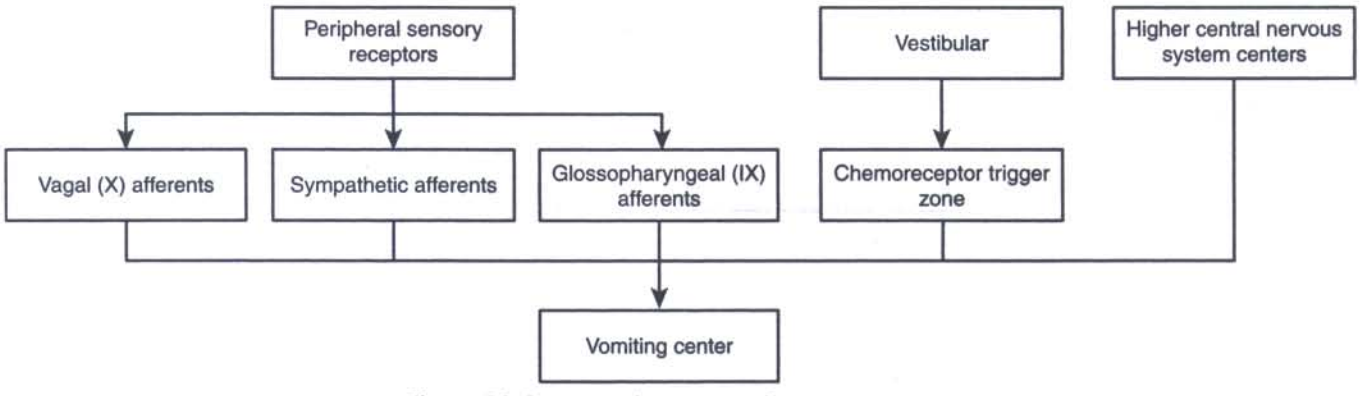


Figure 38-1 Factors that activate the vomiting center.

space-occupying CNS lesions. Supramedullary receptors may also influence the reactivity of the vomiting center. For example, psychogenic vomiting appears to arise from the cerebral cortex and may occur as the result of fear, stress, or pain. Cyclic vomiting in the dog has been associated with autonomic or visceral epilepsy arising from the limbic region in the CNS.

The vomiting center may also be stimulated indirectly via humoral pathway activation of the chemoreceptor trigger zone (CRTZ) in the area postrema. The blood-brain barrier is less effective in this area, which allows the CRTZ to be exposed to chemical stimuli found in the circulation. Blood-borne substances that stimulate the CRTZ include certain drugs, uremic toxins, and electrolyte, osmolar, and acid-base disorders, as well as a number of metabolic derangements. Drugs such as apomorphine, cardiac glycosides, and bacterial toxins are examples. The cat has poorly developed CRTZ dopaminergic receptors and fails to respond adequately to apomorphine as an emetic agent. However, xylazine, an alpha$_2$-adenergic agonist, effectively stimulates the CRTZ in cats. There is evidence that vestibular stimulation passes through the CRTZ before activating the vomiting center. Motion sickness, inflammation of the labyrinth, or lesions in the cerebellum may result in vomiting via this pathway.

CAUSES OF VOMITING

Vomiting has a vast number of etiologies. Box 38-1 presents some of the more common causes of vomiting in small animals.

CLINICAL APPROACH

A complete history is the first step in establishing a correct diagnosis of vomiting. The signalment and history, as well as a description of the vomiting episodes, are important. It also is important to glean from the history whether the animal actually is vomiting. The veterinarian should differentiate the owners' report of vomiting from gagging, coughing, dysphagia, or regurgitation. The signalment may be helpful in that young, unvaccinated pets, for example, are more susceptible to infectious disease, such as parvovirus. Vaccination status, travel history, previous medical problems, and the medication history should be determined. Certain drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs), may cause serious gastrointestinal ulceration. The clinician should also investigate the possibility of toxin or foreign body ingestion and should look for other, concurrent signs that often arise with systemic or metabolic disease. For example, polydipsia,

Box • 38-1

Common Causes of Vomiting

Metabolic/Endocrine Disorders
Uremia
Hypoadrenocorticism
Diabetes mellitus
Hyperthyroidism
Hepatic disease
Endotoxemia/septicemia
Hepatic encephalopathy
Electrolyte disorders
Acid-base disorders

Intoxicants
Lead
Ethylene glycol
Zinc
Strychnine

Drugs
Cardiac glycosides
Erythromycin
Chemotherapy agents
Apomorphine
Xylazine
Penicillamine
Tetracycline
Nonsteroidal antinflammatory drugs (NSAIDs)

Abdominal disorders
Pancreatitis
Peritonitis
Neoplasia
Hepatobiliary disease

Dietary Causes
Indiscretions
Intolerances
Allergy

Gastric Disorders
Gastritis
Helicobacter infection
Parasites
Ulceration
Neoplasia
Foreign bodies
Dilatation-volvulus
Hiatal hernia
Obstruction
Motility disorders

Disorders of the Small Intestine
Inflammatory bowel disease
Neoplasia
Foreign body
Intussusception
Parasites
Parvovirus
Bacterial overgrowth

Disorders of the Large Intestine
Colitis
Obstipation
Parasites

polyuria, and weight loss are typical of vomiting associated with diabetic ketoacidosis or chronic renal failure.

The history should then focus on the actual vomiting episodes. The duration, frequency, and relationship of the episodes to eating or drinking should be determined, and a complete physical description of the vomitus should be elicited. A dietary history, including the type of diet or recent dietary changes, is equally important, because vomiting may be associated with an adverse reaction to food. Vomiting of an undigested or a partly digested meal more than 8 to 10 hours after eating, a point at which the stomach normally would be empty, suggests a gastric outflow obstruction or gastric hypomotility. Gastric outflow obstructions can be caused by foreign bodies, mucosal hypertrophy, tumors, or polyps.

A description of the vomitus should include the volume, color, consistency, odor, and the presence or absence of bile or blood. Undigested food suggests gastric origin, whereas digested vomitus containing bile suggests an intestinal origin. Vomitus with a fecal odor suggests a low intestinal obstruction or bacterial overgrowth in the small intestine. The presence of blood in the vomitus *(hematemesis)*, either as fresh, bright red blood or as digested blood with the appearance of coffee grounds, indicates gastrointestinal erosion or ulceration. Gastric ulceration is caused by metabolic conditions such as hypoadrenocorticism or uremia, by drug-induced ulceration, and by clotting abnormalities, gastritis, or neoplasia.

A complete physical examination should include careful evaluation of the mouth and oral cavity. This examination may reveal icteric membranes, uremic breath and ulceration, or the presence of a linear foreign body around the base of the tongue. The presence of a fever would suggest an infectious or inflammatory process. Bradycardia or cardiac arrhythmias in a vomiting animal may be a sign of a metabolic disturbance, such as hypoadrenocorticism. The abdomen should be carefully palpated for distention and tympany (e.g., gastric dilatation-volvulus syndrome), effusion (e.g., peritonitis), masses or organomegaly (e.g., neoplasia, intussusception, or foreign body), and pain (e.g., peritonitis, pancreatitis, or intestinal obstruction). The presence of gas- and fluid-filled intestines suggests obstruction, whereas plication of the bowel is characteristic of linear foreign body obstruction. A rectal examination provides characteristics of colonic mucosa and feces. Melena suggests upper gastrointestinal bleeding, and the presence of foreign material in the feces supports foreign body etiology. Animals that have colitis or that are severely obstipated may also vomit.

Finally, investigation of the CNS should be considered when the cause of the vomiting is not obvious. Vomiting is seen in some animals with vestibular disease (e.g., nystagmus, head tilt, and/or ataxia). Other CNS disease may be less obvious and usually requires a thorough neurologic evaluation. Occasionally dogs with intervertebral disk disease vomit because of pain or secondary intestinal ileus.

DIAGNOSTIC PLAN

Based on the history and physical examination, the animal should be classified as having either acute or chronic vomiting. The diagnostic and therapeutic approaches differ considerably based on this clinical classification (Figures 38-2 and 38-3).

If the vomiting episodes are acute and of short duration, they may be self-limiting and can be treated with symptomatic therapy. Most often, acute vomiting is associated with gastro-enteritis secondary to dietary indiscretions, and signs resolve quickly. A routine fecal examination for parasites should be performed in all animals with gastrointestinal signs to eliminate the possibility of parasitism. Investigation for environmental intoxicants is imperative. Young, unvaccinated dogs should always be evaluated for parvovirus because the disease frequently begins with vomiting prior to the onset of diarrhea. Radiographic studies may be necessary to confirm gastric dilatation-volvulus (GDV) syndrome, gastrointestinal foreign bodies, or obstructions. Severe acute vomiting or vomiting with concurrent systemic signs requires laboratory diagnostic evaluation and radiographic testing. Common systemic and metabolic diseases that can cause vomiting usually can be identified with basic diagnostic testing, beginning with a complete blood count (CBC), biochemical blood screen, urinalysis, and fecal examination.

Chronic vomiting generally is characterized as vomiting that has persisted for longer than 5 to 7 days or that has failed to respond to initial symptomatic therapy and requires in-depth investigation. In the majority of chronic vomiting cases, routine laboratory and survey radiographs either provide an etiology or direct the next step in diagnostics or therapy.

Vomiting may result in significant fluid, electrolyte, and acid-base changes. The most common electrolyte disturbance is hypokalemia. Acid-base changes generally are minimal in vomiting animals. However, if metabolic alkalosis is found to be associated with hyponatremia, hypochloremia, and hypokalemia, the cause is most likely to be frequent vomiting, gastric outflow, or a high duodenal obstruction.

When routine diagnostic testing fails to identify an obvious etiology, additional tests are required based on the appropriate clinical circumstances of the case. These tests may include viral or heartworm serology, a thyroid evaluation, adrenocortical testing, bile acid determinations, toxologic testing (e.g., lead poisoning), and a neurologic examination.

If laboratory testing fails to identify a nongastrointestinal cause of vomiting, the focus should move to investigation of gastrointestinal disease as a possible cause. The diagnostic approach includes contrast radiography, ultrasonography, endoscopy, or laparotomy. Frequently, inflammatory gastrointestinal lesions are a cause of chronic vomiting; these conditions include gastritis, inflammatory bowel disease (IBD) of the small intestine, and colitis. The diagnosis should be confirmed with gastrointestinal biopsies. In cats with inflammatory bowel disease, vomiting often is the predominate clinical sign, with diarrhea being a minor component of the disease. Conditions such as gastric antral pyloric mucosal hypertrophy, antral polyps, foreign bodies, or neoplasia can cause gastric outflow obstruction, with gastric retention and vomiting. These gastric lesions usually are easily identified endoscopically or by contrast radiography.

Obstructive intestinal lesions, such as foreign bodies, intussusception, and neoplasia, usually require radiographic contrast studies or ultrasonography for diagnosis. The diagnosis of gastrointestinal motility disorders should be considered when clinical signs support abnormal gastric retention and a failure to identify inflammatory or obstructive gastrointestinal lesions. Specialized contrast studies that evaluate motility, or possibly a clinical response to gastrointestinal prokinetic agents, may support a diagnosis of gastric hypomotility.

In summary, vomiting is a complex clinical sign that is associated with a vast number of clinical conditions. Frequently, only through a complete and systematic approach is the cause of the vomiting identified. The veterinarian who understands the mechanisms of vomiting is able to select the appropriate diagnostics or therapy for this clinical sign.

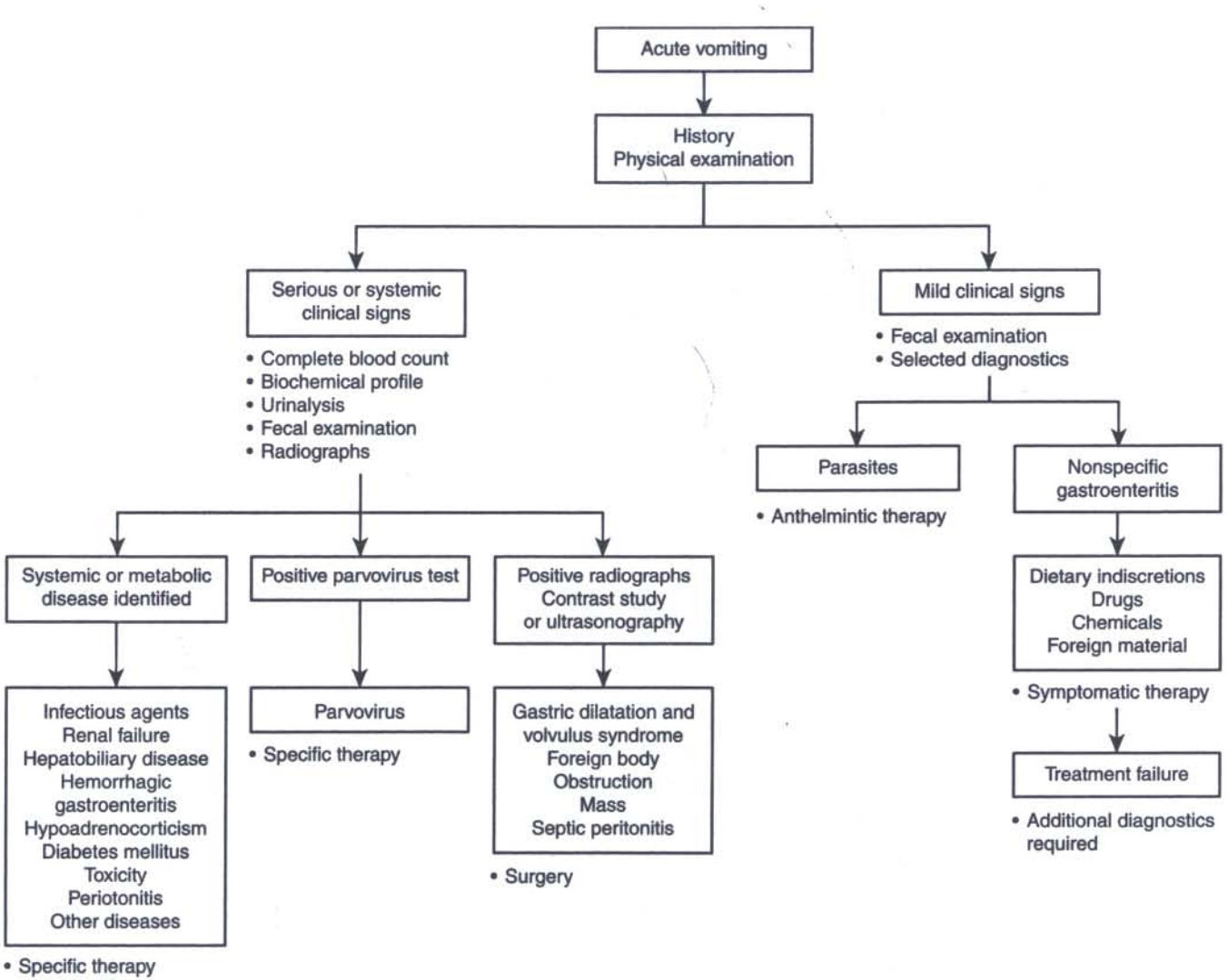


Figure 38-2 Algorithm for the diagnosis of acute vomiting.

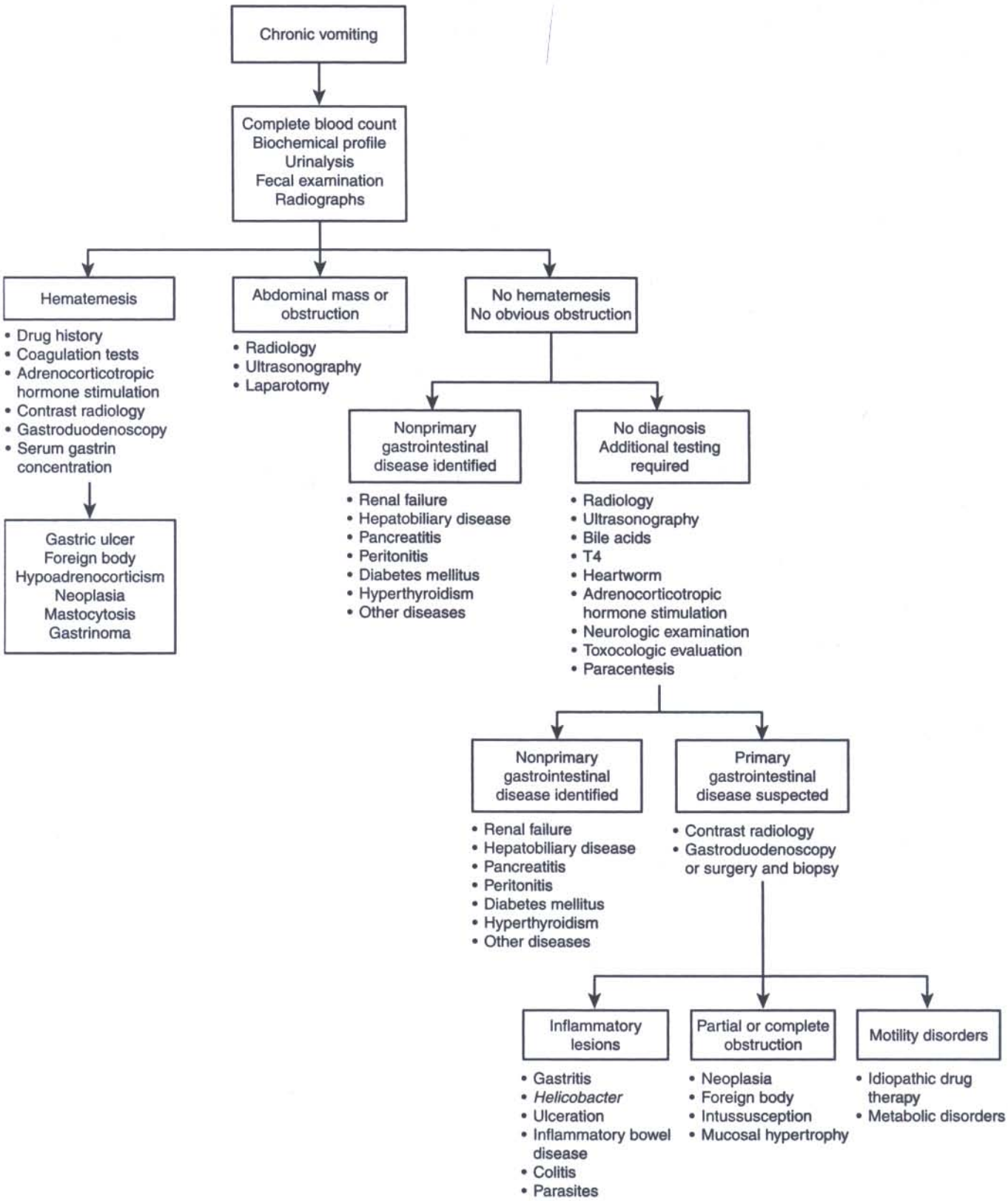


Figure 38-3 Algorithm for the diagnosis of chronic vomiting.

CHAPTER 39

Diarrhea

Jörg M. Steiner

Fecal consistency depends on several factors, including diet, digestion, absorption of nutrients and water, and gastrointestinal milieu and motility. An abnormality of any one of these factors can lead to a change in fecal consistency. However, it is important to note that the compensatory reserve of the gastrointestinal tract is large, and minor changes in one or more of these factors often are compensated for by other components of the system. Only when the compensatory mechanisms are overwhelmed does diarrhea occur. Yet, diarrhea is one of the most common clinical signs seen in dogs and cats. Most cases of diarrhea consist of an isolated episode that does not appear to affect the animal systemically. These dogs and cats are rarely brought to a veterinarian. If they are, they do not pose a diagnostic or therapeutic challenge because no therapy is required, therefore any therapy used will lead to apparent treatment success.

Other cases of diarrhea are also mild, not associated with systemic clinical signs, and resolve naturally after only a few days. These animals require only a minimum amount of diagnostic testing to ensure that systemic complications are not present and in some cases to rule out specific causes, such as infection with *Giardia sp.* Necessary therapeutic efforts are also minimal because remission ensues without treatment or with symptomatic therapy alone. Withholding food for 24 to 48 hours and then introducing small amounts of an easily digestible diet usually is followed by remission of the diarrhea.

A third group of animals, mostly dogs and only rarely cats, have acute or even peracute severe disease. Although gastrointestinal disease is clearly present, the primary disease process is less of a concern than the animal's overall health status. Therefore the clinical approach to these dogs and cats is the same as for any others with a severe condition. The focus is on supportive care, aggressive monitoring for systemic complications, and early intervention against such complications. Finally, there is a large group of dogs and cats that have chronic diarrhea (arbitrarily defined as lasting for more than 3 weeks) that might benefit from a full medical workup. The following discussion pertains to this large group, which is commonly seen in veterinary practice.

CHRONIC DIARRHEA

The workup of chronic diarrhea in dogs and cats can be approached in many different ways. Differences may be due to certain diagnostic modalities that may or may not be readily available. Differences may also be due to the clinical expertise of the veterinarian. In addition, differences may be due to a particularly common problem in a geographic region. For example, fungal disease is more common in some geographic regions than in others, requiring a high degree of suspicion leading to the use of specific diagnostic tests in some areas. Finally, differences in evaluation may be due to a difference of opinion between clinicians.

The workup of a dog or cat with chronic diarrhea also needs to be guided by the severity of illness. Rapid weight loss, emaciation, systemic clinical signs, hypoalbuminemia, or acid-base and electrolyte disturbances all require an aggressive diagnostic approach. The workup and successful treatment of animals with chronic diarrhea could take anywhere from a few days to several months. It is important to establish realistic expectations early during client communication to avoid disappointment later on.

DIFFERENTIATION OF PRIMARY AND SECONDARY GASTROINTESTINAL DISEASE

As for any clinical problem, a careful history is important. It should include questions about the pet's current and past clinical history. Owners should be asked about the environment, husbandry (especially as it relates to the diet), and the clinical history of other pets in the household (see Figure 39-1).

If the history does not reveal any specific indicators for a cause of the diarrhea, a reasonable initial approach includes careful fecal examination (direct smear and zinc sulfate floatation) for evidence of parasitic infestation. This should be followed by treatment with a broad-spectrum anthelmintic agent such as pyrantel pamoate or fenbendazole, regardless of the findings on the fecal examination. Fecal examination is warranted even though anthelmintic therapy will be used because evidence of a specific parasite may alter the choice of treatment. The yield of fecal examination and anthelmintic therapy varies, but the veterinarian should not dismiss the possibility of parasites being the cause of the diarrhea.

An important step for proper diagnosis and treatment is determining whether the diarrhea is caused by a primary gastrointestinal disease or by a disorder of another organ system. In most animals this determination can be made using the history and physical examination findings and performing a complete blood count, serum chemistry profile, and urinalysis. In cats older than 7 to 8 years of age, this minimum data base also should include measurement of a serum total thyroxine (T_4) concentration. If possible, additional serum should be collected and frozen for future analyses.

Central nervous system disease rarely causes chronic diarrhea, and in most cases these dogs and cats have severe neurologic signs that are apparent on physical examination.

Chronic diarrhea rarely occurs in dogs and cats with heart failure. Heart failure can be ruled out by lack of historical findings, such as shortness of breath, exercise intolerance, or coughing and by lack of appropriate abnormalities on physical examination, especially during thoracic auscultation.

Liver failure or portosystemic shunts can cause chronic diarrhea. Dogs and cats with liver failure should have additional clinical signs, such as anorexia, vomiting, weight loss, or even neurologic signs. These animals may have increased serum hepatic enzyme activities and serum bilirubin concentrations and/or decreased serum urea nitrogen, cholesterol, or

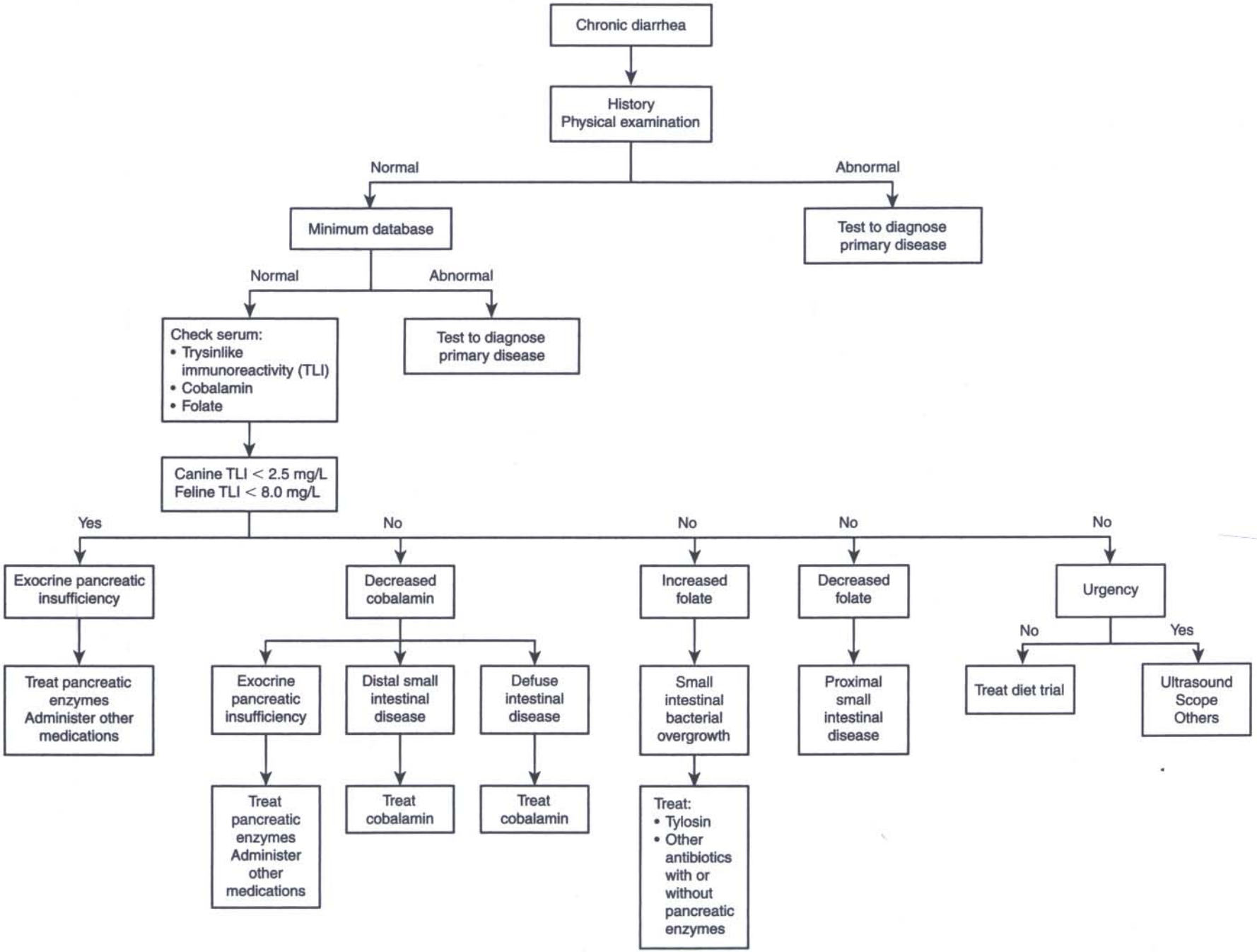


Figure 39-1 Chronic diarrhea.

albumin concentrations. Finally, a decreased urine specific gravity may be noted on urinalysis. Liver failure or portosystemic shunt usually can be ruled out by the minimum data base. However, if suspicion remains, other diagnostic tests, such as measurement of preprandial and postprandial bile acid concentrations, abdominal radiographs, abdominal ultrasonography, or even hepatic biopsy may be necessary to definitively rule out hepatic failure.

Hypothyroidism may cause chronic loose stools or diarrhea. Dogs with hypothyroidism may have a history of weight gain, decreased exercise activity, or heat-seeking behavior. They may also be anemic and have an increased serum cholesterol concentration. If hypothyroidism is suspected, the total serum T_4 concentration should be measured. If the total serum T_4 concentration is decreased, it may be necessary to measure the serum free T_4 concentration (only equilibrium dialysis methods are reliable) and/or the serum thyroid-stimulating hormone (TSH) concentration to differentiate sick-euthyroid dogs from those with true hypothyroidism. If any suspicion remains, a therapeutic trial with thyroid hormone supplementation may be instituted to confirm the diagnosis.

Hyperthyroidism in cats usually is ruled in or out after careful palpation of the neck and determination of the serum total T_4 concentration. In some cats, definitive diagnosis may require repeat testing several weeks later or the use of other diagnostic tests, such as a triiodothyronine (T_3) suppression test.

Renal failure may cause chronic diarrhea in some pets. The most important parameters for ruling out renal failure are the serum creatinine and urea nitrogen concentrations and the specific gravity on urinalysis.

Hypoadrenocorticism (Addison's disease) is another potential cause of chronic diarrhea, mainly in dogs. Dogs with Addison's disease may have waxing and waning clinical signs that include diarrhea, vomiting, and/or weakness. The serum chemistry profile for these animals may show hyperkalemia and hyponatremia. Dogs (rarely cats) with so-called atypical Addison's disease lack only glucocorticoids and thus are able to regulate the serum sodium and potassium concentrations. The differential white cell count may provide a clue for identifying these animals. Ill animals typically have a stress leukogram characterized by neutrophilia, lymphopenia, eosinopenia, and monocytosis. Dogs with glucocorticoid deficiency cannot respond appropriately and thus cannot develop a stress leukogram. Therefore most dogs with Addison's disease, typical or atypical, display a lack of a lymphopenia. Only a few actually show a lymphocytosis, but an elevated, high-normal, or even mid-normal lymphocyte count should raise suspicion of the possibility of hypoadrenocorticism. If the slightest degree of suspicion for hypoadrenocorticism exists, an adrenocorticotropic hormone (ACTH) stimulation test should be performed.

Finally, exocrine pancreatic disease often causes chronic diarrhea. Exocrine pancreatic insufficiency (EPI) in both dogs and cats leads to loose stools or diarrhea. Pancreatitis can also lead to chronic diarrhea but most often is accompanied by other clinical signs. However, cats with chronic pancreatitis may show only chronic diarrhea, possibly because they often have concurrent disease of the small intestine. Exocrine pancreatic disease cannot be ruled out by the history, physical examination, and minimum data base alone. The serum trypsin-like immunoreactivity (TLI) concentration is the test of choice to rule out EPI in both dogs and cats, and it should be performed if the workup has not led to a definitive diagnosis. A canine TLI less than or equal to 2.5 µg/L is diagnostic for canine EPI, and a feline TLI (fTLI) less than or equal to 8 µg/L is diagnostic for feline EPI. If chronic pancreatitis is suspected as a cause of the chronic diarrhea, a serum pancreatic lipase immunoreactivity (PLI) concentration should be evaluated.

WORKUP FOR PRIMARY GASTROINTESTINAL DISEASE

Once secondary disorders have been ruled out, the type of diarrhea should be characterized. In general, small and large bowel diarrhea can be distinguished. Animals with small bowel diarrhea have an increased fecal volume but only a mildly increased frequency of defecation. Blood, if present, is digested, causing melena. In contrast, pets with large bowel diarrhea often strain to defecate and have fresh blood and an increased amount of mucus covering the feces. Also, weight loss does not usually occur in dogs and cats with large bowel diarrhea, whereas those with small bowel diarrhea may or may not show weight loss. These differences, however, are not absolute, and most dogs and cats with clinical signs of large bowel diarrhea have diffuse disease with significant small bowel involvement. In contrast to human beings, isolated colitis is rare in dogs and uncommon in cats. Therefore, although it is useful to characterize the type of diarrhea, the clinician would be ill advised to make a definitive assessment based on the type alone.

Many animals with chronic diarrhea have a normal minimum data base or only nonspecific changes, such as a mild increase in hepatic enzyme activities. These animals should be worked up for primary gastrointestinal disease. As previously mentioned, fecal examination for parasitic infestation and therapy with a broad-spectrum anthelmintic agent should be attempted before any further steps are taken. Also, repeated testing (zinc sulfate floatations or enzyme-linked immunosorbent assay [ELISA]) should be performed to rule out giardiasis.

The serum cobalamin and folate concentrations are of great diagnostic importance and, in the case of cobalamin, also of therapeutic importance and should be measured together with the serum TLI concentration. The serum folate concentration may be decreased in disorders of the proximal small intestine, whereas the serum cobalamin concentration may be decreased in disorders of the distal small intestine and in EPI. In animals with diffuse small intestinal disorders, both the serum folate and cobalamin concentrations may be decreased. Decreases in the serum cobalamin concentration and increases in the serum folate concentration may be seen in dogs with small intestinal bacterial overgrowth (SIBO). The significance of the increased serum cobalamin concentration is unknown. Folate and cobalamin are both plentiful water-soluble vitamins in canine and feline diets. However, dietary folate is poorly absorbed, because it occurs as folate polyglutamate and needs to be deconjugated to folate monoglutamate by folate deconjugase, a brush border enzyme. Folate monoglutamate is absorbed by specific carriers in the proximal small intestine, therefore, longstanding and severe disorders of the proximal small intestine can lead to depletion of folate body stores and ultimately to a decreased serum folate concentration. However, it should be pointed out that a severely decreased serum folate concentration does not commonly occur in either dogs or cats with chronic diarrhea. In SIBO, microorganisms in the small intestine synthesize folic acid, which can lead to an increase in folate absorption and in turn to an increased serum folate concentration.

Dietary cobalamin is tightly bound to dietary protein. In the stomach, dietary protein is partly digested by pepsin and hydrochloric acid (HCl), and cobalamin is released. However, cobalamin immediately binds to R-protein, which in turn is digested by pancreatic proteases in the small intestine. Free cobalamin binds to intrinsic factor, released mostly in pancreatic juice. These cobalamin–intrinsic factor complexes are absorbed through specific receptors in the ileum. Therefore severe and longstanding disorders of the distal small intestine, as well as exocrine pancreatic insufficiency, can lead to depletion of cobalamin body stores and ultimately to a decreased

serum cobalamin concentration. Approximately half of all dogs with EPI have cobalamin deficiency, whereas almost all cats with EPI have cobalamin deficiency. Finally, microorganisms, present in excessive numbers in the small intestine in animals with SIBO utilize cobalamin and compete with the host for dietary cobalamin. A low serum cobalamin concentration combined with an increased serum folate concentration is specific for SIBO, and a therapeutic trial with an antimicrobial agent is indicated. Currently, the antibiotic agent of choice is tylosin (15 to 25 mg/kg given twice a day for 6 weeks). An increased serum folate concentration alone also is indicative of SIBO, and a trial therapy is appropriate. In both situations dogs should respond within approximately 1 week of starting therapy. Failure to show at least a partial response within that period should stimulate further diagnostic workup.

Serum cobalamin is of therapeutic interest. Cobalamin deficiency in human patients has been shown to cause systemic neuropathies, dementia, compromise of the immune system, and gastrointestinal changes, such as villous atrophy, inflammatory infiltrates of the intestinal mucosa, and cobalamin malabsorption. Experimental cobalamin deficiency in cats has led to similar changes, with clinical signs of weight loss, anorexia, and an unkempt haircoat. In a recent study, cobalamin deficiency was present in more than 60% of cats with chronic diarrhea. Clinical experience would further suggest that both cats and dogs with severe cobalamin deficiency often do not respond to therapy of the underlying gastrointestinal disorder until cobalamin is supplemented. Because cobalamin deficiency causes cobalamin malabsorption, oral supplementation is not efficacious in patients with cobalamin deficiency. Also, multivitamin preparations do not contain sufficient amounts of cobalamin. Furthermore, pure cobalamin is needed for therapy. Based on body size, 250 to 800 µg is given subcutaneously in dogs and 150 to 250 µg in cats. Injections should be administered once weekly for 6 weeks, every other week for 6 weeks, one more dose a month later, and a recheck a month after that. Re-evaluation is important in deciding whether further cobalamin supplementation is indicated.

For all dogs and cats that do not have secondary chronic diarrhea, parasitism, or SIBO, additional testing or a therapeutic trial may be chosen. The choice depends on many factors but ultimately on the condition of the pet and the goals of the owner. If the pet does not have any systemic clinical signs and does not deteriorate, a dietary trial is reasonable. Many animals with chronic diarrhea are suspected of having dietary intolerance or dietary hypersensitivity. Clinically, it is not feasible to differentiate between the two. Although those with dietary intolerance would benefit from an easily digestible diet, others with dietary hypersensitivity may benefit from a hypoallergenic diet. A diet with a novel protein and a novel carbohydrate source is one option for a hypoallergenic diet. Note that diets containing a novel protein and a novel carbohydrate source are not intrinsically hypoallergenic but are unlikely to elicit an allergic response in a patient that has not been previously exposed to them. Another option is to use a diet that contains hydrolyzed proteins. Dogs and cats should show some response to a dietary trial 1 to 2 weeks after initiation, but complete remission may take up to 6 to 8 weeks. Depending on the urgency of the situation, several different diets could be introduced to identify the optimal diet for a particular pet.

If a dog or cat is not stable or is quickly deteriorating, or if the owner wants to do anything possible regardless of cost or prognosis, more diagnostic tests should be performed immediately. Some clinicians prefer to do abdominal ultrasonography first because it is not invasive. Abdominal ultrasonography can be useful for identifying neoplastic or fungal lesions or partial obstructions by foreign bodies or an intussusception, or for visualizing mesenteric lymph nodes. However, it must be pointed out that diagnostic yields differ significantly, depending on the quality of the equipment and the expertise of the ultrasonographer. Other clinicians prefer to perform a gastroduodenoscopy first, because the diagnostic yield for this procedure is usually better than that for abdominal ultrasonography. However, it is more invasive and does not allow visualization of other abdominal structures. It should also be pointed out that gastroduodenoscopy may appear more definitive than it is in most cases. Although a definitive answer may be found in some dogs and cats with gastrointestinal lymphoma, parasitism, or fungal disease, most animals show varying degrees of lymphocytic-plasmacytic inflammation that may or may not be normal.

A special scenario is the dog or cat with panhypoproteinemia or hypoalbuminemia with or without chronic diarrhea. These animals need to be carefully screened for hepatic disease and protein-losing nephropathy (PLN). Hepatic disease should be ruled out by a serum chemistry profile and determination of preprandial and postprandial bile acid concentrations; PLN should be ruled out by determination of a urine protein/creatinine ratio. In dogs, if there is no evidence of hepatic disease or PLN, protein-losing enteropathy (PLE) can be confirmed by measuring the fecal alpha$_1$-proteinase inhibitor (alpha$_1$-PI) concentration. This test is also useful for assessing fecal protein loss in dogs that have not yet developed panhypoproteinemia. For example, soft-coated Wheaten terriers with familial PLE/PLN often have increased fecal alpha$_1$-PI before clinical signs develop.

Other diagnostic tests may be useful in specific cases. Culture of fecal material for *Salmonella spp.*, *Clostridium spp.*, and *Yersinia spp.* may be useful for a select group of animals, mostly those immunocompromised by concurrent disease or chemotherapy or dogs with bloody diarrhea. However, indiscriminate bacterial culture of fecal material is of little diagnostic value. Measurement of serum unconjugated bile acids and breath hydrogen can be useful for supporting a diagnosis of small intestinal bacterial overgrowth in dogs. Finally, gastrointestinal permeability and mucosal function testing in dogs is extremely sensitive for altered gastrointestinal integrity and function and shows abnormalities long before histopathologic changes are apparent.

CHAPTER 40

Melena and Hematochezia

Karen M. Kelly

HEMATOCHEZIA

Hematochezia is the term used to describe bright red blood on the surface of or admixed into the stool. The origin of the red blood most commonly is the anus, rectum, or descending colon.

Clinical Signs

It is important to take a thorough history. The owner should be asked if there is any fresh blood in the stool, mucus, straining, or difficulty defecating. It should be determined whether the pet has been given medications, has had a dietary indiscretion or a recent diet change, or has been subjected to trauma (e.g., pelvic trauma), toxin exposure (e.g., rodenticides), or stress (e.g., boarding). In addition, it should be determined whether this is a recurrent problem and if it has responded to previous treatments. Any travel history (e.g., parasite and fungal exposure) should be noted. The veterinarian should observe the animal's demeanor and ask the owner if the animal is lethargic, has been vomiting, or has had a loss of appetite or recent weight loss. Owners often are very concerned when they see blood in the stool, but hematochezia is rarely life threatening. Animals with hematochezia rarely have any other clinical signs aside from the blood with the stool. Exceptions to this are more serious causes, such as neoplasia and hemorrhagic gastroenteritis; for these cases, the physical examination and history can reveal weight loss, shock, lethargy, cachexia, anorexia, or inappetence, along with large volumes of fresh blood. Causes of hematochezia are listed in Box 40-1.

Diagnostics

A physical examination and complete rectal examination should be done. A rectal examination is performed to confirm hematochezia, to obtain a stool sample for fecal examination, and to detect polyps, strictures, neoplasia, or perianal diseases (e.g., fistulas). The anal gland should be palpated and expressed to detect infection, impaction, or neoplasia. The extent of the workup should be based on the severity and duration of the problem and the physical examination findings. For example, an animal that has a normal physical examination, other than hematochezia, could be treated conservatively with a trial course of metronidazole, a broad-spectrum wormer, and a diet with a fermentable fiber. For more persistent and recurrent cases of hematochezia, a more extensive workup is indicated, such as abdominal radiographs, a complete blood count, a serum chemistry profile, colonoscopy, and abdominal ultrasonography.

Box • 40-1

Causes of Hematochezia

Anal Disease
- Perianal fistulas
- Anal sacculitis or abscess
- Stricture
- Neoplasia (e.g., anal sac tumor)
- Trauma (e.g., bite wound)
- Perianal hernia
- Foreign body

Rectum and Colon
- Proctitis (inflammation of the rectal mucosa)
- Colitis
  - Idiopathic
  - Inflammatory bowel disease
  - Stress
  - Infectious
    - *Campylobacter*
    - *Clostridium perfringens*
- Parvovirus
- Parasitism
  - Hookworms
  - Whipworms
  - Coccidia
  - Roundworms
- Neoplasia
  - Rectal polyp
  - Adenocarcinoma
  - Lymphoma
- Prolapsed rectum
- Mucosal trauma
  - Movement of foreign material (e.g., hairballs)
  - Iatrogenic (e.g., thermometers, enemas, fecal loops)
- Automobile trauma
- Ileocecocolic area: intussusception

NOTE: Constipation often can cause excessive straining, which can result in formed stools with blood on the surface.
Modified from Tams TR: Gastrointestinal symptoms. In *Handbook of small animal gastroenterology*, Philadelphia, 1996, WB Saunders.

MELENA

Melena is the presence of dark, tarry, often foul-smelling stools, the result of digested blood in the intestinal tract. Melena is always a more serious clinical sign then hematochezia and

demands a more extensive workup. The blood can originate from the pharynx, lungs (coughed up and swallowed), esophagus, stomach, small intestine, or upper large bowel if transit time is sufficiently slow. It is the duration of the stool in the intestinal tract, not the origin, that determines the ultimate color. Blood must be present in the intestine for some time before the bacteria can break down the hemoglobin, resulting in melena. Also, a sufficient amount of blood must be present before melena can occur. It is important to note that large-volume, upper gastrointestinal bleeding can result in short transit times and can appear as fresh blood. Not all dogs with dark stools have melena.

As with hematochezia, a detailed history should be taken and a thorough physical examination performed. The clinician should ask specifically about administration of nonsteroidal anti-inflammatory drugs and corticosteriods, both of which may cause gastrointestinal bleeding, especially when used concurrently. Any potential exposure to toxins should be addressed. Spurious dark stools can be caused by salicylates, bismuth (e.g., Pepto-Bismol), charcoal, and diets high in iron. A history of coughing (may indicate swallowed blood from pulmonary disease), gagging, and regurgitation (esophageal disease), behavioral changes (hepatic encephalopathy), and polyuria and polydipsia (renal disease) should be noted. A thorough examination of the nares and oropharynx for sources of bleeding should be included. Causes of melena are listed in Box 40-2.

Box • 40-2

Causes of Melena

Ingested Blood
Oral lesions
Nasopharyngeal lesions
Pulmonary lesions
Diet

Parasitism
Hookworms

Neoplasia
Adenocarcinoma
Lymphoma
Leiomyoma or leiomyosarcoma
Mast cell tumor
Gastrinoma

Coagulopathies
Disseminated intravascular coagulation (DIC)
Rodenticide intoxication

Drug Administration
Nonsteroidal anti-inflammatory drugs
Glucocorticoids

Miscellaneous
Liver failure
Pancreatitis
Renal failure
Inflammation (e.g., foreign body, acute gastritis, hemorrhagic gastroenteritis, inflammatory bowel disease)
Hypoadrenocorticism
Gastrointestinal ischemia (e.g., shock, volvulus, intussusception)
Foreign bodies
Gastrointestinal blood vessel malformations (e.g., arteriovenous fistula)
Polyps

Diagnostics

A rectal examination can help confirm the presence of melena and at the same time allows collection of a stool sample (Figure 40-1). In-house packed cell volume and total solids testing should be done to assess for anemia, especially in shocky, debilitated animals. A fecal examination for hookworms should not be overlooked. A complete blood count with a reticulocyte count helps differentiate regenerative from nonregenerative anemia. Regenerative anemia often is present after a few days except with iron-deficiency anemia, which is common with chronic gastrointestinal bleeding characterized by a hypochromic, microcytic anemia and bone marrow disease. A chemistry panel helps in the evaluation for metabolic disease, such as liver and kidney disease. If liver disease is suspected, a bile acid determination may be helpful. A coagulation profile and platelet counts also are indicated to rule out thrombocytopenia and rodenticide intoxication. Survey radiographs of the abdomen and thorax aid detection of esophageal disease, pulmonary disease and evidence of bleeding elsewhere (e.g., ascites and pleural fluid), neoplasia, foreign bodies, and trauma to the pelvic canal.

If additional tests are required to determine the cause of bleeding, abdominal ultrasonography should be preformed. Ultrasound scanning is an easy, noninvasive test that can aid the detection of lesions. If a lesion detected by ultrasound is accessible by endoscopy (e.g., a proximal mass or diffuse small intestinal thickening), biopsies should be taken and submitted. If no lesion is detectable by ultrasound, which often is the case, there are two options. The first is endoscopy with biopsies. Endoscopy is noninvasive and allows the clinician to visualize the mucosal surfaces of the proximal gastrointestinal tract while simultaneously obtaining biopsy samples. A disadvantage is that the lower gastrointestinal tract is not visualized, and a lesion could easily be missed. The second option is exploratory abdominal surgery. The advantage is full examination of the serosal surfaces of all the gastrointestinal tract, full-thickness biopsy samples, and surgical excision of identifiable bleeding lesions. The disadvantages are inability to visualize the mucosal surface and the invasiveness of the procedure. Surgery can be combined with endoscopy to allow visualization of the mucosal surface intraoperatively as an aid to locating a lesion. When the above tests and procedures fail to provide an answer, more specialized tests can be performed, such as scintigraphy using technetium-labeled red blood cells to locate the site of bleeding and arteriography to diagnose gastrointestinal blood vessel malformations.

Treatment

The treatment of melena largely depends on the underlying cause. For animals in shock, hospitalization with intravenous fluid therapy is indicated. Depending on the duration and volume of bleeding, a blood transfusion may be necessary. If a coagulopathy is suspected, plasma or whole blood may be indicated. Gastric acid inhibitors (e.g., famotidine and omeprazole) can be helpful. Antiemetics are indicated if nausea and vomiting are factors.

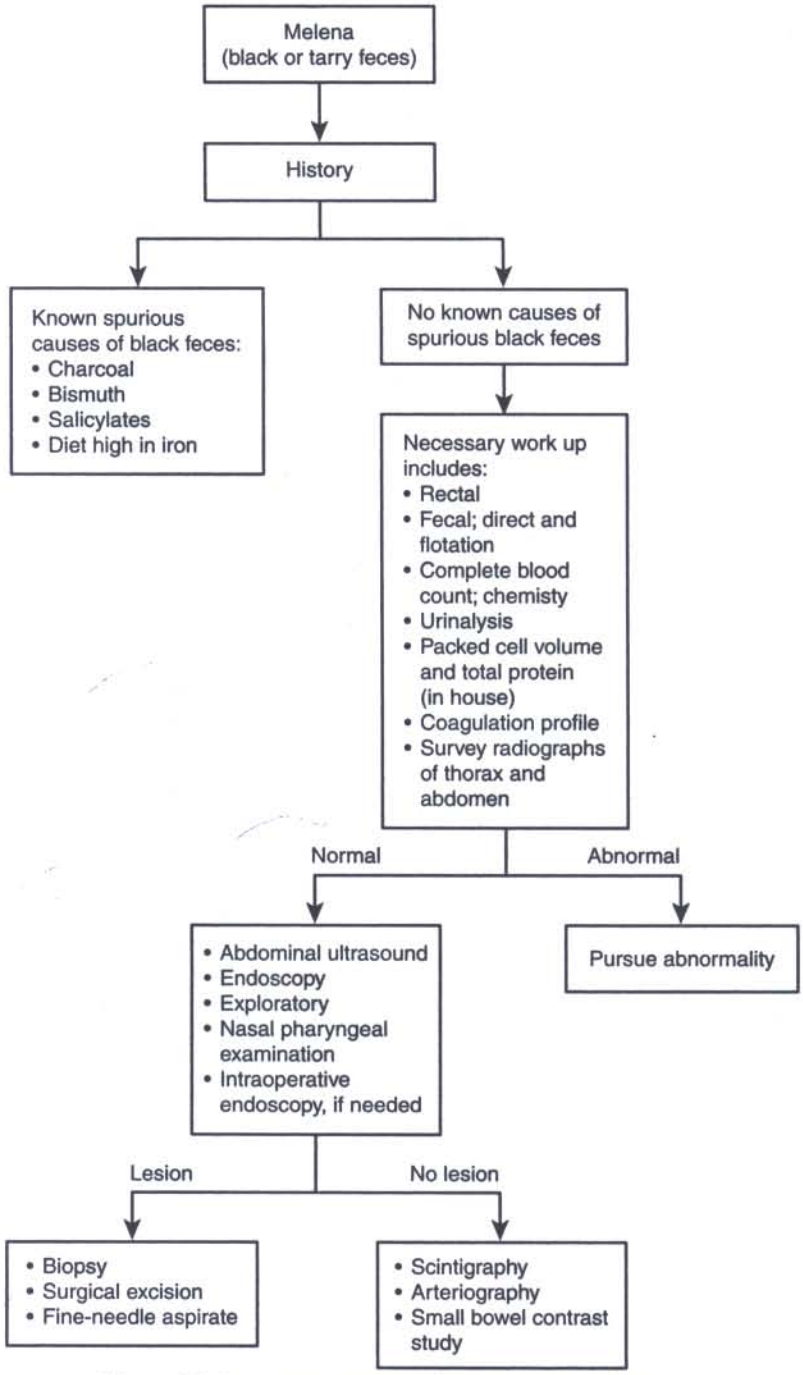


Figure 40-1 Diagnostic approach to a patient with melena.

CHAPTER 41

Constipation, Tenesmus, Dyschezia, and Fecal Incontinence

Kenneth R. Harkin

DEFINITIONS

Constipation is the infrequent or difficult evacuation of feces, typically characterized by the presence of dry, hard feces.

Obstipation is intractable constipation, characterized by an inability to evacuate the mass of dry, hard feces, which can result in an impaction extending from the rectum to the ileocolic valve.

Megacolon is a pathologic condition of hypomotility and dilatation of the large intestine that results in constipation and obstipation.

Tenesmus is ineffectual and painful straining at defecation or urination.

Dyschezia is difficult or painful defecation that arises exclusively from disease of the anal and perianal tissues.

Fecal incontinence is the involuntary passage of feces and flatus as a result of dysfunction of the internal and external anal sphincters.

NORMAL PHYSIOLOGY OF THE LARGE INTESTINE

The primary functions of the large intestine are absorption of water and electrolytes, which occurs predominately in the proximal half, and storage of fecal matter until expulsion, which is the primary function of the distal half.

Movement of contents through the large intestine normally is sluggish and consists of *haustral contractions* and *mass movements*. Haustral contractions, which are combined segmental contractions of the circular and longitudinal layers of smooth muscle of the large intestine, result in focal accumulation of contents in unstimulated segments. These contractions primarily serve to mix the contents of the large intestine, increasing the exposure to the luminal surface for maximal absorption of water and electrolytes. They also serve to propel material slowly from the level of the cecum through the ascending colon.

Mass movements carry fecal material from the transverse colon to the rectum; however only a few of these occur daily, compared with the continuous action of the haustral contractions. Mass movements are maximized after a meal, facilitated by the gastrocolic and duodenocolic reflexes, which are conducted through extrinsic nerves of the autonomic nervous system. Contraction of circular smooth muscle begins at an area of distention or irritation, forcing the mass of feces into the rectum, where the desire for defecation is felt. These mass movements persist for 10 to 30 minutes. Irritation in the colon also can initiate mass movements, which may become continuous.

The stimulus for defecation is initiated by the movement of feces into the rectum. Continence is maintained by tonic contractions of the internal anal sphincter, which is composed of smooth muscle and is under the control of the autonomic nervous system, and by the external anal sphincter, which is composed of striated muscle and is under voluntary control and innervated by the pudendal nerve. Defecation is accomplished by a weak intrinsic defecation reflex (IDR) and a more powerful parasympathetic defecation reflex (PDR). The IDR is initiated when distention of the rectum activates the myenteric plexus and initiates a peristaltic wave and reflex relaxation of the internal anal sphincter. The PDR is stimulated by nerve endings in the descending colon, rectum, and anus, which activate the parasympathetic nervous system (PNS). Motor nerves of the PDR, which arise from the pelvic nerve, intensify the peristaltic wave. Activation of the PNS also stimulates the deep breath, closure of the glottis, and contraction of the abdominal muscles that constitute the abdominal press. Defecation then depends on voluntary relaxation of the external anal sphincter. If the external anal sphincter remains voluntarily closed, the defecation reflexes are terminated after a few minutes. These reflexes can be voluntarily initiated later, but they are less effective than the intrinsic reflex. Frequent voluntary termination of the defecation reflex commonly results in constipation.

Bowel activity can be inhibited by the peritoneointestinal reflex, which is activated by the presence of peritoneal irritation; by the renointestinal and vesicointestinal reflexes, which are activated by irritation of the kidney or urinary bladder, respectively; and by the somatointestinal reflex, which is activated when the skin over the abdomen is intensely irritated.

CONSTIPATION

Although tenesmus is the most common clinical sign for an animal with constipation, vomiting, depression, anorexia, and various degrees of abdominal discomfort may also be reported. Animals may be misdiagnosed as having diarrhea when passage of liquid feces around fecal impaction occurs and consequently a complete physical examination is not performed.

Constipation can occur as a result of extraintestinal disorders or primary intestinal and anorectal disorders. Extraintestinal disorders may inhibit normal neural impulses or muscular function; they may interfere with the PDR through weakness, pain, or dyspnea; they may affect fecal consistency through dehydration; or they may cause mechanical obstruction through compression. Extraintestinal disorders include hypothyroidism, hypercalcemia, hypokalemia, chronic renal failure, myopathies, and thoracic cavity disease. Intestinal and anorectal diseases result in constipation through obstruction, inhibition of the defecation reflex because of pain, and loss of motility.

Clinical Evaluation

History

Detailed information regarding the duration of constipation and influencing factors may help determine the cause. The clinician should determine if there is a history of ingestion of indigestible material (e.g., bone, hair, plastic, sticks, or branches) that may increase fecal bulk or cause pain that can terminate the defecation reflex. Other historical factors that may be relevant include recent surgery, previous pelvic trauma and, possibly, radiation therapy.

Signalment
In the feline, megacolon is a common disease. Specifically, sacral spinal cord deformities are seen in the Manx cat. Intact male dogs should be carefully evaluated for prostate disease, such as abscesses or cysts, and perineal hernia. Aged and large breed dogs should be screened for orthopedic disease, such as hip dysplasia. Juvenile dogs and cats should be evaluated for congenital abnormalities, such as imperforate anus. Dysautonomia has been diagnosed primarily in dogs from Kansas and Missouri and in cats primarily from Great Britain. The German shepherd dog should be carefully evaluated for perianal fistulas.

Physical Examination
In addition to a careful examination of all other body systems, which may yield clues to extraintestinal disease, particular attention should be given to examination of the anorectal area. Visual inspection may identify perianal fistulas or tumors, and careful digital examination may identify prostatic disease, strictures, masses, perineal hernia, foreign material, or pain.

Diagnostic Evaluation
Routine laboratory work usually is of minimal value, except when systemic disease is suspected. Survey and contrast radiography, ultrasonography, and colonoscopy may be helpful when the diagnosis cannot be determined from the history and physical examination.

TENESMUS AND DYSCHEZIA

Tenesmus and dyschezia are clinical signs that often overlap and occasionally are difficult to distinguish. The difference is that dyschezia occurs exclusively as a result of disease of the anal and perianal tissues. Tenesmus, a result of disease of the large intestine, is seen with obstruction, inflammation, and constipation (Figure 41-1).

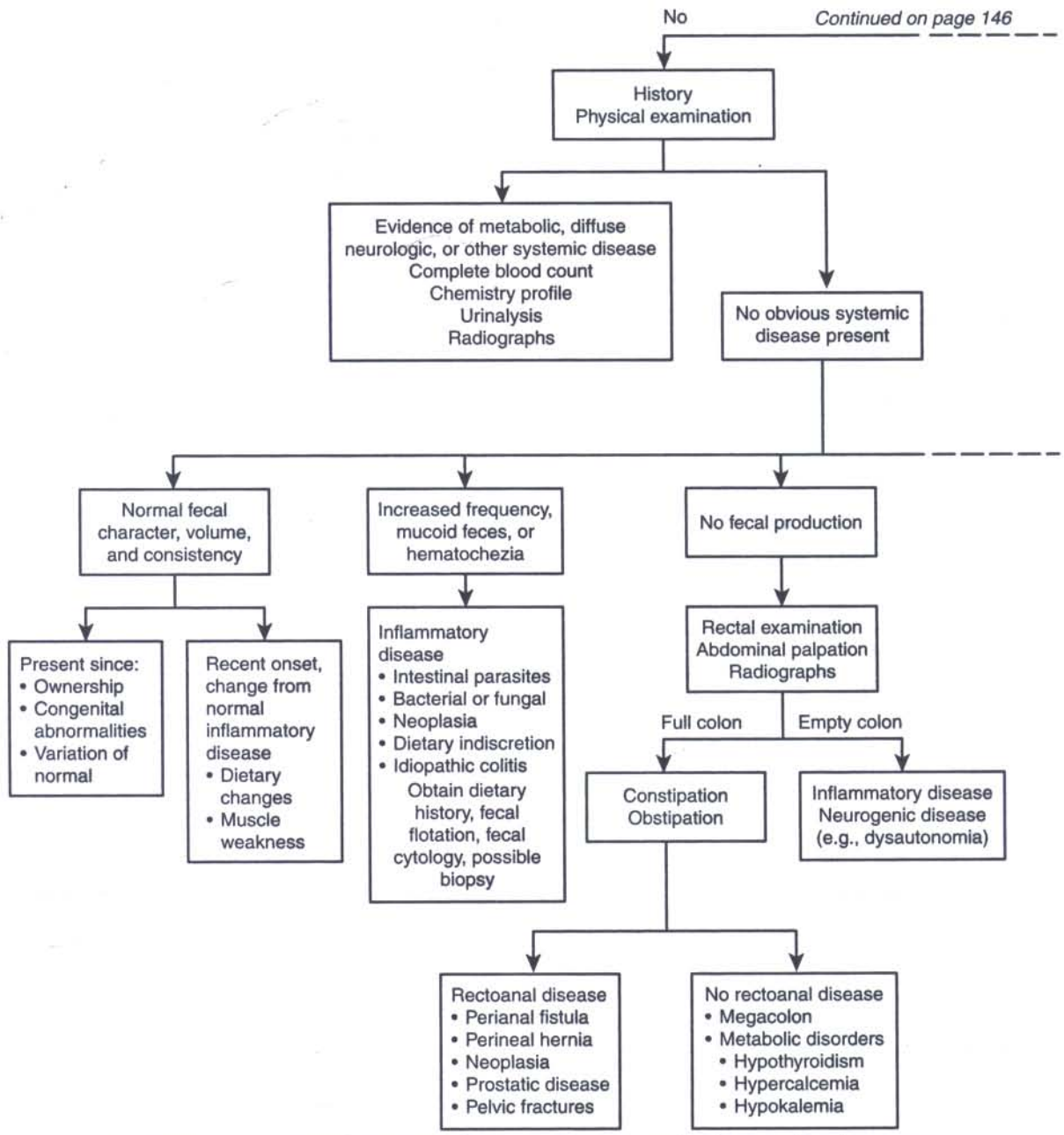


Figure 41-1 Diagnosis and treatment of constipation, tenesmus, dyschezia, and fecal incontinence.

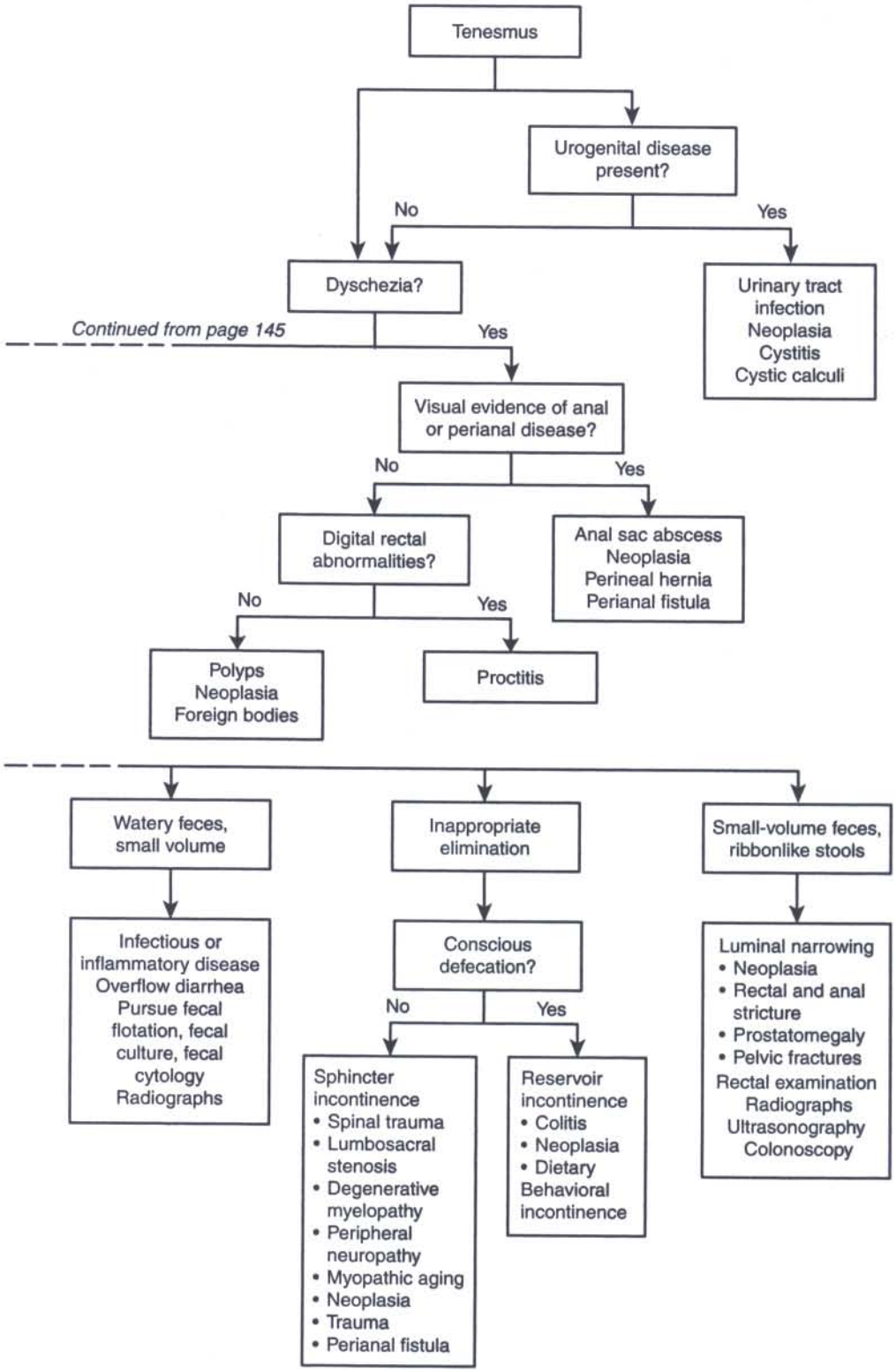


Figure 41-1 Continued.

History

It is important for the clinician to determine whether tenesmus is the result of urinary tract or intestinal tract disease. Cats with lower urinary tract signs frequently are described by their owners as straining to defecate or constipated, which may result in a misguided diagnostic workup. Female dogs adopt similar postures when straining to defecate or urinate. The timing of the event may also be helpful, because tenesmus prior to defecation suggests obstruction, and tenesmus after defecation suggests irritative disorders. The character of the feces may provide further clues to the diagnosis. The presence of fresh blood or mucus suggests an inflammatory component, such as with infectious colitis, idiopathic colitis, dietary indiscretion, or neoplasia. Small volumes of ribbonlike stool suggests luminal narrowing, such as with a stricture or prostate disease.

Signalment

There are a few breed-specific disorders, such as histiocytic ulcerative colitis in the boxer and perianal fistulas in the German shepherd dog. Other inflammatory conditions can be seen in a variety of breeds. Infectious and inflammatory disease is suspected in young animals, whereas neoplastic disease is a primary concern in the aged animal.

Physical Examination

The principles of a complete physical examination are identical to those outlined for constipation. Absence of fecal material may be suggestive of an inflammatory condition. Additional care must be given to examination of the urinary tract, particularly palpation of the urinary bladder transabdominally and the urethra per rectum.

Diagnostic Evaluation

Routine laboratory work provides few clues to the diagnosis. Radiography, ultrasonography, fecal flotation, fecal culture, fecal cytology, colonoscopy/proctoscopy, and biopsy usually provide the information necessary to confirm a diagnosis.

FECAL INCONTINENCE

Incontinence occurs as a result of dysfunction in the ability of the anal sphincters to prevent involuntary leakage (sphincter incontinence) or the loss of the storage ability of the large intestine (reservoir incontinence).

Animals with reservoir incontinence are aware of their need and act of defecation. As a result of small intestinal or colorectal disease, which can result in irritation, loss of storage capacity or compliance, overwhelming fecal volume, or disturbances of motility, voluntary inhibition of external anal sphincter relaxation is lost.

Sphincter incontinence typically is a result of a neuromuscular disorder affecting the *continence reaction*, the reflexive and conscious contraction of the external anal sphincter. Sphincter incontinence occurs with denervation or damage to the external and internal anal sphincters or the muscles that support the pelvic canal or, possibly, with loss of sensory function. Patients with sphincter incontinence are plagued by the involuntary passage of feces. Disease of or damage to the levator ani and coccygeus muscles, damage to the pudendal nerve or sacral spinal cord, and disease or trauma to the perianal tissues can result in sphincter incontinence.

Clinical Evaluation

History

If the animal is conscious of defecation, characterized by posturing and possibly tenesmus, the clinician can focus on causes of reservoir incontinence. Frequent defecation, fresh blood in the stools, and mucoid stools also are clues to reservoir incontinence. Other information that may be important includes a dietary history, a history of trauma or orthopedic problems, previous dystocia, previous surgery, and the duration of disease. Behavioral problems can be mistaken as reservoir incontinence, and attempts should be made to distinguish the two. Dogs with behavior problems usually do not display the tenesmus and urgency of reservoir incontinence and defecate at inappropriate times and places. The animal's ability to urinate normally should give clues as to the integrity of the nervous system.

Signalment

Large breed dogs have a higher incidence of lumbosacral stenosis and degenerative myelopathy, older dogs may have neoplastic disease or geriatric incontinence, and younger dogs and cats may have congenital abnormalities, such as vertebral malformations.

Physical Examination

In addition to a complete physical examination, careful visual and digital examination of the perianal, anal, and rectal areas may provide clues to the diagnosis. Anal sphincter tone should be carefully evaluated; however, it is not a reliable indicator of anal sphincter function. The clinician should also assess urinary bladder tone and tail tone, as well as hindlimb function and reflexes and whether paresthesia is present. Hyperesthesia or paresthesia of the pelvic limbs is supportive evidence of lumbosacral stenosis. Depressed pelvic limb reflexes are seen with lumbosacral cord lesions, lumbosacral stenosis, peripheral neuropathies and, possibly, myopathies.

Diagnostic Evaluation

Routine laboratory work is of limited value except when systemic disorders are present. Radiography, myelography, computed tomography (CT) or magnetic resonance imaging (MRI), colonoscopy, and electromyography may be performed as needed based on suspicion of disease localization.

CHAPTER 42

Flatulence

Michael E. Matz

The term *flatulence* refers to excessive accumulation of gas in the gastrointestinal tract. It may be associated with eructation, borborygmus, or flatus. *Eructation* is the expulsion of gas from the stomach. *Borborygmus* is a rumbling noise caused by the propulsion of gas through the gastrointestinal tract. *Flatus* is the anal passage of intestinal gas.

Flatulence is more commonly observed in dogs than cats and is most often noted in inactive indoor dogs. It usually results from dietary intolerances but occasionally can signal more serious gastrointestinal disease, particularly of the small bowel or pancreas. Most owners accept flatulence and borborygmus in their pets as normal and are unconcerned about its consequences.

PATHOPHYSIOLOGY

The major gastrointestinal gases are nitrogen and oxygen, which are derived from swallowed air and diffusion from blood, and hydrogen, carbon dioxide, and methane, which are primarily products of bacterial metabolism and fermentation and nonbacterial reactions (e.g., pancreatic bicarbonate interacting with acid to produce carbon dioxide) that occur in the bowel lumen. In human beings, and probably in dogs and cats, as much as 99% of flatus is composed of these odorless gases. The remaining 1% is composed of odoriferous gases, including hydrogen sulfide, methanethiol, dimethylsulfide, ammonia, skatole, mercaptans, volatile amines, and short chain fatty acids. These odoriferous gases also result from bacterial metabolism and fermentation. Sulfur-containing gases, particularly hydrogen sulfide, have been shown to be a major determinant of the malodor of canine flatus.

Most of the gas that enters the digestive tract is thought to come from swallowed air. Aerophagia mainly occurs during the ingestion of liquids and solids and can be exacerbated by rapid or competitive eating situations. Most swallowed air is subsequently eliminated by eructation from the stomach and esophagus. If not eructated, the nitrogen contained in swallowed air travels through the gastrointestinal tract with minimal absorption and subsequently is passed. It is noteworthy that the transit time for gas is considerably shorter than that for liquids or solids. Air entering the intestinal tract can be passed out the rectum rapidly (within minutes). Gases can also be removed by diffusion into blood or consumption by bacteria.

The composition and volume of flatus are affected by the quantity and variety of nutrients eaten, as well as by the type and abundance of bacterial flora. A significant amount of gas is formed from the bacterial fermentation of both dietary (e.g., fiber and poorly digestible carbohydrates and proteins) and endogenous (e.g., mucin, bile acids) substrates. Foods such as legumes (soybeans, beans, peas) that contain large amounts of indigestible oligosaccharides are apt to produce large amounts of intestinal gas. The oligosaccharides are fermented to hydrogen and carbon dioxide by *Clostridium* organisms and other bacteria. Variations in the metabolic capacity of the bacteria flora may explain the different responses animals may have to nonabsorbable carbohydrates. Fiber-containing pet foods may contribute to flatulence directly, if the fibers are fermentable by colonic bacteria, and/or indirectly through reduced dry matter digestibility. Pectins and most gums are rapidly fermentable fibers found in pet foods. Sulfur-reducing bacteria convert dietary sources of sulfur, including sulfate and sulfur-containing amino acids, to the odoriferous gases hydrogen sulfide, methanethiol, and dimethylsulfide. The production of these gases usually is increased by foods containing increased amounts of sulfate (cruciferous vegetables, onions, nuts, carrageenan) or protein.

Maldigestion due to exocrine pancreatic insufficiency or malabsorption resulting from small intestinal diseases often leads to excessive intestinal gas caused by the fermentation of malassimilated substrates. Lactose intolerance also can cause flatulence.

CLINICAL EXAMINATION FINDINGS

Owners may describe an increase in the frequency of flatus, an objectionable odor associated with flatus, the presence of borborygmus, or abdominal distention. Occasionally these signs are associated with concurrent abdominal pain, vomiting, diarrhea, or weight loss, any of which suggest more serious gastrointestinal disease. The owner may report that the pet has a hunched posture, exhibits unsettled behavior, or adopts a praying position. These signs may result from excessive intestinal gas, motility disorders that disrupt the passage of gas through the bowel, or increased visceral sensitivity to bowel distention. The animal's temperament may be important. Excessive aerophagia in a nervous animal, or animals with aggressive or competitive eating habits, can increase gastric gas, although it is unclear whether ingested air contributes significantly to intestinal gas or flatus.

A complete dietary history is essential. Owners should be questioned about any recent dietary change or dietary indiscretion. An assessment of specific foods, food ingredients, treats, and supplements, as well as the potential for dietary indiscretion, should be made. In human beings, diets high in soybeans, whole wheat products, bran, and fats can cause flatulence. Similar associations appear to occur in some dogs and cats. Spoiled food and diets high in protein or fat are more likely to yield odoriferous gases. Milk products can cause flatulence in animals with lactase deficiency. The feeding method should also be thoroughly evaluated. The amount fed, feeding frequency, how the food is offered, access to other food, and the relationship of feeding to exercise should be determined.

With the exception of borborygmus, the physical examination of an animal with flatulence usually is unremarkable unless concomitant gastrointestinal disease is present. Additional diagnostic tests are warranted in the latter animals.

MANAGEMENT

The management of flatulence begins with changing the diet (Figure 42-1). Feeding a highly digestible diet reduces the

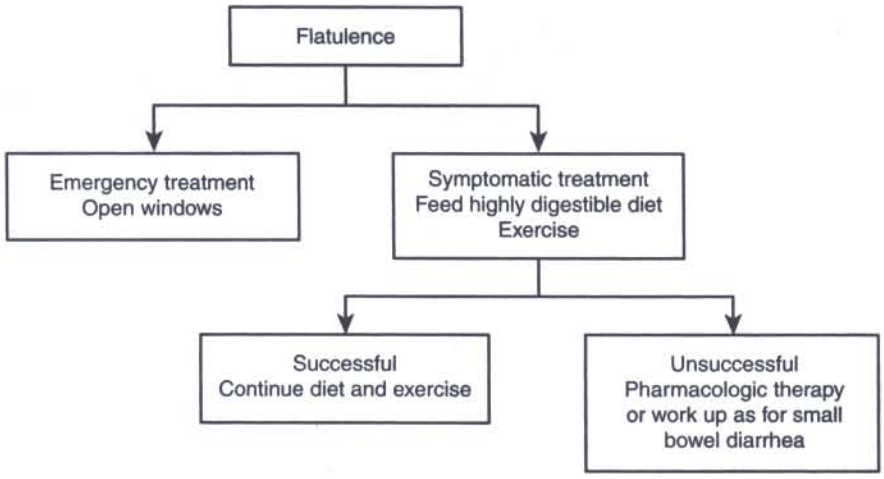


Figure 42-1 Algorithm for management of flatulence.

food residues available for bacterial fermentation. The diet should not contain excessive amounts of rapidly fermentable fiber. Vegetarian-based diets should be avoided because these products often have sulfur-containing vegetables and legumes. Optimally, the diet should be lactose deficient. Changing sources or amounts of dietary protein, carbohydrate, and fat may benefit individual animals. Diets containing rice as the primary carbohydrate source may produce less intestinal gas than diets containing other sources of carbohydrate. Suitable commercial foods are available from most major pet food manufacturers. Dietary trials may be necessary to find a food that reduces flatulence or objectionable flatus. Vitamin-mineral supplements may increase intestinal bacterial activity and probably should be avoided.

Reducing aerophagia, by avoiding situations that provoke nervousness and discouraging rapid or competitive eating, may also be helpful. Feeding several small meals daily may alleviate some of these problems.

Regular exercise also is beneficial, presumably because exercise stimulates gastrointestinal motility and defecation. In the event that dietary manipulation and regular exercise are not successful, symptomatic pharmacologic intervention should be considered.

Pharmacologic management involves reducing or controlling the amount of flatulence and/or the objectionable odor of flatus. Substances that can be used include simethicone, activated charcoal, *Yucca schidigera* preparations, zinc acetate, bismuth subsalicylate, alpha-galactose, and pancreatic enzyme supplements.

Simethicone (25 to 200 mg per dose, given every 6 hours) frequently is used as a treatment for borborygmus, gaseous colic, and flatulence in human beings. It is an antifoaming agent that reduces surface tension, allowing bubbles to coalesce so that they can be passed more easily. Simethicone is not absorbed from the gastrointestinal tract and can be safely used in dogs and cats at or near the dosage for human beings. Its effectiveness as an antiflatulent in dogs and cats is unknown. Both veterinary and human (over the counter) products containing simethicone are commercially available.

Activated charcoal is one of the more commonly used adsorbent antiflatulents in human beings. Its absorbency results from its porous structure, which confers a tremendous internal surface area. Charcoal is of questionable benefit for the relief of flatulence, but it may be effective in absorbing small amounts of sulfur-containing gases, which are primarily responsible for malodorous flatus. Commercial treats containing activated charcoal are available for dogs.

Y. schidigera, zinc sulfate, and bismuth subsalicylate also may be effective in reducing the unpleasant odor of flatus. The efficacy of *Y. schidigera* appears to be related to its ability to bind hydrogen sulfide and/or to decrease the numbers or activity of sulfate-reducing bacteria that generate hydrogen sulfide. Poorly absorbed divalent cations (e.g., zinc, bismuth) bind sulfhydryl compounds such as hydrogen sulfide and methanethiol to form insoluble salts, and this effectively prevents the liberation of these gases. To be of benefit, bismuth subsalicylate probably needs to be given multiple times per day, which can make it impractical to use. Like charcoal, these agents do not appear to be particularly effective in reducing flatulence. The efficacy of the agents may be improved if administered together.

Anecdotal reports indicate that alpha-galactosidase and pancreatic enzyme supplements may be effective in reducing flatulence in some dogs and cats. Alpha-galactosidase works by improving digestion of nonabsorbable carbohydrates found in legumes. Both veterinary and human products containing alpha-galactosidase are available. Pancreatic enzyme preparations are claimed to assist the digestion of fermentable nutrients that are digested poorly by the gastrointestinal systems of monogastrics.

In most dogs and cats, flatulence can be controlled successfully, often through dietary management alone. Relapses in controlled animals often are due to dietary indiscretion. If dietary management, exercise, and supplementary therapy are unsuccessful in reducing or controlling flatulence, an investigation similar to that for a dog or cat with small bowel diarrhea (see Chapters 39 and 222) should be considered.

CHAPTER • 43

Abdominal Distention, Ascites, and Peritonitis

Stephen A. Kruth

Abdominal distention is potentially a serious sign of disease and should be evaluated reasonably quickly, especially when associated with discomfort, restricted breathing, fever, weakness, or other clinical signs. The initial diagnostic goal should be to identify obesity, pregnancy, a distended urinary bladder, obstipation, or gastric dilatation. If these are not the cause of the distention, the clinician should determine whether hepatomegaly, splenomegaly, or some other mass is present or whether the predominant abnormality is the accumulation of fluid in the peritoneal cavity (i.e., an effusion). In some cases both a mass and an effusion may be present. Distinguishing between organ enlargement or masses and effusion is accomplished through physical examination and abdominal imaging.

When organomegaly or a mass is the predominant abnormality, a specific diagnosis usually can be made through needle biopsy. When an effusion is present, a sample should be obtained by paracentesis and characterized as a transudate, modified transudate, exudate, chyle, or blood. If the effusion is a *transudate* (low to moderate cellularity and a low protein concentration), modified transudate, or chyle, the animal is said to have *ascites*. If the effusion is an *exudate* (high cellularity and a high protein concentration), the animal has *peritonitis*. Exudates can be septic or nonseptic (e.g., feline infectious peritonitis, bile, urine, pancreatitis).

PATHOPHYSIOLOGY OF ABDOMINAL ORGAN ENLARGEMENT

Distention of the stomach or intestines usually is due to the accumulation of gas and fluid in the lumen of the affected organ. Gas can accumulate as a consequence of aerophagia (usually secondary to respiratory disease), gastric dilatation, ileus, or obstruction. Obstipation can cause abdominal enlargement, especially in cats with megacolon. Renal or urinary bladder enlargement can follow ureteral or urethral obstruction; bladder enlargement can also be associated with neurologic dysfunction. Enlargement of the liver can be a consequence of venous congestion secondary to right heart failure; splenic enlargement can be caused by venous congestion secondary to splenic torsion. Gross organ enlargement often is due to infiltrative disorders (especially lymphosarcoma and other neoplasms), which may cause either diffuse or localized enlargement of the involved organ. Hyperadrenocorticism can also cause remarkable hepatomegaly, abdominal wall weakness, and abdominal distention.

PATHOPHYSIOLOGY OF ABDOMINAL EFFUSIONS

The peritoneum is a serous membrane consisting of mesothelial cells overlying a connective tissue stroma. The parietal portion covers the transversalis fascia of the abdominal wall, and the visceral portion envelops the abdominal viscera. The peritoneal cavity formed by these two layers is almost nonexistent in normal animals, containing only a small volume of fluid, which serves to lubricate the parietal and visceral peritoneal surfaces. Normally, peritoneal fluid (lymph) is formed at the arteriolar end of capillaries and reabsorbed both at the venous end of capillaries and by means of lymphatic uptake (predominately via the large lymphatic vessels of the diaphragm). In the normal animal, fluid movement is balanced; a large exchange of fluid and solute occurs, but a low and stable volume is maintained.

The primary event leading to the development of an effusion is an alteration in one or more of the Starling forces governing fluid movement across membranes. Increased portal hydrostatic pressure caused by obstruction of venous flow, decreased plasma colloidal oncotic pressure associated with hypoalbuminemia, and/or increased permeability of the capillary endothelium secondary to inflammation can all lead to the development of an effusion. Decreased lymphatic uptake, usually due to reduced flow of lymph from the peritoneal cavity, can also cause effusion.

An important consequence of the redistribution of extracellular fluid into the peritoneal cavity is a decreased effective plasma volume and reduced cardiac output. This stimulates the renin-angiotensin-aldosterone system, resulting in sodium and water retention. Antidiuretic hormone levels increase in response to sodium retention, leading to isotonic expansion of the extracellular fluid space. In heart failure, elevations in the levels of endothelin and insensitivity to circulating atrial natriuretic peptide contribute to sodium retention. The net effect in any ascitic condition is an increase in total body water and sodium, which perpetuates the ascitic state if the underlying cause is not resolved.

Ascites caused by portal hypertension can be classified as *prehepatic* (restriction of blood flow into or through the portal vein), *hepatic*, or *posthepatic* (from the level of hepatic vein tributaries, through to the right ventricle) in origin, and to some extent the effusion characteristics are determined by where the abnormality lies. Ascites caused by prehepatic disorders is rare as recruitment of collateral portosystemic vessels often occurs when portal pressure increases. Portal vein obstruction due to compression by a mass, or increased circulation and thus increased hydrostatic pressure in the portal system caused by a *hepatic artery–portal venous fistula* are possible causes. With prehepatic portal hypertension, the elevated hydrostatic pressure causes increased lymph formation from the intestinal serosa, and the effusion typically is a pure transudate (at least initially; the presence of any fluid in the peritoneal cavity irritates the peritoneum, causing protein loss, increased cellularity, and formation of a modified transudate).

The most common posthepatic cause of portal hypertension is *right-sided heart failure* (which can be caused by cardiac disease or can occur secondary to tamponade resulting from pericardial effusion). Ascites secondary to right heart failure is more common in dogs than cats because the hepatic veins of

dogs are more likely to act as postsinusoidal sphincters, which increase portal pressure. Rare causes of posthepatic ascites include *obstruction of the caudal vena cava* by a thrombus, compression by a mass, or anatomic changes associated with a diaphragmatic hernia. In posthepatic portal hypertension, excess lymph is formed primarily in the hepatic sinusoids and then diffuses across the liver capsule. Hepatic lymph is relatively high in protein compared with lymph formed from the intestinal capillaries, and the typical effusion of posthepatic disease is a modified transudate.

Ascites secondary to hepatic disease is due largely to portal hypertension, and the effusion can be either a transudate or a modified transudate, depending on the type of pathology and its distribution. In human beings, the mechanism of effusion formation in cirrhosis is complex and not completely understood. Three theories have been invoked to explain this form of ascites: the underfill theory proposes that the primary abnormality is a decrease in effective circulating volume (underfilling), which occurs when fluid is sequestered in the splanchnic vascular bed secondary to portal hypertension. Secondary renal sodium and water retention occurs, and an increase in hydrostatic pressure in hepatic sinusoids and splanchnic capillaries leads to increased lymph formation, which exceeds the drainage capacity of the lymphatic system. Alternatively, the overfill theory suggests that the primary abnormality is renal retention of sodium and water in the absence of volume depletion (by an unknown mechanism), leading to an increase in extracellular fluid volume (overfilling). In the presence of pre-existing hepatic venous outflow obstruction and portal hypertension, ascites develops. The third hypothesis proposes that the primary abnormality is splanchnic arteriolar vasodilatation (possibly mediated by nitric oxide), leading to underfilling of the systemic arterial vascular space and baroreceptor-mediated stimulation of the renin-angiotensin-aldosterone system. Concurrent hypoalbuminemia and decreased colloidal oncotic pressure may contribute to the formation of ascites in all of these situations.

Abdominal effusion can be caused by mechanisms other than portal hypertension. Severe hypoalbuminemia secondary either to *glomerular disease* or to severe *protein-losing enteropathies* can lead to ascites (usually a transudate). Widespread miliary *carcinamatous* seeding of the serosa *(carcinomatosis)*, as well as other cancers, can induce the formation of modified transudate or exudate through obstruction of capillaries and inflammation. With any form of inflammation, mediators increase endothelial permeability and recruit neutrophils and other phagocytic cells, which may lead to the formation of an exudate. Septic exudates usually are caused by bacterial infections and are relatively small in volume. Nonseptic exudates can be caused by *neoplasia, bile, urine,* or *feline infectious peritonitis. Chyle* (lymph of intestinal origin with a high lipid content) can leak into the peritoneal cavity from lymphatics; the causes of *chylous ascites* in dogs and cats include neoplasia, trauma, infection, and right heart failure. Rupture of blood vessels, the ureters, bladder, or biliary tree can occur secondary to *trauma*. Bleeding caused by coagulopathies (usually affecting the clotting cascades) or tumors (especially splenic or hepatic *hemangiosarcoma*) can cause hemoabdomen.

CLINICAL SIGNS

Owner concerns for a dog or cat with abdominal enlargement can include weight gain, decreased activity and decreased exercise tolerance, inappetence, or increased respiratory rate. The rate of abdominal enlargement is variable, and the condition may develop over hours to weeks, depending on the underlying cause. The history should include a review to identify signs suggestive of pathology of the cardiac, renal, hepatic, or other organ systems. Abnormalities identified by abdominal palpation can include hepatomegaly, splenomegaly, or one or more mass lesions. Low-volume effusions can give the impression of a "slippery" feel when the small bowel is palpated, and a fluid wave usually can be appreciated with large-volume effusions. Tachypnea can result from restricted ventilation caused by cranial displacement of the diaphragm by an enlarged liver or by fluid. Signs of abdominal pain may be present with peritonitis of any cause.

A careful general examination may reveal signs that direct the diagnostic approach. For example, cardiovascular abnormalities, such as jugular distention or pulsation, murmurs, or arrhythmias, are suggestive of right heart failure, and muffled heart sounds are consistent with pericardial effusion and tamponade. Jaundice is consistent with liver failure or rupture or obstruction of the biliary system, fever is suggestive of an inflammatory disorder, and generalized lymphadenopathy is consistent with lymphosarcoma.

DIAGNOSTIC APPROACH

Radiographs can be used to help differentiate organomegaly, other mass lesions, and effusions. Ultrasonographic examination of the abdomen is more useful for identifying specific organ enlargement, and alterations in organ echogenicity may be suggestive of some types of neoplasia, hepatic lipidosis, or other pathology. Abdominal ultrasound is also useful for identifying low-volume effusions. Ultrasound-guided needle biopsies and/or fluid aspiration can be performed, and cytologic diagnosis may be possible. However, histopathologic evaluation of biopsy tissue may be more reliable in terms of making a specific diagnosis. Tissue samples can also be submitted for bacterial culture, if indicated. The animal's hemostatic ability should be evaluated prior to biopsy: platelet number and function (as evaluated by mucosal bleeding time) are important considerations, along with assays of the coagulation cascades (activated clotting time or activated partial thromboplastin and prothrombin times).

A sample of effusion can be safely obtained by aspirating the peritoneal cavity using a 22-gauge needle attached to a 12 mL syringe. After aseptic skin preparation, the needle is placed through the body wall at the ventral midline slightly caudal to the umbilicus, avoiding the liver, spleen, and urinary bladder. The animal can be standing or in lateral recumbency, and local anesthesia usually is not necessary. Nondiagnostic samples are obtained when blood is aspirated from the liver or spleen or when only small amounts of effusion are present. Other than coagulopathies, there are few contraindications for paracentesis. Complications include laceration of the liver, spleen, or, if present, a tumor, and bacterial contamination of the peritoneal cavity.

The specific gravity, protein content, and cell count of the effusion should be determined, and cytologic evaluation should also be performed. Depending on the situation, creatinine, cholesterol, triglyceride, and bilirubin levels or other assays may be indicated. Smears of aspirated fluid should be made immediately, and the remaining fluid split into ethylenediamine tetra-acetic acid (EDTA) and clot tubes so that additional smears can be made from a centrifuged pellet or, preferably, as a cytospin slide. If the fluid is bloody, the packed cell volume should be determined and compared with that of peripheral blood. Blood obtained from the spleen or other organs contains platelets and usually clots, whereas blood from previous abdominal hemorrhage usually does not contain platelets and does not clot. A sample should be saved for bacterial culture if indicated. The characterization of an effusion as a transudate, modified transudate, exudate, chyle, or hemorrhage is presented in the algorithm (Figure 43-1).

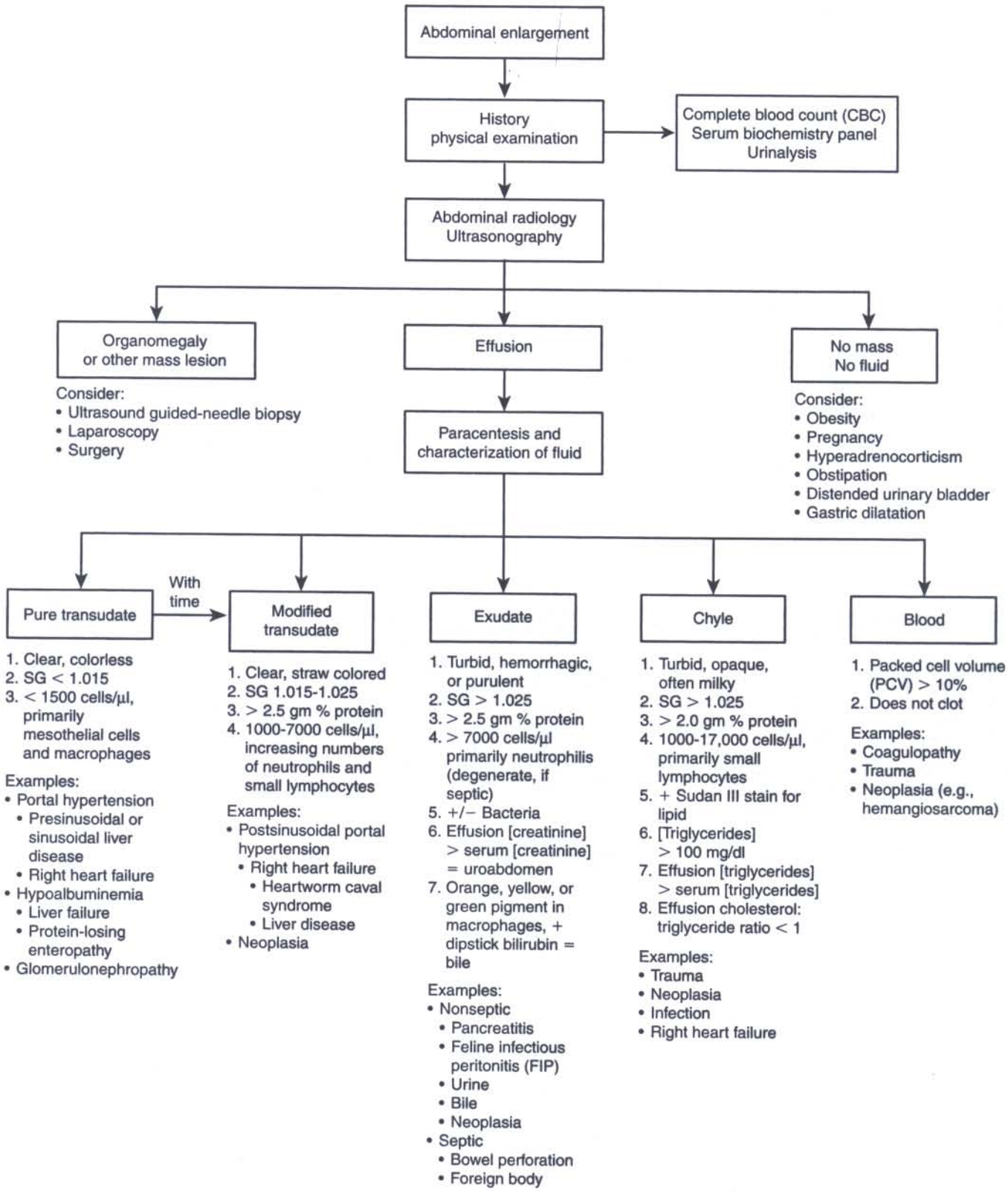


Figure 43-1 Algorithm for diagnostic approach to abdominal enlargement.

In human beings, characterization of effusion often is based on the serum ascites-albumin gradient, which correlates directly with portal hypertension; however, the utility of this test has not been adequately determined in dogs and cats.

A complete blood count (CBC), serum biochemistry panel, and urinalysis are indicated for any animal with abdominal effusion. Although animals with effusions have an increase in total body water and sodium, hyponatremia sometimes is present, likely caused by increased thirst and water consumption and by impaired free water excretion. Hyperkalemia may also be present due to decreased renal distal tubular function. These animals usually have normal adrenal function (i.e., do not necessarily have hypoadrenocorticist. For animals with proteinuria, a urine protein/creatinine ratio should be determined, and an ultrasound-guided renal biopsy can be performed to diagnose and characterize glomerulonephropathies. Animals with signs of right-sided heart failure should be evaluated with thoracic radiographs, echocardiography, and electrocardiography (ECG), and tested for heartworm. Dogs or cats that may have cancer should have thoracic radiographs evaluated for pulmonary metastases. External masses or enlarged lymph nodes should be aspirated for cytology; core biopsies can be obtained for histopathology.

MANAGEMENT OF ABDOMINAL EFFUSIONS

Animals with hemoabdomen (due to trauma or hemangiosarcoma), rupture of the urinary bladder or biliary tree, or chylous effusion usually require surgical management. Dogs and cats with exudative effusions associated with pancreatitis or bacterial peritonitis should also be considered as surgical candidates, and septic effusions must be managed with appropriate antibiotics and supportive therapy. Cats with the effusive form of feline infectious peritonitis (FIP) can be made more comfortable with large-volume paracentesis while medical management of FIP is considered. Large-volume paracentesis is also indicated as a palliative measure for animals with carcinomatosis, when there is significant respiratory distress secondary to any effusion of any cause, or when diuretics are not effective for controlling ascites. Large-volume paracentesis appears to be well tolerated by most animals with abdominal effusions. The management of malignant effusions is dictated by the type of cancer and the clinical stage of the animal. Colloid therapy with plasma, albumin, hetastarch, or pentastarch may be useful for short-term management of effusions secondary to hypoalbuminemia.

The management of ascites caused by cardiac failure is based on improving cardiac performance as dictated by the primary disorder. Animals with portal hypertension of any cause (e.g., right-sided heart failure, liver disease) should be managed with diuretic therapy (furosemide, 1 mg/kg PO, IV, IM given twice daily, and/or spironolactone, 1 mg/kg PO given twice daily, increasing the dosage as necessary; these drugs can be administered concurrently to minimize electrolyte abnormalities). As total body sodium increases in ascitic disorders, a sodium-restricted diet is indicated.

Neurologic

CHAPTER 44

Neurologic Manifestations of Systemic Disease

Karen L. Kline

The evaluation of a dog or cat with neurologic dysfunction is based on two questions: (1) Does this patient have disease of the nervous system? and (2) If so, is it brain, spinal cord, or neuromuscular in origin? The neurologic examination can reveal whether the animal has evidence of focal, diffuse, or multifocal, central or peripheral nervous system disease. From these findings, a differential list can be formulated and the appropriate diagnostics performed. What is essential, however, is a thorough physical examination to help determine if the signs observed are primarily of neurologic origin or are secondary to underlying systemic or metabolic disease. At times this distinction can be difficult until further diagnostics are performed; it is determining which diagnostics are appropriate that can be confusing to the clinician. Underlying systemic or metabolic illness can have a dramatic effect on the nervous system. The diagnosis and treatment of the diseases responsible for these effects are discussed in greater detail in Chapter 190. This chapter concentrates on categories of these diseases, areas of the nervous system affected, and the diseases' common neurologic presentations.

The different categories of diseases that affect the nervous system can include disorders of energy supply, ionic or electrolyte disturbances, endocrine dysfunction, metabolic dysfunction, hematologic disorders, infectious agents, immune dysfunction, and paraneoplastic syndromes (Figure 44-1).

In general, the neurologic target areas for these disturbances are the cerebral cortex and the peripheral nervous system (peripheral nerves and muscle), although other portions of the central nervous system (CNS) can be affected. These two regions tend to have a high demand for energy supply, and even subtle changes can instigate neurologic manifestations.

CENTRAL NERVOUS SYSTEM EFFECTS

Signs of CNS dysfunction vary with the location of the insult. Changes in energy supply, electrolyte disturbances, and endocrine and metabolic dysfunction tend to cause more diffuse neurologic signs, such as behavior changes, seizures,

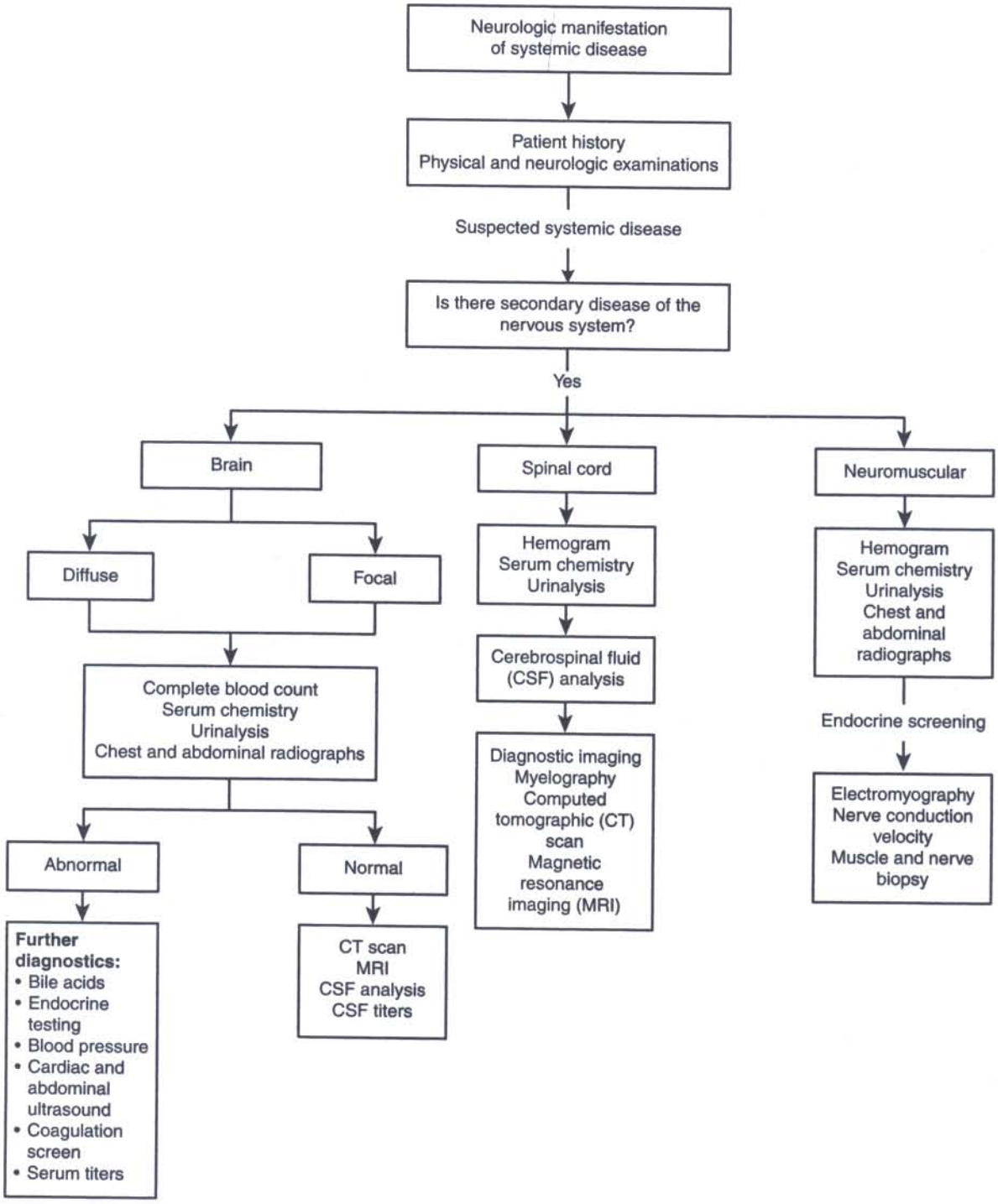


Figure 44-1 Algorithm for the evaluation of neurologic manifestations of systemic disease.

circling in either direction, pacing, partial cranial nerve and visual deficits, and generalized weakness. Hematologic, infectious, immune-mediated, and paraneoplastic disorders tend to cause more focal or asymmetric signs, although exceptions do occur. The cerebral cortex and thalamus are two areas especially prone to even subtle changes in energy supply. The brain stem and cerebellum, however, are not immune to these changes. Examples of fuel deprivation include (1) hypoxemia secondary to underlying cardiopulmonary disease, anesthetic-related injuries, bleeding diatheses, or cerebrovascular ischemic disease; (2) hypoglycemia resulting from sepsis, endogenous or exogenous hyperinsulinism, or lack of glucose production as a result of severe hepatic dysfunction or increased metabolic demand; and (3) nutritional deficiencies, the most recognized of which is thiamine deficiency, which can result in both cerebrocortical and central vestibular dysfunction.

Aberrations in water and electrolyte balance can result in secondary cerebrocortical dysfunction. Examples include hypernatremia and hyponatremia that result in shifts in the brain osmolality and that have an acute or chronic course.

Changes in ion balance, such as those that occur secondary to hypercalcemia or hypocalcemia and hyperkalemia or hypokalemia, have a direct effect on ion channels in the CNS and can lead to excitatory or inhibitory neurotransmission.

Metabolic disorders that have secondary effects on the CNS and, more specifically, on the cerebral cortex and thalamus are those that liberate endogenous neurotoxins that affect the blood-brain barrier and neurotransmission and that alter the brain's neurochemical balance. Examples of such disorders include (1) hepatic encephalopathy caused by portosystemic shunting, microvascular dysplasia, hepatic cirrhosis, hepatic neoplasia, or inflammatory or infectious causes of hepatic dysfunction (the major causative agents involved in these diseases are hyperammonemia and false neurotransmitter production); and (2) uremic encephalopathy as a result of end-stage renal dysfunction. Exogenous neurotoxins, including strychnine, metaldehyde, illicit drugs, and lead, all can cause secondary CNS effects that, left untreated, can result in death.

Endocrine dysfunction can result in a wide range of CNS effects. Examples of such diseases include hypothyroidism, hyperthyroidism, hyperadrenocorticism, and hypoadrenocorticism. Each of these diseases can disturb the normal resting metabolic energy requirements of the brain and can cause structural changes in the brain parenchyma (pituitary macroadenoma) and vessels (atherosclerosis secondary to hypothyroidism and cerebrovascular accidents secondary to hyperthyroid toxicosis).

HEMATOLOGIC DISORDERS

Diseases associated with thromboembolism and polycythemia (relative and absolute) have a direct effect on brain function secondary to resultant infarction, changes in cerebral blood flow, and vascular sludging. Thromboembolism often is a sequela to cardiac disease, hyperadrenocorticism, glomerulopathies, immune-mediated disease, and sepsis and results in focal infarction of the surrounding brain parenchyma. Absolute polycythemia, either primary or secondary, results in an increased red blood cell mass that causes an increase in blood viscosity and resultant vascular hindrance, decreased microcirculation, and local hypoxia.

IMMUNE-MEDIATED DISEASE

Systemic lupus erythematosus (SLE) has been recognized as causing CNS signs in human beings as a result of immune complex deposition and plaque formation. Although this has not been recognized in the dog, evidence is strong that the same sequelae can occur in this species.

INFECTIOUS DISEASE

Disseminated fungal infections (histoplasmosis, blastomycosis, cryptococcosis), viral infections (canine distemper virus, rabies, and feline infectious peritonitis), and protozoal infections (toxoplasmosis, neosporosis) tend to have a neurotropism and can cause severe CNS dysfunction. In these cases, all portions of the CNS can be affected, and resolution of disease can be difficult because the organisms cause secondary, sometimes permanent, neuronal necrosis and death.

PARANEOPLASTIC SYNDROMES

Two of the most common paraneoplastic CNS effects are hypoglycemia induced by insulin-secreting tumors and hypercalcemia secondary to lymphoma and apocrine gland adenocarcinoma. Although the peripheral nervous system (PNS) is more prone to the effects of hypercalcemia, animals with this electrolyte disturbance can manifest CNS signs secondary to the effect on ion pumps and neurotransmission. Metastasis to the central nervous system from a distant site (hemangiosarcoma, feline renal lymphoma) is also an important sequela in this disease category.

PERIPHERAL NERVOUS SYSTEM

The components of the peripheral nervous system are the nerve root, peripheral nerve, neuromuscular junction, and muscle. Clinical signs vary according to the region affected; most commonly, the peripheral nerve, junction, and muscle are affected.

PERIPHERAL NEUROPATHIES

Clinical signs associated most commonly with peripheral neuropathies include weakness (either diffuse or focal) with or without normal proprioception, decreased or absent reflexes, and a voice change (if the lesion involves the laryngeal innervation). Common causes of neuropathies that occur secondary to changes in energy supply include (1) hypoglycemia, in which peripheral nerve degeneration and demyelination have been reported; (2) hyperglycemia (e.g., feline diabetic neuropathy manifested in a plantigrade stance), in which increased serum glucose concentrations are thought to impede axonal transport; and (3) hypoxia, which is observed in cases of aortic or iliac thromboembolism in the dog or cat and in cases of chronic cardiovascular disease.

Endocrine causes of peripheral neuropathies include (1) hypothyroidism, which can cause both focal clinical signs (most commonly cranial nerves VII and VIII are affected) and diffuse clinical signs, secondary to axonal degeneration, necrosis, and demyelination; and (2) hypoadrenocorticism, in which sudden shifts in electrolyte balance can affect axonal health and result in hyporeflexia and profound weakness.

Other examples of diseases that cause secondary peripheral neuropathies include (1) the infectious protozoan *Neospora caninum*, which causes a lumbar intumescence neuritis in puppies; (2) paraneoplastic syndromes associated with multiple types of cancer; and (3) immune-mediated polyradiculoneuritis, which is theorized to occur secondary to immune destruction of the myelin sheath.

JUNCTIONOPATHIES

Junctionopathies are characterized by either complete lower motor neuron paralysis or progressive exercise intolerance with normal reflexes. Examples of the former condition include tick paralysis and botulism, in which an endogenous toxin binds to the presynaptic membrane at the endplate and blocks acetylcholine (ACh) release. Examples of the latter condition include acquired myasthenia gravis, in which ACh is blocked from its reception at the postsynaptic membrane by immune complexes bound to the ACh receptor site.

MYOPATHIES

The previously described causes of neuropathies can also affect the muscles. The clinical signs associated with myopathies include weakness with normal proprioception; normal to decreased myotatic reflexes; voice change; a stiff,

stilted gait, and ventral neck flexion (observed most commonly in the cat). Decreased energy supplies, including glucose and oxygen, can lead to abnormal muscle oxidative metabolism and resultant weakness. Endocrine disturbances, such as hypothyroidism and hyperthyroidism, have been implicated, because thyroid hormone is very tightly regulated within the muscle membrane, and even subtle changes result in aberrant oxidative metabolism. Hyperadrenocorticism results in abnormal glycogen deposition in the muscle and may have permanent effects, even with treatment for the disease, whereas the weakness induced by hypoadrenocorticism is reversible with therapy. Electrolyte disturbances, most importantly hypokalemia and hypocalcemia, can result in severe muscle weakness and tetany, respectively, due to the importance of these two electrolytes in the regulation of muscle ion channels. Other causes of secondary myopathies include the infectious agent *Toxoplasma gondii*, hematologic aberrations such as absolute polycythemia, immune-mediated diseases such as masticatory myositis, the polymyositis associated with SLE, and paraneoplastic syndromes (cancer cachexia).

CHAPTER 45

Tremor Syndromes

Dominik Faissler

DEFINITIONS

Tremor is a common presentation in dogs and cats. The terms *tremble, shake, quiver,* and *shiver* are used interchangeably to describe this involuntary, rhythmic, and oscillatory movement. Tremor results from simultaneous or alternating contractions of agonist and antagonist muscle groups. Electromyographically, biphasic rhythmic bursts can be recorded. Clinically, tremor syndromes present with continuous, rapid, back-and-forth movements of the head, hind legs, or whole body; these movements cease with sleep.

Tremor must be distinguished from myoclonus, fasciculations, tetany, dyskinesia, and seizures. *Myoclonus* is defined as a sudden, short, jerky, shocklike, involuntary movement caused by an abrupt muscular contraction. Myoclonic jerks arise from electrical discharge of the central nervous system and can involve the head, limbs, or trunk. *Fasciculations* are arrhythmic, involuntary, visible contractions of groups of muscle fibers that indicate pathologic discharge of spinal motor neurons. *Tetany* is characterized by skeletal muscle rigidity and spasm. *Dyskinesias* are rare disorders of the central nervous system that result in involuntary, ticlike, repetitive, and episodic movements of individual muscle groups. The terms *dystonia, atheosis, chorea,* and *ballism* are used in human neurology to describe various clinical manifestations of dyskinesia.

PHYSIOLOGIC TREMOR

Physiologic tremors are difficult to see in normal animals, but they are present at low-amplitude movements, at rest or with posture. Shivering is a normal response to hypothermia, and a fast-rising body temperature in the course of a febrile process may lead to trembling. In both cases, the caudal hypothalamus plays an important role in the induction of muscle oscillations. Fear, stress, joy, and anger are the manifestations of a complex response processed in the limbic system, prefrontal cortex, and hypothalamus. These emotional conditions produce a complex pattern of reactions, including increased muscle tone, adrenergic stimulation, and physiologic muscle tremor. Trembling may also be seen after heavy exercise as a result of metabolic exhaustion and weakness.

PATHOLOGIC TREMOR

Tremor is considered pathologic when it impairs the patient's normal function. Abnormal tremor has a more synchronous activation and larger amplitude and is more easily visualized. No classification system has been devised for pathologic tremor in animals, and little information is available on the etiology and pathogenesis of this condition.

Type

A *kinetic tremor* (or, as it is commonly called, an *intention tremor*) is evident when the patient performs a voluntary movement, and it is most obvious when the movement is goal oriented. *Intention tremor* usually presents with slow, high-amplitude, to-and-fro movements. *Resting tremor* is most visible at rest and diminishes with voluntary movement; the amplitude of these oscillations is much lower, and the frequency is midrange. A fine, fast *action tremor* occurs when parts of the body are activated in certain positions; this type of tremor may occur when the animal is attempting greater precision of movement. *Static tremor* is manifested when antigravity muscles are activated.

Distribution

Involuntary movements can be restricted to the head, and intention tremor is the most common presentation. Head bobbing in either a vertical or horizontal direction also is possible. Localized tremor may be confined to the lumbosacral area and hind legs. *Generalized (whole body) tremors* seem to be more common than focal tremors.

LOCALIZATION OF THE PACEMAKER

Lesions in the lateral cerebellar hemispheres, nucleus interpositus, and cerebellar vermis are associated with intention tremor.

Experimental lesions in the rubro-olivo-cerebellar system of cats can induce either intention tremor or resting tremor. In general, except for intention tremor, anatomic localization of the pacemaker is uncertain in dogs and cats.

PREDOMINANCE OF CLINICAL SIGNS

Some diseases may cause trembling accompanied by other signs. Another group of selective, functional disorders presents with tremor syndromes in which shivering is the predominant complaint.

DISORDERS IN WHICH TREMBLING IS ACCOMPANIED BY OTHER SIGNS

Metabolic Disorders

In addition to other signs, head or whole body tremors may be present in renal disease, hypoglycemia, hypocalcemia, and hypoadrenocorticism.

Intracranial Diseases

A large number of brain diseases may cause tremors, most often with cerebellar involvement. Head tremors, intention tremors and, less frequently, whole body tremors may be part of the syndrome. Other signs often are more obvious than the tremors, such as ataxia, hypermetria, paraparesis or tetraparesis and, less frequently, broad-based stance, abnormal behavior, cranial nerve deficits, opisthotonos, and seizure-like activity. Tremors are reported to be a possible sign in multisystemic inflammatory disease in borzois and in cerebellitis caused by *Neospora caninum;* cerebellar hypoplasia due to mutation or intrauterine panleukopenia viral infection; fibrinoid leukodystrophy; the late course of neuraxonal dystrophy and Labrador retriever axonopathy; spongiform encephalopathy; neuronal abiotrophies; subacute necrotizing encephalopathy; and several lysosomal storage diseases.

Hind End Weakness

Tremor may be part of the clinical presentation in various disorders, including degenerative lumbosacral stenosis; lumbosacral disc herniation, tumors, or discospondylitis; and nerve root compression. In some peripheral neuropathies, synaptic dysfunction, and certain myopathies, shivering may be an additional sign. This static tremor is most pronounced when the animal is standing. Weakness and pain are possible causes.

DISORDERS IN WHICH TREMBLING IS THE PREDOMINANT SIGN

Corticoid-Responsive Tremor Syndrome

A generalized tremor syndrome first was reported in white Maltese dogs. However, the widely used term *white shaker syndrome* turned out to be misleading, because a recent study showed that one half of affected dogs had no or only a partial white haircoat. The disease is reported in young to middle-aged West Highland terriers, Maltese dogs, poodles, dachshunds, miniature pinschers, Pekingese, and mixed-breed dogs. An inflammatory process of the central nervous system is suspected. Histopathologically, mild, diffuse meningoencephalitis, characterized by lymphocytic infiltrates and perivascular cuffing, is reported. Immune-mediated disruption of neurotransmitter metabolism, resulting in reduced conversion of tyrosine to dopamine, has been proposed as a mechanism, but this hypothesis appears less likely in light of the high number of nonwhite dogs. The most consistent clinical sign of generalized tremor syndrome is a whole body tremor that worsens with excitement. Other abnormal findings include, in rare cases, spontaneous nystagmus, head tilt, ataxia, and reduced menace response. Cerebrospinal fluid analysis reveals a mild mononuclear pleocytosis and, in some dogs, an elevated protein level. Most patients respond well to treatment with prednisone and propranolol.

Hypomyelination

An inherited genetic defect results in hypomyelination or dysmyelination in the central nervous system but normal peripheral nerves. In shaking pup syndrome, for example, quantitative studies have shown normal axonal diameters but a marked reduction in the number of oligodendrocytes and decreased myelin volume and thickness. Brain structures are affected more than the spinal cord white matter. Failure of precursor cell division and insufficient migration, abnormal maturation, and early cell death of oligodendrocytes are suspected. The origin of the tremor in animals with this developmental myelin disorder is not well understood.

Clinical signs correlate with the degree of myelin deficiency. Affected puppies start to show signs within the first weeks and months of life. Hypomyelinated or dysmyelinated animals have a whole body tremor that worsens when the puppy begins to move (intention tremor may be present in some cases). Exercise or excitement worsens the tremor, which resolves with sleep. Severely affected animals show a "rocking horse" stance or a bunny hop gait or are unable to stand or ambulate. A perpendicular nystagmus is possible. In some mildly affected animals, the tremor plateaus at the end of the first year of life and improves later. There is no known therapy.

In springer spaniels and Samoyed pups, hypomyelination is transmitted by a sex-linked recessive trait. An autosomal recessive mode of transmission is suspected in the dysmyelination syndrome of the chow chow. Hypomyelination also has been reported in the weimaraner, Bernese mountain dog, lurcher, and Dalmatian and in two Siamese kitten littermates.

Spongy Degeneration

The histologic feature of a spongy appearance of the central nervous system has been reported in several breeds. A congenital disorder of amino acid metabolism is suspected but has not been proved in dogs and cats. A generalized tremor syndrome is reported in the Samoyed, silky terrier, Scottish terrier, and Malinois shepherd–cross puppies. No treatment is available.

TREMORGENIC TOXINS

Numerous toxins are reported to cause generalized tremor. The mycotoxins penitrem A and roquefortine are produced by *Penicillium* spp. growing on garbage, moldy dairy foods, bread, nuts, grains, or blue cheese. Clinical signs of ingestion of these mycotoxins include generalized tremors, ataxia and, in rare cases, seizures. Metaldehyde, a slug and snail poison, causes generalized tremors. Hyperesthesia, salivation, and seizures vary from mild to severe (see Chapter 70). Hexachlorophene, bromethalin, organophosphates, carbamates, chlorinated hydrocarbons, zinc phosphide, methylated xanthines (caffeine, theophylline, theobromine), pyrethroids, macadamia nuts, and strychnine are other toxins that can cause generalized tremors and ataxia. Strychnine induces severe seizures. Therapy is limited to supportive care.

IDIOPATHIC HEAD TREMOR IN DOBERMANS AND BULLDOGS

A localized tremor of the head is reported in Dobermans and bulldogs. The head movement may be in a vertical direction, similar to the affirmation tremor seen in human beings. Head bobbing in the horizontal plane also occurs. The underlying mechanism is unknown.

IDIOPATHIC TREMOR OF THE HIND LEGS

A tremor of the hind legs has been described in geriatric dogs, particularly in terrier breeds. No weakness or other neurologic abnormalities are noted. A similar syndrome has been observed in young Leonberger dogs. In this breed, a dysfunction of serotonin metabolism is suspected.

CHAPTER • 46

Ataxia, Paresis, and Paralysis

Donald C. Levesque

All levels of the nervous system, from the brain to the peripheral nerves, have neurons that in some way are associated with sensory, motor, or integrative functions of locomotion. Disturbances of these pathways cause some degree of ataxia, paresis, or paralysis. However, because some orthopedic and systemic diseases can mimic these signs, the first goal of a neurologic examination is to determine whether the signs observed in the patient actually are due to neurologic dysfunction. Once neurologic deficits have been confirmed, the next goal becomes localization of the lesion or lesions. A general algorithm for localization of nervous system lesions, based on the presence of ataxia, is presented in Figure 46-1. Accurate interpretation of clinical signs, consistent use of terminology, and an awareness of the ways in which various disease processes can affect the nervous system are essential for the most effective use of any algorithm for localization of nervous system lesions. Recognition of the various forms of ataxia and of the significance of paresis in association with ataxia is important in lesion localization and may aid in the determination of the etiology and prognosis.

TERMINOLOGY

Ataxia, *paresis*, and *paralysis* are terms ascribed to neurologic deficits. These conditions must be distinguished from limb lameness and weakness caused by non-neurologic manifestations of gait abnormalities. Ataxia is an abnormality of movement, particularly gait, characterized by a degree of sway and incoordination; it may affect the head, trunk, or limbs. Paresis is a partial loss of voluntary movement and usually is accompanied by conscious proprioceptive deficits. Paralysis is the absence of voluntary motor function and is described as flaccid or spastic. Prognostically, it is important to determine whether pain sensation is present or absent. Paralysis is not be confused with nonambulatory paresis.

Ataxia, paresis, and paralysis are characterized as generalized or localized. Ataxia and paresis are graded on a scale ranging from mild to severe. Ataxia is further categorized as proprioceptive, vestibular, or cerebellar.

SIGNS BASED ON THE NEUROANATOMIC LOCATION OF LESIONS

Forebrain (Diencephalon, Basal Nuclei, Cerebral Hemispheres)

In the conscious patient, forebrain disease generally causes relatively mild limb paresis and ataxia. Unilateral lesions usually cause contralateral conscious proprioceptive deficits with minimal gait disturbance. Generalized forebrain disease (e.g., encephalitis, hydrocephalus, midline thalamic lesions) often causes generalized ataxia and mental dullness with only mild to moderate paresis. Although ataxia and paresis often are present in forebrain disease, other signs, such as seizures, disorientation, behavioral changes, circling, and visual deficits, usually predominate. Paralysis is seen only during deep stupor or coma. In general, forebrain disease has less profound effects on locomotion than do lesions of the brain stem, cerebellum, spinal cord, and peripheral nerves.

In some instances, cerebral dysfunction mimics thoracolumbar myelopathy by causing rear limb ataxia and paraparesis without detectable forelimb deficits. This apparent paradox can be seen postictally; it also occurs secondary to side effects of anticonvulsant medications, particularly potassium bromide, in some patients. In nearly all these cases, mentation and forelimb dysfunction likely are present but subclinical. Postictal paraparesis can be differentiated from myelopathic paresis by its transient nature. Recovery from postictal paraparesis usually occurs within minutes to hours, compared with days to weeks in patients with myelopathies.

Brain Stem

In the conscious patient, brain stem disease can cause moderate to marked ataxia, hemiparesis, or tetraparesis but rarely paralysis. Unilateral lesions caudal to the pyramidal decussation in the medulla affect ascending sensory and descending motor pathways, causing marked ipsilateral hemiparesis. Vestibular nuclei are commonly affected, causing superimposed vestibular ataxia, head tilt, and nystagmus. The ataxia of central vestibular disease, although sharing many similarities with peripheral vestibular disease, is distinguished by the presence of ipsilateral conscious proprioceptive deficits. Other cranial nerve signs, such as facial paralysis, head muscle atrophy, or

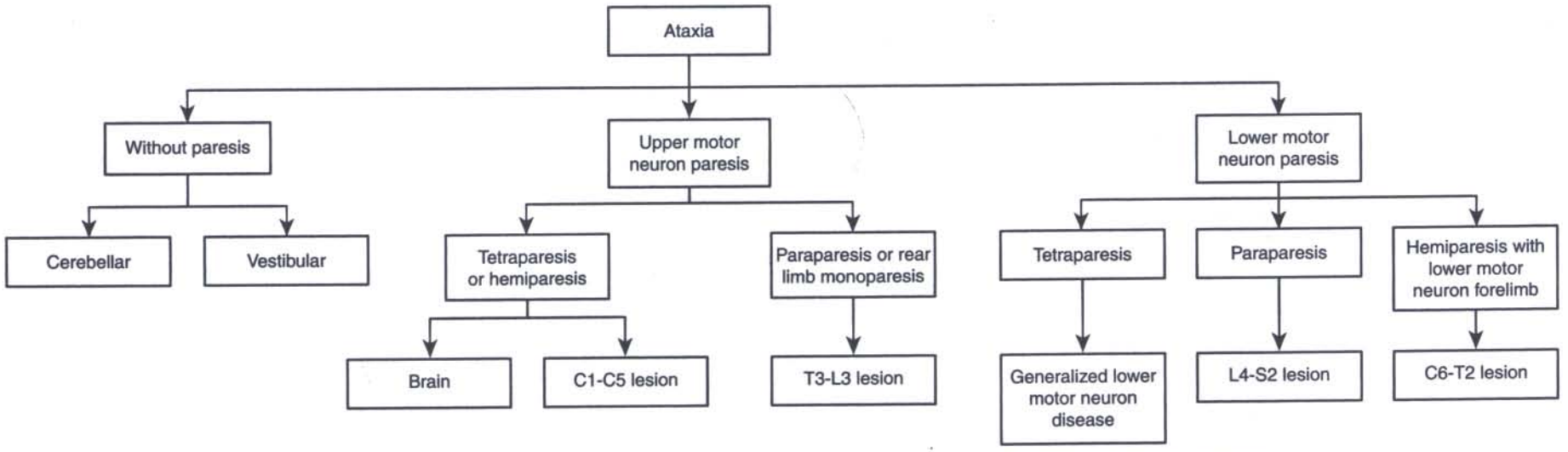


Figure 46-1 Algorithm for localization of nervous system lesions based on presence of ataxia with or without paresis.

dysphagia, may also be present. Hemiplegia and tetraplegia can occur, but lesions severe enough to cause paralysis usually result in respiratory arrest.

Peripheral Vestibular System

Unilateral lesions of the membranous labyrinth or cranial nerve VIII can cause ataxia ranging from mild and barely perceptible to profound and extremely debilitating. Head tilt, horizontal or rotatory nystagmus, positional strabismus, and abnormal oculovestibular eye movements are nearly always present to some degree. Bilateral peripheral vestibular disease most often causes symmetric, generalized ataxia with characteristic wide, swaying head excursions in both directions; oculovestibular eye movements, including pathologic nystagmus, are absent.

Peripheral vestibular disease does not cause paresis or paralysis, therefore proprioceptive deficits are not present. However, because of the strong influence of the vestibular system on limb muscle tonus, vestibular dysfunction results in an increase in contralateral and a decrease in ipsilateral extensor muscle tone, often making it difficult for the examiner to interpret proprioceptive reactions in severely affected patients.

Cerebellum

Because the cerebellum functions as modulator rather than as a site of initiation of motor function, cerebellar disorders cause mild to marked ataxia without paresis or paralysis. Unilateral lesions of the cerebellum cause ipsilateral limb ataxia with dysmetria, usually hypermetria. The flocculonodular lobe of the cerebellum modulates posture and movement based on vestibular input; consequently, lesions at this location cause disequilibrium and ataxia.

Cervical Spinal Cord

Cervical spinal cord disease can cause mild to marked ataxia and forelimb monoparesis, hemiparesis, or tetraparesis. Forelimb monoplegia, hemiplegia, or tetraplegia also can occur. Deep pain sensation is always present in tetraplegic animals with normal respiratory function, because functional transection of the cervical spinal cord cranial to the sixth spinal cord segment results in loss of innervation of the diaphragm and intercostal musculature, with subsequent apnea. Cervical cord lesions caudal to C6 disrupt innervation of the intercostal musculature, leaving only diaphragmatic respiration.

Lesions affecting spinal cord segments C6-T2 cause forelimb hyporeflexia owing to injury of the cell bodies of lower motor neurons that innervate forelimb musculature. Forelimb reflexes are preserved with lesions cranial to C6. Cervical spinal cord disease most often causes injury to ascending and descending axons serving the rear limbs and results in rear limb ataxia with normal to exaggerated rear limb reflexes.

In unusual cases, very focal spinal cord lesions (usually a vascular or contusive type) selectively affect grey matter and spare ascending and descending white matter tracts. If such lesions affect spinal segments C6-T2, flaccid forelimb paresis or paralysis without rear limb deficits can result. Conversely, chronic caudal cervical spinal cord compression, such as can occur in cervical spondylolisthesis, may selectively affect descending and ascending white matter tracts serving the rear limbs, resulting in rear limb ataxia and paresis and no detectable forelimb deficits.

Thoracolumbar (T3-L3) Spinal Cord

Thoracolumbar spinal cord disease can cause mild to marked rear limb ataxia, paraparesis, paraplegia, monoparesis, or monoplegia. Rear limb reflexes are normal to exaggerated. The panniculus reflex generally is reduced or absent two to three spinal segments caudal to the site of a thoracolumbar lesion. Mildly to moderately compressive injuries generally result in ataxia with paraparesis. More severely compressive lesions can cause paraplegia. Contusive or vascular injuries are usually more acute but cause similar signs. Cranial thoracic spinal cord lesions often cause a more "lumbering," swaying rear limb ataxia than do more caudal lesions as a result of paresis of the thoracic paraspinal musculature. Nonambulatory paraparetic and paraplegic patients with cranial thoracic lesions often are laterally recumbent and unable to rise to a sternal position. Focal spinal cord ischemia can selectively affect only a portion of the spinal cord, causing monoparesis or monoplegia. Examples of this condition are seen in patients with fibrocartilaginous embolization or ischemia secondary to vasculitis.

Shiff-Sherrington sign, an increase in extensor tone of forelimb musculature after acute thoracolumbar spinal cord injury, is an indicator of severe spinal cord injury but does not necessarily carry a grave prognosis. Generally, the more cranial the lesion, the more exaggerated the forelimb hypertonia.

Lumbosacral (L4-S2) Spinal Cord

Lumbosacral spinal cord disease causes mild to marked rear limb ataxia, paraparesis, paraplegia, or monoplegia with reduced to absent rear limb reflexes. Lesions that affect segments L4 and L5 cause decreased to absent knee-jerk reflexes. Lesions that affect segments L6 through S2 cause decreased withdrawal reflexes of the rear limbs, as well as bladder hypotonia and bladder and anal sphincter hypotonia.

Peripheral Nerve

Peripheral nerve lesions also can cause mild to marked ataxia, paresis, or paralysis of one or more limbs. Hyporeflexia is a consistent finding.

Nerve root avulsion or severance of a major peripheral nerve to a limb results in areflexia and paralysis of the affected muscle or muscles as a result of loss of sensory and motor innervation. Degenerative, inflammatory, and toxic neuropathies generally affect all peripheral nerves and result in varying degrees of ataxia, paresis, and paralysis. Hyporeflexia is a common denominator in these patients. Gait disturbances of patients with polyneuropathy can vary from marked paresis to paralysis to almost cerebellar-appearing dysmetria. Even though the histopathologic changes in nerve fibers and affected muscles may be similar in the forelimbs and rear limbs, it is not unusual for gait abnormalities to be more obvious in the rear limbs. Presumably, this phenomenon is due to the longer distance from the brain to the motor endplates and sensory receptors in the rear limbs, which allows for greater dispersion of motor and sensory action potentials.

Most polyneuropathies in dogs and cats appear to preferentially affect motor fibers, causing ataxia, paresis, and paralysis with preservation of superficial pain sensation and, often, conscious proprioception. With very few exceptions, therefore, a patient presenting with tetraplegia, hyporeflexia, and preservation of superficial pain sensation has a neuromuscular disorder (neuropathy, junctionopathy, myopathy). A notable exception is focal myelomalacia, in which descending motor tracts are affected but ascending superficial and deep pain fibers are preserved.

CHAPTER 47

Altered States of Consciousness: Stupor and Coma

Karen L. Kline

DEFINITIONS

Stupor and coma are pathologic abnormalities caused by an interruption in the structural, metabolic, and/or physiologic integrity of the brain stem or cerebral cortex. *Stupor* is characterized by a state in which the animal appears to be asleep or unconscious but can be aroused by a noxious stimulus. Once the stimulus is withdrawn, however, the animal may lapse back into the sleeplike state. *Coma* is characterized by a state of unconsciousness in which the animal cannot be aroused even by a noxious stimulus. A strong toe pinch, for example, may elicit a flexion reflex or increased extensor tone but does not cause a behavioral response, such as crying or biting. In either case, prompt action is required to attempt to reverse these signs and correct the underlying cause.

PATHOPHYSIOLOGY

Consciousness is maintained by sensory stimuli that act through the ascending reticular activating system (ARAS) on the cerebral cortex. Decreasing levels of consciousness indicate abnormal cerebrocortical function or interference with cortical activation by the ARAS. The cerebral cortex controls the content of consciousness, whereas the brain stem controls the level of consciousness. In a sense, the cerebrum is the light bulb, and the brain stem is the rheostat that regulates its brightness. All sensory pathways have collateral input to the ARAS in the pons and the midbrain, and this information is projected diffusely to the cerebral cortex, where cholinergic synapses communicate constantly with cortical neurons. Balance is maintained between the ARAS and the adrenergic (sleep) system, which projects from the midbrain and diencephalon (thalamus). Signs ranging from hyperexcitability to coma can be observed if imbalance exists between the two systems.

The causes of stupor and coma are numerous. The three most important are (1) increased intracranial pressure, (2) cerebral edema, and (3) herniation of brain tissue. Increased intracranial pressure can occur secondary to an increase in the volume of tissue or fluid (e.g., cerebrospinal fluid, edema, or blood) within the cranial vault; even small shifts in these volumes can have dramatic consequences. Causes of increased intracranial pressure include encephalitis, meningitis, mass lesions (e.g., neoplasia, granulomas, or abscesses), vascular events, traumatic injury, or underlying metabolic disturbances, such as hypertension.

Cerebral edema is an abnormal accumulation of fluid in the brain parenchyma. It is classified into three types: (1) vasogenic, which is most commonly associated with brain masses and is due to a breakdown in blood-brain barrier integrity; (2) cytotoxic, which is most commonly associated with metabolic disturbances, such as hypoxia and neuroglycopenia, that cause cell or neuronal death; and (3) interstitial, which is most likely associated with hydrocephalus. The end result of progressively increased intracranial pressure and/or cerebral edema is brain herniation.

There are four different types of herniation, two of which can induce stupor or coma: (1) caudal transtentorial herniation, in which portions of the temporal lobe shift ventral to the tentorium cerebelli and cause midbrain compression; and (2) foramen magnum herniation, the most common form, which occurs when the caudal cerebellar vermis moves through the foramen magnum, causing a compression of the displaced cerebellum and the medulla oblongata. In these cases, injury to the respiratory center, descending motor pathway tracts, and cardiovascular centers in the caudal brain stem can lead to midbrain and cerebral hypoxia and coma, which can be irreversible.

APPROACH TO THE PATIENT WITH STUPOR OR COMA

After the pet's initial presentation, close attention must be paid to immediate life-threatening injuries and their sequelae, such as hemorrhage, hypoxia, or shock. The ABCs of critical care medicine—airway, breathing, and cardiovascular status—are paramount. Concurrently, a thorough history, including onset and progression of signs, previous illness or injury, and drug use or toxin exposure, should be ascertained. Thorough physical and neurologic examinations should be performed, with emphasis placed on the cardiac rate and rhythm and the respiratory pattern. Simply observing the patient for a short time can yield considerable information. An anatomic diagnosis can be ascertained on the basis of the following: (1) mental status and level of consciousness; (2) neuro-ophthalmologic signs (vision, pupil size and symmetry, and ocular movements); (3) alterations in respiratory pattern; and (4) skeletal motor responses. Following these trends can aid prognostication and the development of treatment protocols and is essential for patient management.

Mental Status and Level of Consciousness

Consciousness is maintained by the midbrain ARAS, which acts as a rheostat, projecting diffusely to the cerebral cortex. Consequently, diffuse cerebral disease or midbrain disease can result in stupor, coma, or other alterations in consciousness, such as dementia. Differentiation between stupor and coma can be achieved with the application of a noxious stimulus, such as a hemostat or needle. Care must be taken to follow trends when evaluating the patient, and hasty prognostication should be avoided. In general, stupor has a better initial prognosis than coma, but exceptions can occur. Other factors include the patient's age, the underlying medical history, and the cause of the alteration in consciousness.

Neuro-Ophthalmologic Signs

Pupillary Reactions

Pupil size and reactivity to light can be normal in the comatose patient; alterations in these parameters can aid in neurolocalization and prognostication. Integrity of the retinae, optic nerves, and chiasm and of the rostral brain stem is consistent

with pupils that are equal in size and that respond well to light and darkness. In general, lesions of the cerebral cortex and thalamus result in normal or constricted pupils that respond to both darkness and light. Lesions in the brain stem can result in unilateral or bilateral pupillary constriction (pons) or dilatation (midbrain), depending on the location. Peripheral lesions involving cranial nerve (CN) III usually result in dilated pupils with normal vision. Pupils that are bilaterally dilated (fixed) and unresponsive to light imply a guarded to grave prognosis.

Ocular Movements

The pathways that mediate ocular movements lie adjacent to the brain stem regions responsible for consciousness, making it clinically useful to evaluate ocular movements in the stuporous or comatose patient. Physiologic nystagmus or conjugate eye movements (the oculocephalic and doll's eye reflexes) are normal and require integrity of CN VIII (vestibulocochlear nerve), the brain stem (vestibular nuclei, medial longitudinal fasciculus), the cerebellum (flocculonodular lobe), and the nuclei of CN III, IV, and VI. Any disruption in this pathway results in pathologic nystagmus (rotary, horizontal, or vertical downbeat). Ocular movements are evaluated by moving the head in a slow or rapid fashion from side to side while it is held in a fixed position. In the normal animal, this movement results in several beats of horizontal nystagmus (with the fast component toward the direction of the head movement) that stops once the head movement stops. If the nystagmus continues after the movement stops, if it occurs spontaneously, or if it changes with position, a lesion in the vestibular system is likely to exist. If there is absence of ocular movements in the comatose patient, severe brain stem injury should be suspected, and the prognosis for return to function is guarded to grave.

Alterations in Respiratory Pattern

Severe or progressive brain injury can result in changes in breathing patterns. *Cheyne-Stokes respiration* is characterized by hyperpnea alternating with apnea and can be an indication of a bilateral cerebral hemisphere or diencephalic lesion. Central neurogenic breathing or hyperventilation is associated with lesions in the midbrain pneumotaxic center, whereas lower pontine and medullary lesions result in apneustic or ataxic (gasping) respirations, respectively. When a change in breathing patterns is noted, aggressive therapy may need to be instituted to counteract herniation.

Skeletal Motor Responses

The examination of motor function in the comatose patient provides valuable localizing information. Trends must be monitored in order to follow the disease course. Injury to the descending motor systems can result in either increased or decreased extensor and flexor tone, depending on where the injury occurs. Involuntary movements, such as twitching or paddling, may indicate seizure activity. Decerebrate posture (all four limbs extended) indicates a lesion in the midbrain or pons and can occur primarily or secondary to cerebrocortical herniation; decerebrate posture indicates that the motor pathways that aid in flexion are damaged, and stupor or coma is present. Decerebellate posture (forelimbs extended with alternating hind limb flexion and extension) indicates a rostral cerebellar lesion, and the level of consciousness may not be impaired. Flaccid paralysis due to injury to the descending motor pathways implies a grave prognosis, especially when the patient is stuporous or comatose.

DIAGNOSTIC PLAN

The causes of stupor and coma are numerous (Figure 47-1). Routine laboratory data (hemogram, serum chemistries, urinalysis) can aid in determining a metabolic cause of the alteration in consciousness. Inflammatory, infectious, or toxic agents may cause changes in the hemogram, whereas metabolic or endocrine disorders may result in changes in the blood chemistries, which would suggest the need for other diagnostic tests, such as evaluation of blood ammonia levels and serum bile acids, adrenocorticotropic hormone (ACTH) stimulation, and thyroid profiles. Chest and abdominal diagnostic imaging (radiographs, ultrasonography) may also be indicated if metastatic or infectious disease is suspected. If minimal changes are noted in these parameters, a primary or intracranial cause of stupor or coma should be considered. Noninvasive methods used to determine the cause of intracranial disease include electroencephalography (EEG) and brain stem auditory evoked response (BAER). These methods are useful for evaluating the integrity of the cerebral cortex and brain stem, respectively, and they can be performed without general anesthesia. Ophthalmic evaluation may help to determine whether high intracranial pressure or infectious disease is present. Computed tomography (CT) and magnetic resonance imaging (MRI) are quite useful for confirming the presence and character of intracranial lesions, such as tumors, hydrocephalus, and vascular injuries. If the dog or cat is comatose, general anesthesia may not be necessary. Spinal fluid analysis typically is useful for determining whether the animal has an inflammatory or a neoplastic intracranial process; general anesthesia is required and does carry some risk if high intracranial pressure exists.

TREATMENT GOALS

Most dogs and cats with stupor or coma have life-threatening injuries that require immediate attention. Establishing a patent airway and maintaining respirations and cardiovascular status (in particular blood pressure) are critical to stabilization, regardless of the underlying cause of the insult. Bloodwork should be evaluated, and intravenous administration of fluids, anticonvulsants, osmotic diuretics and, in some cases, corticosteroids can be instituted to aid patient stabilization. Elevation of the head may help reduce excessive cerebral blood flow, and body temperature should be continuously monitored, especially in the case of seizures. Cerebral edema can be treated using injectable corticosteroids (once the blood pressure has stabilized), osmotic and loop diuretics (mannitol and furosemide, respectively), and hyperventilation. Seizures can be controlled using injectable anticonvulsants such as diazepam, phenobarbital, and pentobarbital. These treatments are discussed in more detail in the chapters on specific brain diseases. Intensive nursing care is paramount. Frequent turning (to avoid hypostatic lung congestion), bladder evacuation, ocular lubrication, optimal nutrition, and proper bedding are imperative.

PROGNOSIS

The prognosis for animals with stupor or coma depends on the cause of the insult, other underlying disease processes, the location of the injury, the signalment of the patient, and the response to therapy. Serial neurologic evaluations that concentrate particularly on the level of consciousness, ocular movements, pupillary size, motor tone, and breathing patterns can guide the practitioner in terms of treatment options and prognostication. Patience is necessary, especially in cases of brain trauma, and trends in improvement or deterioration need to be followed. If the patient survives the immediate injury, sequelae such as seizures, permanent neurologic deficits, and long-term nursing care should be addressed with the client.

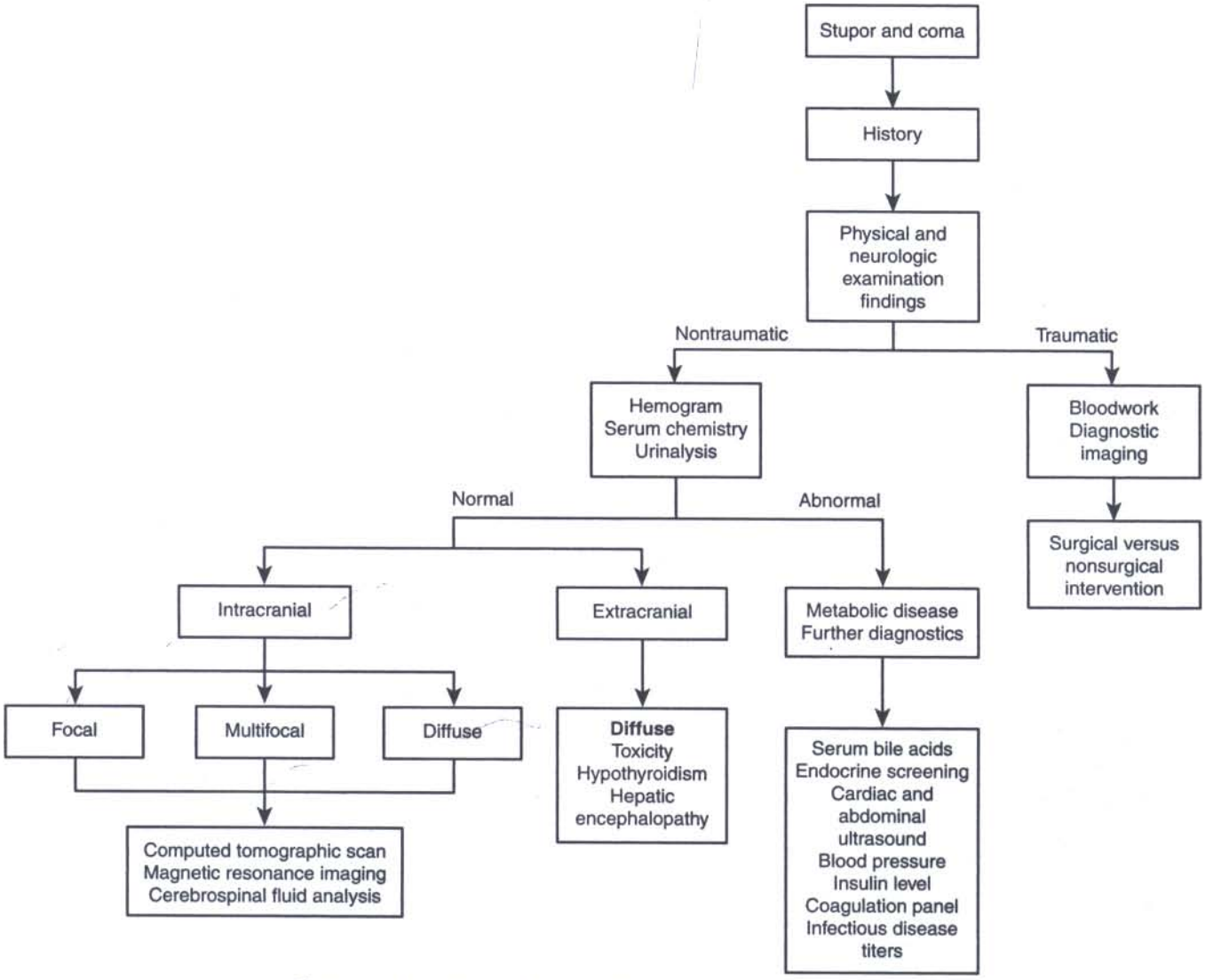


Figure 47-1 Algorithm for diagnostic approach to stupor and coma.

CHAPTER 48

Seizures

Andrée D. Quesnel†

A *seizure* is the clinical manifestation of an excessive discharge of hyperexcitable cerebrocortical neurons. Depending on the location and extent of the seizure discharge, the clinical appearance of seizures can vary a great deal.

Without the use of electroencephalography, seizures can be classified only according to their clinical manifestations. *Generalized seizures* have a widespread onset within both cerebral hemispheres and manifest with loss of consciousness, recumbency, and generalized symmetric motor signs. Most generalized seizures manifest with violent motor activity that involves the whole body (convulsions), such as *tonic* (sustained) and/or *clonic* (repetitive) muscle contractions, limb paddling, and trembling. Jaw chomping and facial twitching are frequently observed. Signs of autonomic hyperactivity (e.g., pupillary dilatation, salivation, piloerection, micturition, defecation) are common. Rarely, the seizures may be atonic ("drop-attack") and must be differentiated from syncope and narcolepsy-cataplexy.

Partial seizures have a focal onset in one cerebral hemisphere and limited spreading within the brain. Their occurrence indicates the presence of a focal acquired structural brain lesion. Partial seizures may be simple or complex, depending on whether consciousness is disturbed. *Simple partial seizures* arise from and are confined to neocortical structures of one cerebral hemisphere. These do not cause consciousness alterations. Unilateral motor signs such as facial twitching, tonic or clonic movements of one or both limbs, and spasmodic turning of the head to one side are often observed and are contralateral to the side of the seizure focus.

In *complex partial seizures,* the spread of the seizure involves allocortical structures and often continues bilaterally. Consciousness is either impaired or lost. There may be contralateral or bilateral asymmetric or symmetric motor signs, usually limited to some parts of the body. Bizarre activity, both stereotypical (e.g., circling) and behavioral (e.g., startling, growling, hissing, chasing and attacking imaginary or real objects, running in a panic), may also be observed, particularly in cats.

Some seizures thought to be mild generalized seizures are likely complex partial seizures. In the latter type, consciousness is impaired or lost and there is bilateral motor activity that usually does not result in recumbency; however, there is an arrest of the animal's ongoing activities (e.g., it stops if moving and may sit if standing). Motor signs are limited to bilateral facial twitching, jaw chomping ,or lip smacking, sometimes with mild generalized trembling or spasms of the neck and front end. Occasionally, there may be decreased motor function that causes stumbling, crawling, or inability to get up and walk. The dog or cat may still be aware and responsive to varying degrees. Because these seizures are not manifested by complete loss of consciousness and generalized motor signs, the underlying neuronal discharge likely has a limited spread within the brain, which is a feature of partial seizures.

A third class of partial seizures are those that secondarily evolve to generalized seizures. Secondary generalization may occur so quickly that no features of partial seizures may be observed clinically.

Another hallmark of partial seizures is an *aura.* An aura is considered to be the initial portion of the seizure, experienced before the consciousness is altered and for which memory is retained in people. It corresponds to the onset of a simple partial seizure before it evolves into a complex partial or a generalized seizure. In animals, it is most often manifested by behavioral changes within a few seconds or minutes of the apparent seizure onset (e.g., attention seeking or withdrawal, depression or agitation, pacing, whining, howling). Mood changes that precede seizures for several hours or even longer should not be confused with an aura. This is rather a prodrome and is not the result of the onset of cerebral epileptic activity. It may be observed before many seizure types and has no diagnostic value.

Localized postictal motor deficits also indicate that a partial seizure has occurred. This phenomenon, referred to as *Todd's paralysis* in human beings, consists of a transient (minutes to hours) localized loss of motor function that follows some partial seizures. It may be attributed to neuronal exhaustion or increased inhibition in the region of the seizure focus. It is observed contralateral to the focus.

Seizures may occur as brief, isolated events (usually lasting 2 minutes or less), cluster seizures (two or more over a 24-hour period), or status epilepticus (sustained or serial seizures lasting at least 30 minutes and without intervening periods of full recovery). They can be convulsive with generalized and violent motor activity (e.g., tonic-clonic generalized seizures) or nonconvulsive with milder and often subtle motor signs (e.g., partial seizures limited to facial twitching).

The term *epilepsy* should be restricted to seizure disorders with inactive intracranial causes. *Primary epilepsy* (functional, asymptomatic) is the result of functional cerebral disturbances for which there would be no underlying cause other than a hereditary predisposition (e.g., canine idiopathic epilepsy). *Secondary epilepsy* (structural, symptomatic) is caused by acquired but inactive brain lesions (e.g., posttraumatic,

†During the preparation of this manuscript, Dr. Andrée Quesnel died at the age of 44 after fighting lung cancer for a year.

Neurology was a great passion in her life. She had been a Diplomate in the specialty of neurology since 1994. Her main interests were seizure disorders and feline diseases.

As a professor at the University of Montreal, she was instrumental in building the neurology department. She made neurology understandable and even enjoyable for her students. As a friend and colleague, she taught us much. Not surprisingly, she was the recipient of many teaching awards.

She was rigorous, independent, and a perfectionist, but all of those who knew her will remember her laugh and her friendship more than anything. She will be greatly missed.

— Dr. Veronique Sammut, Former Resident in Neurology, University of Montreal. February 2004.

postischemic, and postencephalitic gliosis). The term *cryptogenic epilepsy* may be used when evidence exists of a structural brain lesion (e.g., partial seizures), but this cannot be further documented, and the etiology remains unknown.

GENERAL PATHOPHYSIOLOGY

The neuronal hyperexcitability that underlies the generation of seizures is the result of an imbalance between normal excitatory and inhibitory mechanisms. This may be due to an intracranial or an extracranial disease process. Intracranial causes of seizures include primary brain disorders, either functional disturbances of neurons (e.g., idiopathic epilepsy) or structural brain lesions that irritate the surrounding neurons. Structural brain lesions can be active (e.g., neoplasms, encephalitides) or inactive (e.g., glial scars). Extracranial causes of seizures alter the brain biochemical homeostasis in favor of excitation and may be exogenous (seizurogenic toxins) or endogenous (severe metabolic disturbances).

It is important to appreciate that seizures enhance the likelihood of further seizures, regardless of their cause. The development of progressive and refractory seizure disorders correlates well with the cumulative number of seizures, especially when they have a high rate of recurrence, and the seizures may occur relatively early in some cases. Such self-perpetuating phenomena may also be involved in acutely recurring seizures (cluster seizures and status epilepticus), which often become more difficult to control the longer interval from their onset. Rapidly recurring seizures may recruit adjacent as well as remote areas of the brain into the epileptic discharge *(kindling phenomenon)* and may also produce neuronal damage. These factors likely contribute to the development of progressive and refractory seizure disorders. Early diagnostic and therapeutic procedures, especially aggressive antiepileptic drug therapy, are crucial for optimal seizure control in both acute and chronic seizure disorders.

DIAGNOSTIC APPROACH

Historical Findings

Careful scrutiny of the seizure history (age at the first seizure, seizure type, and initial frequency) often brings to light critical information about the underlying cause. An overview of this process appears in Figure 48-1.

In dogs, idiopathic epilepsy should be excluded if the first seizure did not occur between the ages of 6 months and 5 years, if all seizures are not primarily generalized tonic-clonic, if aura or localized postictal motor deficits have been observed, or if the first few seizures occurred at less than 4- to 6-week intervals. High-frequency seizures may develop with idiopathic epilepsy in many medium or large breeds of dogs (e.g., Border collie, Dalmatian, German shepherd, golden retriever, Siberian husky, Saint Bernard), but this usually occurs several months after the seizure onset. Another cause should be suspected in some breeds of dogs (e.g., Doberman pinscher, rottweiler, Newfoundland, brachycephalic breeds) and in cats, which are less likely to suffer from idiopathic epilepsy.

Physical Findings

Physical and fundic abnormalities may be related to seizures, revealing the existence of a multisystemic infectious, metabolic, hypoxic (e.g., polycythemia), or neoplastic disease.

In the neurologic examination, particular attention should be paid to tests that evaluate the thalamocortex (e.g., menace response, facial [nasal septum] sensation, and postural reactions [proprioceptive positioning and hopping]). Postictal disturbances may include bilateral and systemic deficits and should not be interpreted as evidence of structural brain disease. Subtle unilateral or bilateral but asymmetric deficits are frequently found in patients with a seizure disorder; these can be overlooked if the response obtained on both sides is not carefully compared. Such deficits indicate the presence of a structural lesion in the contralateral cerebral cortex or thalamus. Neurologic deficits that cannot all be attributed to a focal cortical or thalamic lesion indicate multifocal central nervous system involvement, which is usually caused by infectious or noninfectious (immune mediated) encephalitides.

Diagnostic Plan

Once the seizure history has been scrutinized and the clinical examinations performed, the likelihood of an intracranial or extracranial cause can often be established, and a rational diagnostic evaluation can be planned (see Figure 48-1).

Despite extensive diagnostic investigation, an etiology is often difficult to establish in seizure disorders with intracranial causes. However, the main objective is not necessarily to reach a precise diagnosis, but rather to rule out conditions that would require or benefit from specific medical treatment (e.g., encephalitides) and/or surgical treatment (e.g., neoplasms). Once this has been done, symptomatic antiepileptic drug therapy is the only treatment option.

TREATMENT

Status epilepticus and cluster seizures, whether convulsive or nonconvulsive, are emergencies. Their management is outlined in Box 48-1.

Oral maintenance antiepileptic (AED) drug therapy should be initiated as soon as two consecutive seizures have occurred in an interval of less than 6 to 8 weeks; this includes cluster seizures and status epilepticus, even the first occurrence of seizures. The importance of early, aggressive, and rational treatment cannot be overemphasized. Guidelines for oral maintenance therapy are presented in Boxes 48-2 and 48-3. The goal of treatment is to reduce the seizure frequency to less than one single seizure every 6 to 8 weeks as soon as possible.

Potassium bromide has replaced phenobarbital as the first-choice antiepileptic drug for dogs. It offers the advantage of being eliminated by the kidneys with no risk of hepatic toxicity and minimal drug interactions. When used as a first-line drug, potassium bromide seems to be as effective as phenobarbital, yet has no toxicity potential other than causing excessive side effects with overdosing or individual intolerance. Also, it can be administered once daily; it is not expensive; precise therapeutic guidelines have been devised; serum bromide concentration testing is available in most veterinary laboratories at the same cost as for phenobarbital; and it is not a controlled drug. The main inconvenience of potassium bromide is its very long half-life (3 to 4 weeks), with the resulting long delay (4 to 5 months) before steady state and maximal antiepileptic effect for a given dosage are obtained. In cases of high seizure frequency, therefore, treatment must be initiated with a loading dose in order to reach a low therapeutic serum concentration within 24 to 48 hours. However, a long half-life is an advantage for minimizing both serum concentration fluctuations between dosing intervals and the effect of missed doses.

Adverse effects of potassium bromide are similar to those of phenobarbital (polydipsia, polyuria, polyphagia). Gastrointestinal disturbances (vomiting, diarrhea, loss of appetite) are also occasionally observed and may be due to the hypertonic and osmotic nature of bromide formulations. Medicating with food or dividing the daily dosage into two doses may alleviate this problem. Signs of an excessive bromide serum concentration include sedation and hindlimb paresis that is strikingly more marked than ataxia. These are usually seen

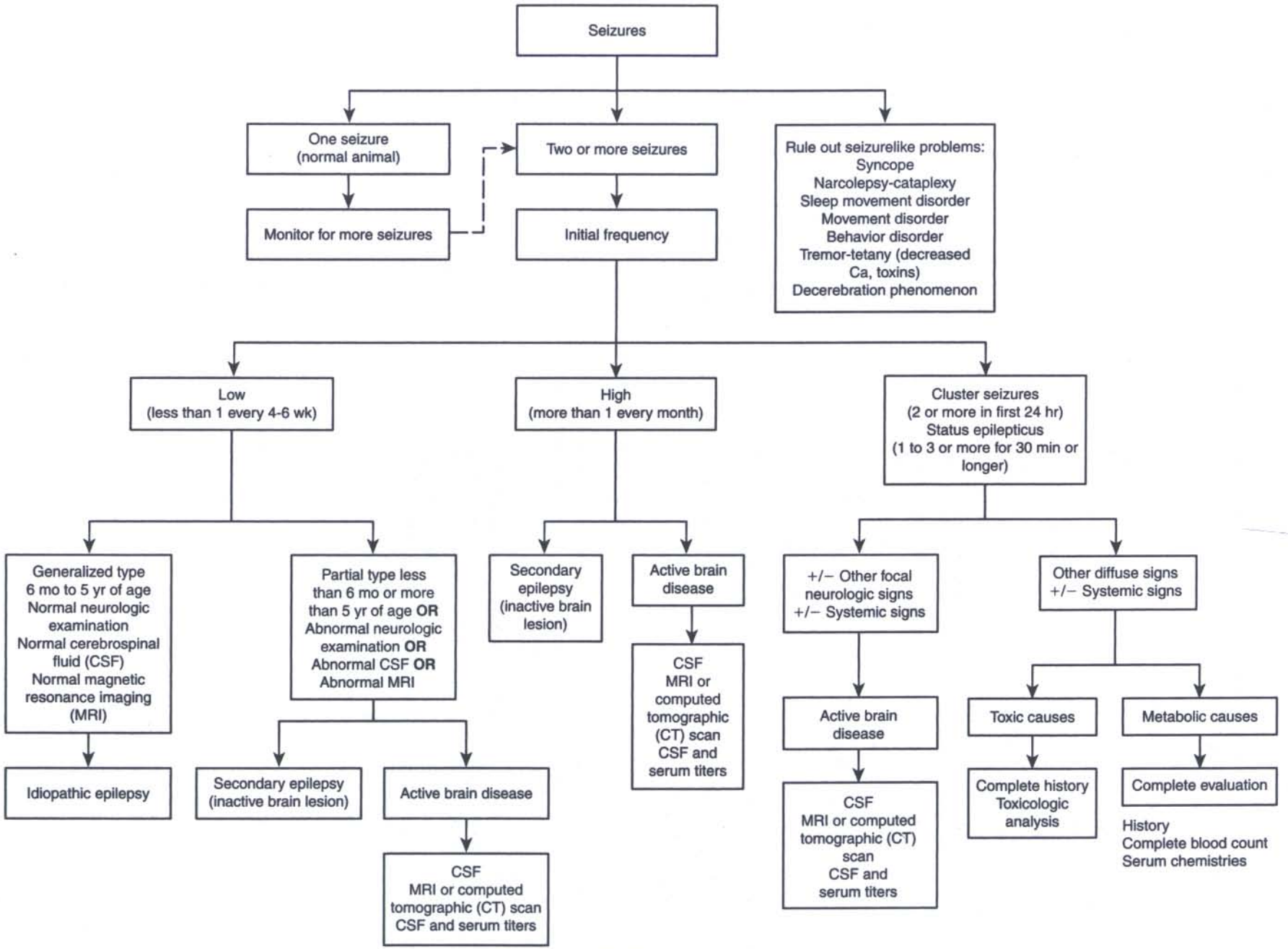


Figure 48-1 Algorithm for diagnostic approach to seizures.

Box • 48-1

Emergency Treatment of Cluster Seizures and Status Epilepticus in Dogs and Cats

I. **The animal is not seizing** at the time of presentation but has had cluster seizures (CS) or status epilepticus (SE) within the previous 12 to 24 hours.
   A. Perform a complete physical and neurologic examination.
   B. Collect appropriate samples for eventual laboratory testing: complete blood count (CBC), biochemical profile, urology and, in patients already on maintenance therapy, determination of the serum antiepileptic drug concentration ($[AED]_S$).
   C. In naive patients, initiate oral maintenance AED therapy with a loading dose.
      1. *Dogs*: Potassium bromide (KBr) 450-600 mg/kg.
         a. Divide into 4 subdoses to be administered with food q 3-4h. Continue with the maintenance dosage (40-50 mg/kg q24h) the next day. If marked side effects (e.g., difficulty walking) develop within the next few days, administration of the daily maintenance dose may be stopped for a few days.
         b. Measure $[Br]_S$ on day 3. If it is <12-15 mmol/L, especially if seizure recurrence is likely in the next few weeks (e.g., more than 1 seizure/1-2 weeks before treatment onset), give another oral mini-loading dose of 250 mg/kg for each desired 5 mmol/L increment of the [Br]s.
         c. Measure $[Br]_S$ again 3 weeks later. If it is lower than on day 3 or if it is suboptimal (<15-20 mmol/L), increase the maintenance dosage accordingly. A mini-loading dose may also be given if more than 1 seizure has occurred since the treatment onset.
         d. Measure $[Br]_S$ 3 months after treatment initiation or modification and adjust the dosage accordingly (see Box 48-2).
      2. *Cats*: Phenobarbital (PB) 15-20 mg/kg slow IV. This should immediately provide a therapeutic serum PB concentration ($[PB]_S$) of 80-110 µmol/L.
         a. Continue with a maintenance dosage (2.0-2.5 mg/kg q12h) 12 or 24 hours later, depending on the degree of sedation.
         b. [PB]s may be measured just before administration of the first oral dose. A mini-loading dose of 1 mg/kg IV may be added for each 5 µmol/L to be added to the $[PB]_S$.
         c. Measure $[PB]_S$ 2 weeks later and adjust the dosage if necessary, aiming at an optimal $[PB]_S$ of 100-130 µmol/L.
   D. In patients already treated with AED, measure $[AED]_S$ (this first can be estimated based on the administered dosage). Add a mini-loading dose and increase the maintenance dosage if $[AED]_S$ is suboptimal, or add another AED (initial loading dose) to the treatment regimen if the $[AED]_S$ is optimal (see Boxes 48-2 and 48-3).
   E. If the animal has 2 or more seizures or a prolonged seizure during the 24 hours after its presentation, continue to section II, *A*, below.

II. **The animal is seizing** at the time of presentation (convulsive or nonconvulsive seizures).
   A. Immediately stop the ongoing seizures.
      1. Give a diazepam (DZ) IV bolus of 1.0 mg/kg in dogs and 0.5 mg/kg in cats. If seizure activity does not subside within 1-2 minutes, repeat the DZ bolus (can be repeated 1-2 times without significant risk of cardiorespiratory depression).
      2. Restore and maintain homeostasis.
         a. Maintain patent airway and administer oxygen if necessary.
         b. Maintain body temperature between 38° C and 39.5° C.
         c. Do not give glucose or calcium unless a deficiency is documented by laboratory testing (or is highly suspected and laboratory testing is not readily available).
         d. Continuously monitor vital signs and look for potential complications (e.g., signs of increased intracranial pressure, neurogenic pulmonary edema, cardiac arrhythmias, intravascular disseminated coagulation). Provide intensive supportive care to a markedly sedated or stuporous patient.
      3. Obtain samples for laboratory analysis as soon as possible (see section I, *B*, above).
   B. Prevent seizure recurrence over the following hours.
      1. If a maintenance PB treatment will be started (first-choice AED in cats or add-on drug in dogs), administer an IV loading dose of 15-25 mg/kg in dogs and 15-20 mg/kg in cats (see section I, *C*, step 2, above).
         a. Maximal antiepileptic effect after IV administration of PB is obtained only after 20-30 minutes (slow brain penetration). If ≥ 1 seizure occurs before that time, administer another DZ bolus.
         b. If maintenance PB therapy is not to be initiated or if 1 or more seizure occurs despite the administered IV boluses of DZ and PB, continue to the next step (II, *B*, no. 2).
      2. Administer a continuous IV infusion of DZ at the rate of 0.5-1.0 mg/kg/h in dogs and 0.5 mg/kg/h in cats.
         a. Add the DZ to maintenance fluids in an in-line burette. Avoid using saline in patients treated with KBr (this would rapidly lower $[Br]_S$ and possibly precipitate withdrawal seizures). Prepare only 1-2 hours of solution at a time (DZ is rapidly adsorbed into the administration set plastic and is inactivated by light).
         b. If more than 20 minutes have elapsed since administration of the last DZ bolus, give another one at the beginning of the infusion to rapidly return to a therapeutic serum benzodiazepine concentration ($[BZ]_S$) that will be maintained by the infusion afterward.
         c. If no other seizures occur within the first 4-6 hours of the infusion onset, progressively decrease the infusion concentration by 25%-steps every 4-6 hours. If 2 or more seizures occur at any time during the infusion, continue to section II, *C*, below.

Continued

Box • 48-1

Emergency Treatment of Cluster Seizures and Status Epilepticus in Dogs and Cats—Cont'd

3. If it is absolutely impossible to administer an IV infusion (e.g., prohibitive cost for the owners, unavailable continuous in-hospital monitoring, no possibility for referral), administer repeated IV boluses as a "salvage procedure."
   a. After an initial bolus (1 mg/kg in dogs and 0.5 mg/kg in cats), give other boluses of 0.5 mg/kg q20min for a total of 4-5 boluses, even if no other seizures have yet occurred. A therapeutic $[BZ]_S$ should be maintained for several hours.
   b. Marked sedation should subside within a few hours.
4. Oral maintenance AED therapy should be initiated (loading dose protocol), or continued but improved to provide adequate long-term antiepileptic protection.
   a. In patients that cannot swallow safely due to marked sedation, administer the AED scheduled doses parenterally (PB and DZ by the IM route and KBr per rectum).

C. Control refractory seizures.
1. If ≥2 seizures occur during the DZ infusion, administer another DZ bolus and increase the infusion rate (up to 1.5 mg/kg/h in dogs and 1.0 mg/kg/h in cats) for 6-8 hours before attempting to progressively decrease it.
   a. In patients naive to PB, an IV loading dose may also be given (give only 15 mg/kg to avoid the risk of cardiorespiratory depression with combined IV administration of DZ and PB).
   b. If ≥2 seizures recur, discontinue the DZ infusion and administer a propofol infusion (see next step [II, C, no. 2], below).
2. Propofol
   a. Give an initial bolus of 1.0-3.5 mg/kg or more, to effect.
   b. Initiate a constant-rate infusion of 0.01-0.25 mg/kg/min (use an automated syringe) and administer for at least 6-12 hours before progressively decreasing the infusion rate. If seizures recur when the infusion rate is decreased, increase the rate. Up to 24-48 hours of treatment may be necessary to control very severe CS and SE. In cats, proceed to frequent evaluation of the hematocrit and red blood cell morphology to detect Heinz body formation and possible hemolytic anemia.
   c. If frequent seizures persist, proceed to general anesthesia.
3. General anesthesia
   a. Propofol (dogs only): IV bolus of 4-6 mg/kg followed by an infusion of 0.1-0.3 mg/kg/min, to effect.
   b. Isoflurane
   c. Pentobarbital: IV bolus of 2-5 mg/kg, to effect, followed by an infusion of 5 mg/kg/h for several hours. Do not confuse dysphoric anesthetic recovery (e.g., paddling, stiffness) with seizure recurrence.
   d. Always provide optimal anesthetic monitoring and supportive care (e.g., intubate, ventilate, prevent or correct hypothermia and hypotension).

III. Treatment of cluster seizures at home.
A. For dogs known to have CS, provide injectable DZ (in its original vials, not in a plastic syringe) to be administered per rectum at home: 1 mg/kg after the second or third seizure has occurred within 12 to 24 hours. This should be repeated 3-4 times at 20-minute intervals to obtain and maintain therapeutic $[BZ]_S$ for several hours. If ≥2 seizures recur despite this treatment, emergency in-hospital IV administration of AED is necessary.

Box • 48-2

Guidelines for Maintenance Oral Antiepileptic Drug Therapy in Dogs

I. Perform a complete blood count (CBC), serum biochemistry profile, and urology to establish pretreatment values.
II. First-choice antiepileptic drug (AED): Potassium bromide (KBr).
A. Initial dosage: 40-50 mg/kg q24h
B. Contraindication: Renal insufficiency
C. Follow-up
1. Measure $[Br]_S$ 3 weeks after initiation of therapy (50% of steady state is reached at that time) and adjust dosage accordingly, aiming at an optimal $[Br]_S$ of 20-25 mmol/L (2.0-2.5 mg/mL) at steady state (practically reached 3 months after treatment initiation or modification).
2. Measure $[Br]_S$ again at steady state and adjust the dosage using the following formula:

$$\text{Optimal daily dose} = \frac{\text{Desired } [Br]_S}{\text{Actual } [Br]_S} \times \text{Actual daily dose}$$

$[Br]_S$ may be increased up to 25-30 mmol/L as long as this does not cause excessive side effects while significantly improving the seizure control.

Continued

Box • 48-2

Guidelines for Maintenance Oral Antiepileptic Drug Therapy in Dogs—Cont'd

3. Monitor $[Br]_S$ and renal function at least once a year in young adults and every 6 months in older dogs.
4. As soon as adequate seizure control (less than 1 seizure/6-8 weeks) is not obtained or is no longer maintained despite $[Br]_S$ of 20-25 mmol/L, add a second AED (phenobarbital) to the treatment regimen. Continue KBr and maintain the $[Br]_S$ in the optimal range.

D. Other considerations
1. Initiate KBr therapy with an oral loading dose (450-600 mg/kg) if the interval is <3-4 weeks between successive seizures, including recent cluster seizures (CS) or status epilepticus (SE) (see Box 48-1 for treatment protocol).
2. Ensure a stable dietary chloride intake (brand and amount of food and treats) to avoid $[Br]_S$ fluctuations (renal elimination of bromide is directly proportional to the chloride intake). Seizure breakthrough may occur if $[Br]_S$ decreases, or excessive side effects may develop if $[Br]_S$ increases. If a dietary change must be made, monitor $[Br]_S$ 6 weeks and then 12 weeks later and adjust the dosage if necessary.

III. Second-choice antiepileptic drug: Phenobarbital (PB).
A. Initial dosage: 2.5-4 mg/kg q12h. Increase the dosage by about 50% in puppies (possibly in kittens also) because of their higher metabolic rate.
B. Contraindication: Liver disease
C. Follow-up
1. Always measure PB serum concentration ($[PB]_S$) 2 weeks (1 week in immature animals) after treatment onset and dosage modification. Adjust the dosage to reach an optimal $[PB]_S$ of 100-130 µmol/L (23-30 µg/mL). Use the following formula:

$$\text{Optimal daily dose} = \frac{\text{Optimal } [PB]_S}{\text{Actual } [PB]_S} \times \text{Actual daily dose}$$

Also perform a CBC to detect rare but possible PB-induced blood dyscrasias (e.g., neutropenia, thrombocytopenia).
2. As soon as adequate seizure control (less than 1 seizure/6-8 weeks) is not obtained or is no longer maintained despite an optimal $[PB]_S$ and $[Br]_S$, add a third AED to the treatment regimen. Continue PB and KBr and maintain their serum concentrations within the optimal ranges.

D. Other considerations
1. Initiate PB therapy with an IV loading dose of 15-25 mg/kg if seizures are occurring at intervals of less than 7 days, including recent CS or SE (see Box 48-1 for treatment protocol).
2. PB often causes a progressive and marked liver enzyme induction that stabilizes after the first 4-6 months of treatment in dogs. This increases the metabolism of PB to the point that $[PB]_S$ may significantly decrease and may not even increase after dosage increment during the first months of treatment. Ideally, $[PB]_S$ should be monitored, and the dosage increased if necessary, at 2 and 6 weeks, then at 3 and 6 months after treatment initiation. Liver enzyme induction also leads to a mild increase of the serum alanine aminotransferase (ALT) (4-5 times the upper reference limit) and a marked elevation of ALP (sometimes >1000 U/L). This should not be interpreted as liver toxicity unless there are other laboratory abnormalities (e.g., hypoalbuminemia, elevated preprandial and postprandial bile acids), accompanied or not by clinical signs suggestive of liver failure.

IV. Third-choice antiepileptic drugs: Several human AEDs may be tried. Consult a veterinary neurologist for the most suitable AED, its recommended dosage, follow-up schedule, and so on.

V. Client communication (verbal and written)
A. Define the treatment goals and side effects/toxicity.
B. Emphasize the importance of complying with drug administration regimens, of keeping a seizure calendar (dates, duration, and intensity), and of consulting as soon as adequate seizure control has not been obtained within the expected time or is no longer achieved, as well as for any treatment modification.
C. Insist on the importance of initial determinations of $[AED]_S$ and periodic blood analysis (CBC, biochemistry and $[AED]_S$) every 6-12 months.
D. Define emergency situations and establish a precise emergency plan.
E. Recommend that intact females be spayed as soon as a diagnosis of epilepsy is made.

VI. Drug interactions and contraindications
A. Do not administer drugs that may lower the seizure threshold: acepromazine, xylazine, ketamine, estrogens, tricyclic antidepressants (e.g., amitriptyline), and bronchodilators (e.g., aminophylline, terbutaline, theophylline).
B. Do not administer drugs that interfere with the metabolism of PB (may result in rapid accumulation of a toxic $[PB]_S$): chloramphenicol, cimetidine, ranitidine, and tetracyclines.

VII. Only if no seizures have occurred for 6-12 months, consider slow weaning of AED over a period of a few months. If more than 1 seizure/6-8 weeks recurs during or after weaning, resume therapy, probably for life.

Box • 48-3

Guidelines for Maintenance Oral Antiepileptic Drug Therapy in Cats

Recommendations are the same as for dogs (see Box 48-2) with the following differences:

I. First-choice antiepileptic drug: Phenobarbital (PB).
   A. Initial dosage: 2.0-2.5 mg/kg q12h.
   B. Hepatic toxicity and enzymatic induction has not been documented in cats; significant elevation of liver enzymes should be investigated.

II. Second-choice antiepileptic drug: Diazepam (DZ).
   A. Initial dosage: 0.5-1.0 mg/kg q12h.
   B Measure serum total benzodiazepine concentration ($[BZ]_S$) 5 days after onset of therapy and adjust the dosage (use the same formula as for PB), to reach a therapeutic range of 500-800 nmol/L (500-800 ng/mL). Evaluate liver enzymes at the same time to detect rare but possible idiosyncratic acute hepatic necrosis; if elevated, discontinue DZ and add potassium bromide.

III. Third-choice antiepileptic drug: Potassium bromide (KBr).
   A. Initial dosage: 30-40 mg/kg q24h.
   B. Because the half-life of KBr is shorter in cats (slightly less than 2 weeks), first monitor the $[Br]_S$ at 2 weeks (50% of steady state reached) and then at steady state (2 months).
   C. Bromide has been reported to induce bronchial asthma in up to one third of treated cats. The onset is often acute, 2 weeks to 2 years after treatment initiation, and sometimes is life-threatening. KBr is therefore contraindicated in cats with past or actual asthmatic problems. Although glucocorticoids may alleviate clinical signs in some cats, it is preferable to discontinue treatment to avoid possible life-threatening deterioration.

with serum concentrations above 15 mmol/L (1.5 mg/mL), although many dogs tolerate well levels up to 25 to 35 mmol/L, which may provide additional antiepileptic protection in some cases. Rare idiosyncratic reactions to bromide include pruritic dermatitis, paradoxical hyperactivity, and pancreatitis. The point is unclear, but some speculate that the pancreatitis may be due to marked polyphagia and dietary indiscretion, mainly when bromide is used in combination with phenobarbital.

Phenobarbital is the first-choice antiepileptic drug for cats. In dogs it is the drug of second choice, to be added to the treatment regimen when adequate seizure control cannot be obtained despite achievement of an optimal or supraoptimal serum bromide concentration. Phenobarbital is effective; safe when adequate follow-up is assured; and inexpensive. Although the therapeutic range is reported to be 65 to 175 µmol/L (15 to 40 µg/mL), levels below 100 µmol/L (23 µg/L) are often insufficient to obtain and maintain adequate seizure control, and levels higher than 140 µmol/L (32 µg/mL) are more likely change in behavior, to cause excessive side effects and hepatic toxicity on a long-term basis. Rare hypersensitivity reactions attributed to phenobarbital include hyperactivity in dogs and pruritic dermatitis, neutropenia, and thrombocytopenia in both species.

OUTCOME

The prognosis of seizure disorders depends mainly on the nature of the underlying cause and on the response to therapy. Idiopathic epilepsy often progresses to refractoriness despite adequate treatment in some large breed dogs; this is less common in small breeds. Although seizure disorders of cats are almost always the result of structural brain lesions, these are most often inactive or self-limiting. Even if cats have severe seizures at some point during the course of the disease, the seizures can most often be well controlled or even completely stopped with adequate therapy. Refractoriness to antiepileptic drug therapy appears to be less common in cats.

CHAPTER 49

Deficits of Function Due to Peripheral Cranial Neuropathies

Vince Pedroia

Signs of the most common peripheral cranial neuropathies in animals are acute blindness, Horner's syndrome, jaw drop, unilateral facial paralysis, loss of balance, dysphagia and regurgitation, and stridor (Figure 49-1 to 49-6). The same clinical scenario may introduce either a benign, self-limiting condition or a relentless, hopeless disease. Therefore it is crucial to evaluate these dogs and cats appropriately so that hasty decisions regarding euthanasia are not made, nor are useless pursuits undertaken. Furthermore, the dysfunction in question may be due to neuropathy, but the same dysfunction may be due to abnormality of the effector organ, such as the eye, vestibule, neuromuscular junctions, or muscles. In general, dogs and cats presenting with these disorders can be managed along the guidelines below. Otherwise, referral for evaluation would be recommended.

DISCOVERY AND THE NEUROLOGIC EXAMINATION

Clinical scenarios involving peripheral cranial neuropathies can be dramatic and disturbing to dog or cat guardians. These problems have a tendency to be noticed suddenly. However, they also can be incidental discoveries made during the physical examination. As always, it is important that clinicians remain attentive during the physical examination so that incidental neurologic deficits are not missed. Any of these presentations would be reason for a neurologic examination. The expression "complete neurologic examination" is often heard; this is redundant. The presence of any of these conditions would dictate that the entire nervous system be surveyed, because some signs may be very difficult to detect. For example, a patient with a balance disorder may have conscious proprioceptive deficits that may be subtle or difficult to detect, depending on the severity of the disturbance. Also, some disorders may be multifocal, and that discovery would be crucial to the differential diagnosis. Because some nerves, such as the trigeminal nerve, serve multiple functions and multiple areas, it is important to survey all its realms. In this example, there may be deficits of one sensory area but not another. It is important to tax the nervous system to reveal some signs. For example, the animal should be inverted to evoke and detect positional nystagmus.

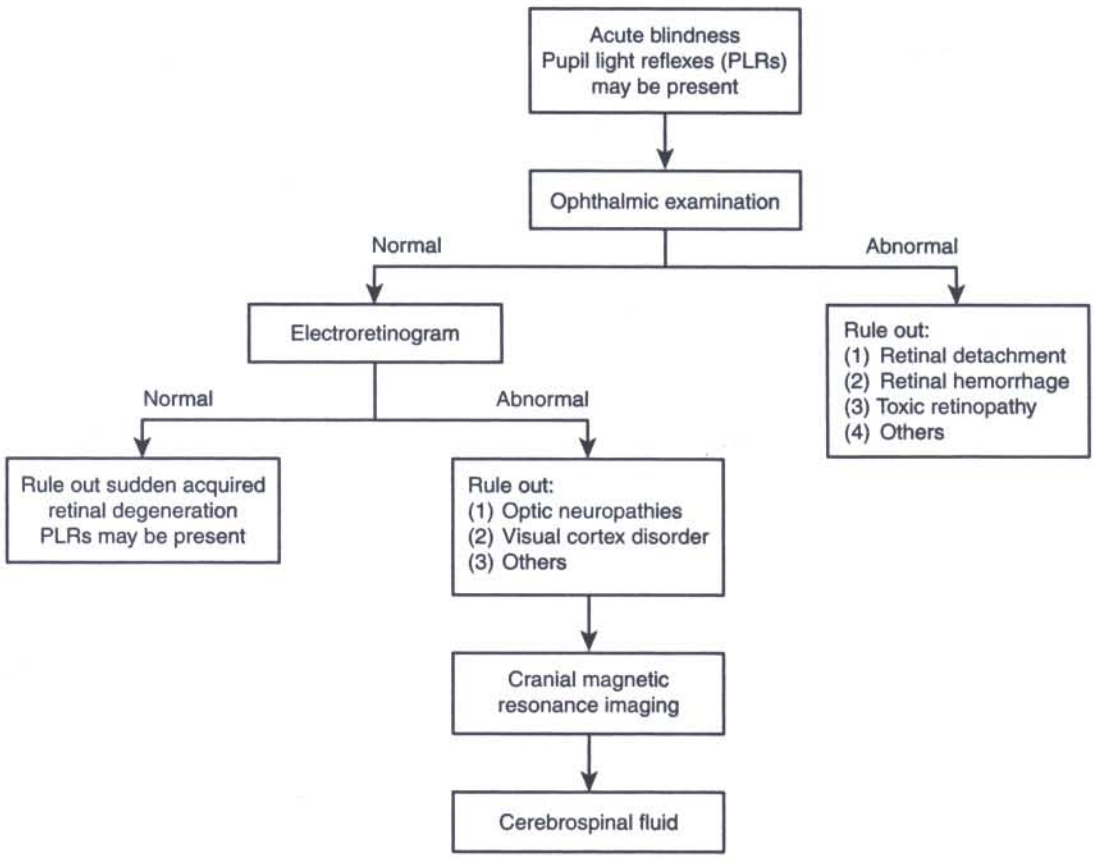


Figure 49-1 Acute blindness with pupil light reflexes.

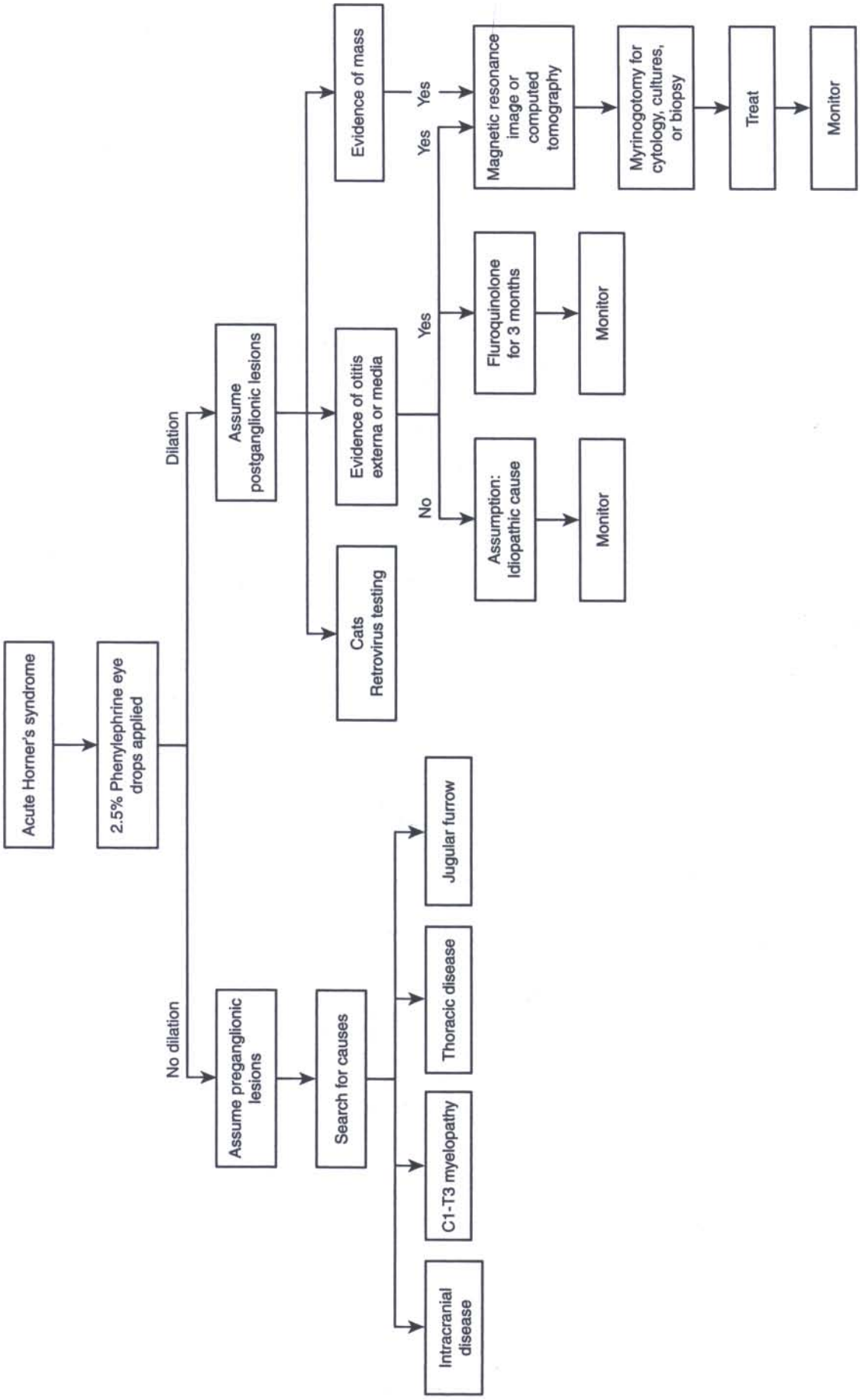


Figure 49-2 Acute Horner's Syndrome.

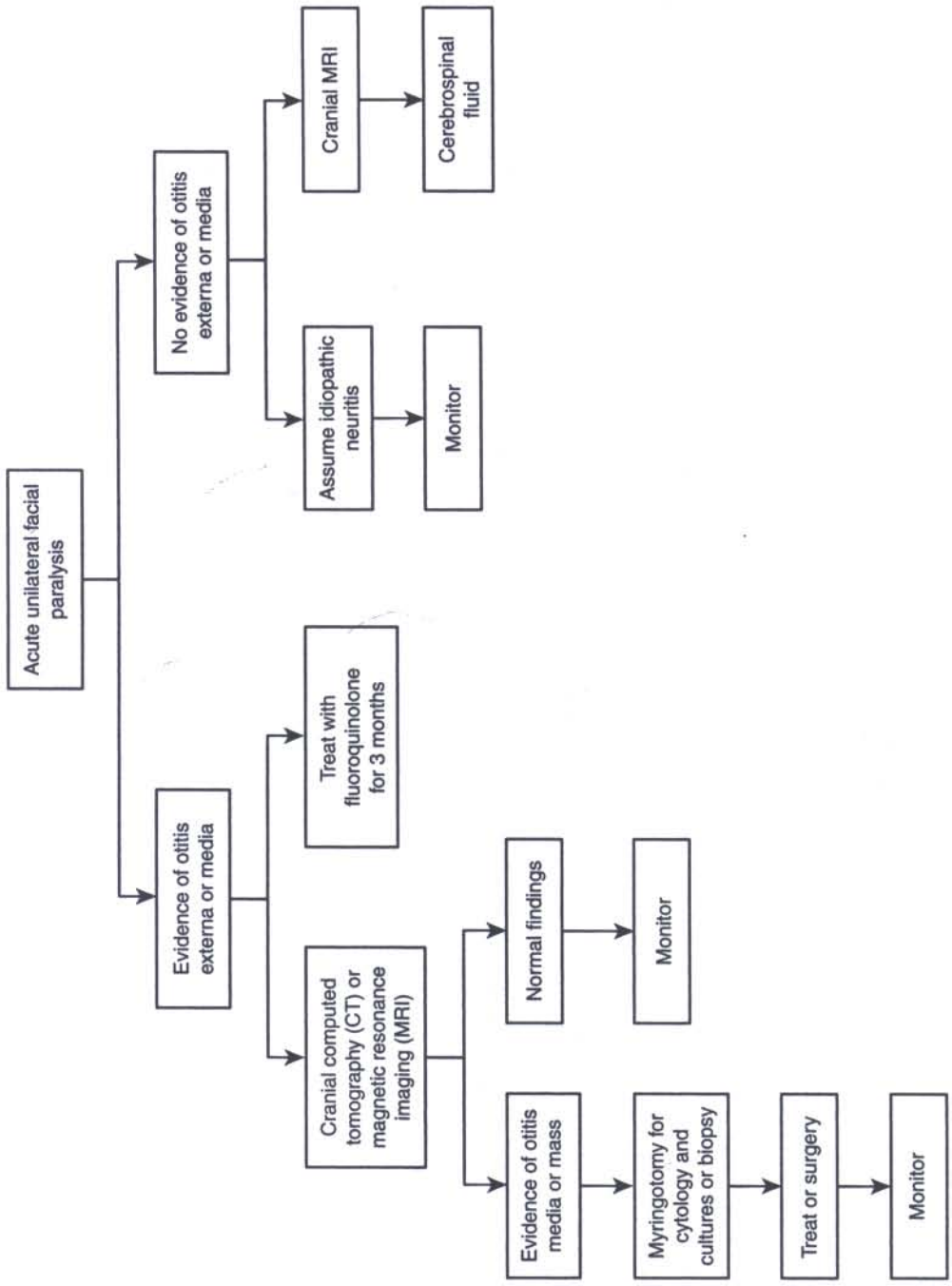


Figure 49-3 Acute urilateral facial paralysis.

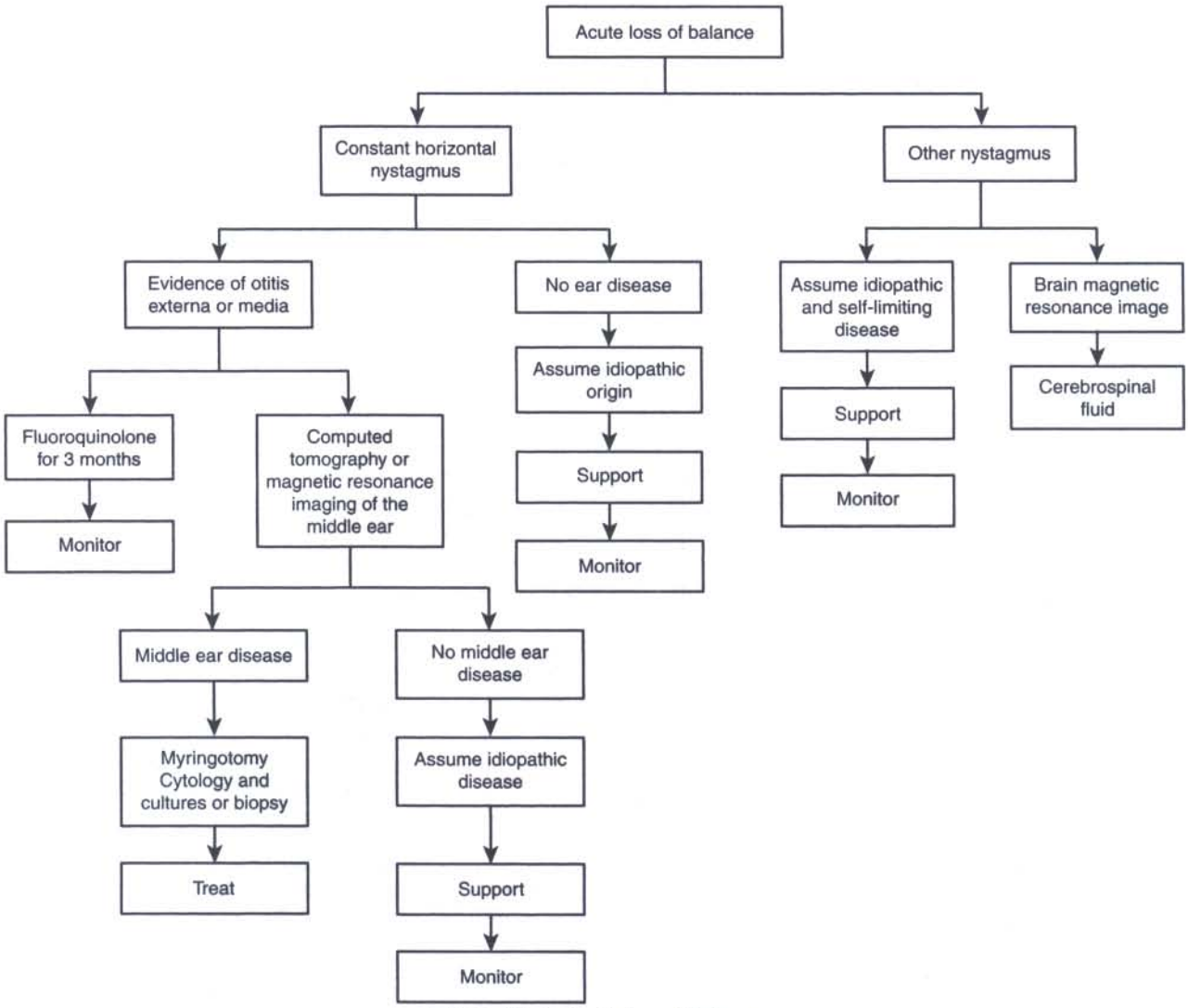


Figure 49-4 Acute loss of balance.

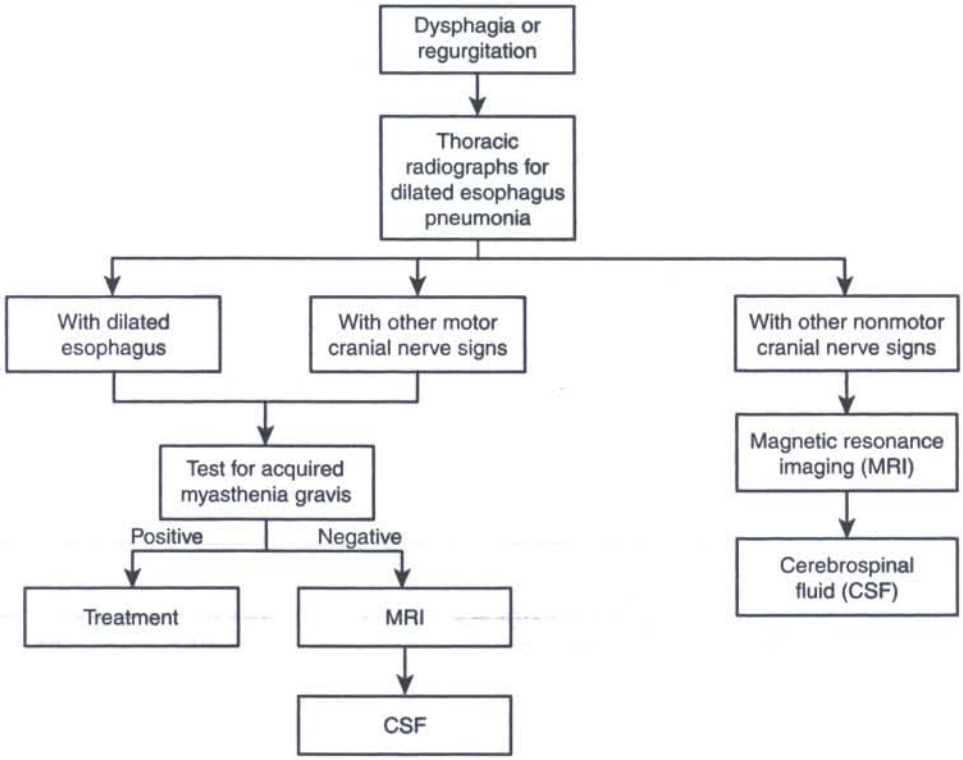


Figure 49-5 Dysphagia or regurgitation.

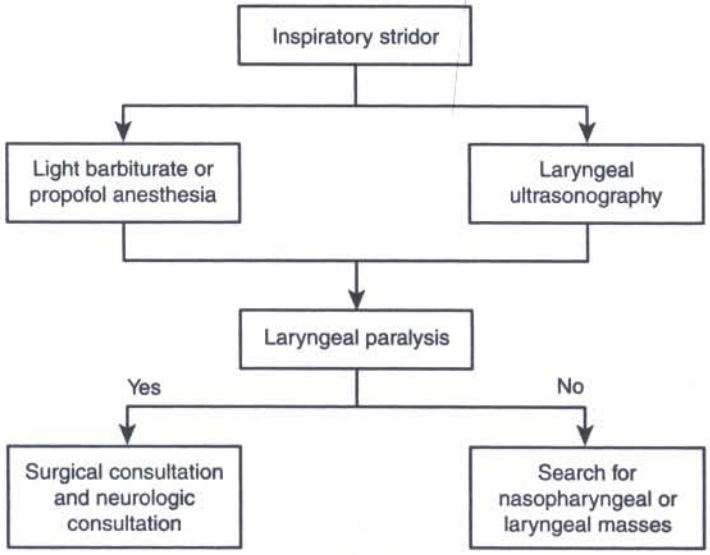


Figure 49-6 Algorithm for inspiratory stridor.

LOCALIZATION AND CLASSIFICATION

First, no neurologic discussion is complete, or worthy of notice, without a repetition of the rule that localization is foremost. Differential diagnosis, hence prognostication, cannot ensue without localization. Because cranial nerves have their origins in the brain, because they may serve afferent, efferent, or both afferent and efferent functions, and because they may also serve autonomic functions, the basic neuroanatomy must be remembered or reviewed. For example, if the palpebral reflex is absent, it must be remembered that the deficit may be on the trigeminal afferent side of the reflex arc (rather than the facial efferent side or the brain stem), where this reflex is integrated. In general, a catalog of deficits is created as the first step in the assessment process. Some constellations of signs have powerful localizing value. For example, any combination of Horner's syndrome, facial palsy, and peripheral vestibular disorder suggests a lesion in the middle ear region.

Second, the problem should be defined from the history as chronic, acute, progressive, static, or improved.

Finally, a unifying statement about the problem is made, such as "an acute left facial paralysis and left peripheral vestibular syndrome." This leads to a differential diagnosis. For example, using the condition described, the differential diagnosis list would include all causes of simultaneous otitis media and interna, neoplasms of the petrous region, and idiopathic cranial neuritides.

DIFFERENTIAL DIAGNOSIS

Several generalities can serve as useful guidelines:

- The causes of peripheral cranial neuropathies usually fall into three pathologic categories: idiopathic inflammation, infectious inflammation, and neoplasia.
- Afferent or autonomic abnormalities exclude myasthenia gravis and other skeletal myopathies. Facial paralysis, for example, is a common feature of acquired myasthenia gravis. However, if Horner's syndrome or vestibular signs are present, myasthenia gravis would be eliminated from the differential list.
- Deficits of facial sensation exclude a diagnosis of masticatory myopathies.
- Most of the common peripheral cranial neuropathies are idiopathic and self-limiting. Included in this list are Horner's syndrome, facial paralysis, acute jaw drop, and acute peripheral vestibular syndromes. The neuropathies leading to laryngeal paralysis, pharyngeal paralysis, and megaesophagus are likely also self-limiting, but the consequences are more severe than for the other conditions.
- Some cranial neuropathies can originate peripheral to the brain but within the cranial vault (e.g., in the cavernous sinus syndrome), usually as a result of tumors.
- Trauma is rarely a cause of cranial neuropathy in dogs and cats, except for facial nerve injury associated with surgery of the ear and Horner's syndrome as part of the brachial plexus avulsion syndrome.
- Hypothyroidism has not been proven to have a role in these conditions.

Acute Blindness

In general, it is important to know that most acute disturbances of vision without ophthalmoscopic abnormalities represent sudden acquired retinal degeneration. Pupillary responses may not be definitively abnormal. An electroretinogram is the test of choice. If visible fundoscopic abnormalities are present, alternative differential diagnoses must be entertained. Optic neuritis is the second most likely differential diagnosis.

Horner's Syndrome

Horner's syndrome can be preganglionic or postganglionic, and the differentiation can be made with topical application of 2.5% phenylephrine; this will cause a denervated iris to dilate, confirming a postganglionic localization. A few days must elapse before denervation sensitivity develops. Without other neurologic signs or physical findings, most postganglionic lesions are idiopathic and benign. Establishing the presence of preganglionic Horner's syndrome may be more problematic because the lesions may be in areas where occult disease may difficult to confirm.

Acute Jaw Drop

Trigeminal neuropathies are common, and the condition often diagnosed is the acute jaw drop syndrome. This syndrome is usually idiopathic, presumed to be an acute neuritis, but it can be caused by infections (e.g., *Neospora caninum*) and by

lymphoma. Unilateral trigeminal neuropathy may manifest as sensory impairment and, eventually, atrophy, but bilateral involvement is required to produce masticatory dysfunction. It is reasonable to assume a diagnosis of acute, self-limiting, presumed immune-mediated trigeminal neuritis in acute jaw drop if the signs are limited to trigeminal dysfunction. Whether corticosteroids benefit these animals has not been proven. Typically, the animals can eat and drink, with assistance, until recovery ensues in a few weeks.

Acute Unilateral Facial Paralysis

Facial neuropathy is probably the most common cranial neuropathy. Most cases are idiopathic, and deficits are limited to the muscles of facial expression. The onset, or at least guardian notice, is usually abrupt. The disorder is presumed to be a peripheral neuritis. Central causes are implied by the presence of other deficits, such as a central vestibular syndrome or deficits of ipsilateral limb function. Facial muscle paralysis can be due to acquired myasthenia gravis, which should always be included in the differential diagnosis. Suspects should be tested for serum antiacetylcholine receptor antibodies. Other peripheral causes include disorders of the middle ear and the petrous temporal region, including otitis media and neoplasms.

Animals with facial paralysis and any evidence or history of ear disease should undergo diagnostic imaging. Bullae radiographs can be useful, but either computed tomography (CT) or magnetic resonance imaging (MRI) is an ideal means of imaging the middle ear. If any evidence of middle ear disease is found, sampling from within the bullae is indicated. Careful cleaning of the outer ear, followed by myringotomy, should be performed. Cytology and cultures also should be performed. Ideally, all dogs and cats with facial paralysis that do not have evidence of middle ear disease should have a cranial MRI that explores both the peripheral and central realms. If a diagnosis of idiopathic facial paralysis is made, there is no proof of benefit from corticosteroids. Keratitis sicca due to poor production of tears is not usually a problem, but dryness due to exposure may be, and treatment or monitoring should be recommended.

Acute Loss of Balance

Unilateral hearing loss can be difficult to detect, but loss of function of the vestibular component of the vestibulocochlear nerve produces a dramatic set of signs. In general, it is not possible to distinguish clinically between a lesion in the nerve and one in the sensory organ, whether auditory or vestibular. However, the neurologic ground rule that differentiates peripheral from central vestibular syndromes is reliable: Peripheral syndromes produce a constant horizontal or rotary nystagmus, and central syndromes cause all the others. Most acute vestibular disorders are idiopathic, presumably an acute neuritis or vestibulitis, and these are self-limiting. An idiopathic disorder is distinguished from a relentless disorder by the presence of other historical, physical, or neurologic evidence that suggests the latter. A dog or cat with an acute peripheral vestibular disorder should be managed in the same fashion as for facial palsy if evidence of any ear disease is present. As with facial paralysis, all pets with a vestibular syndrome ideally should have a cranial MRI. However, because signs often abate rapidly, resolution in a short time may be used as proof that a relentless disorder is not present. If a diagnosis of idiopathic vestibular syndrome is adopted, there is no proof of benefit from corticosteroids.

Dysphagia and Regurgitation

Dysphagia may be due to disturbances of the glossopharyngeal and vagus nerves, but specific pathologic disorders have not been well defined. Acquired myasthenia gravis should be included in the differential diagnosis, and testing should ensue. These patients should have thoracic radiographs to detect esophageal dilatation and aspiration pneumonia. Except for acquired myasthenia gravis, these patients represent a mysterious group and often have a poor prognosis.

Stridor

Inspiratory stridor can be caused by various conditions, such as neoplasia or polyps of the larynx, but most cases are due to laryngeal paralysis, presumed to be the result of neuropathy of the vagus nerve or recurrent branches. The cause can be confirmed using light anesthesia achieved with a short-acting barbiturate or propofol; failure of arytenoid abduction confirms the diagnosis. These cases are treated surgically. Although solitary laryngeal paralysis has not been a feature of acquired myasthenia gravis, that diagnosis should be given consideration.

CHAPTER • 50

Sleep Disorders

Joan C. Hendricks

Sleep-associated problems in cats and dogs are uncommon owner complaints. Owners and clinicians cannot easily assess subjective disorders of sleep such as pathologic hypersomnolence and insomnia. Slight-to-moderate disruption of daily behavior patterns that accompany many changes in sleep do not substantially alter an animal's ability to function as a pet. The disorders that prompt an owner to bring a pet for veterinary treatment tend to be those that dramatically change the animal's overt behavior, such as sleep-associated epilepsy or narcolepsy with cataplexy. Other disorders, such as sleep apnea or cardiac arrhythmias, can be triggered by sleep and may have profound consequences for an animal despite being overlooked by most owners. It is interesting to realize that relatively minor changes in sleep behavior may herald future manifestations of abnormal central nervous system (CNS) function.

Sleep is a complex physiologic state with two distinct stages in normal mammals. During the first of these, the animal seeks a quiet, secure resting place and takes a characteristic relaxed species-specific posture. A few minutes after closing its eyes and becoming immobile, changes in CNS activity occur in the electroencephalogram (EEG): the cerebral activity alters from the rapid, desynchronized neural firing patterns of waking to synchronous discharges that produce high-voltage, slow (approximately 5 to 12 per second) wave activity. The pulse and respiratory rates slow, blood pressure decreases, and reflex arcs maintain homeostasis in autonomic systems. After a specific duration of uninterrupted slow-wave sleep (approximately 30 minutes in cats and dogs), behavioral and physiologic signs of a second stage appear. The observer notes a further relaxation of muscle tone, as a powerful postsynaptic inhibitory influence descends from the pontine brain stem along a ventral reticulospinal tract to the spinal motor neurons to produce postural muscle atonia. Several seconds to minutes after this atonia begins, volleys of distal small muscle twitching occur, producing rapid movements of the eyes, facial muscles, paws, and tail. Irregular respiration, heart rate, and blood pressure surges accompany these phasic bursts of small muscle movements. These small movements are the external manifestation of a highly activated brain: the flaccid musculature and lack of responsiveness belie a high rate of neural discharge throughout virtually all areas of the brain. During this second phase, most commonly known as rapid-eye movement (REM) sleep, the autonomic systems are driven by cerebral and brain stem influences during the bursts of twitching activity, which override reflex control. REM lasts as long as 10 to 15 minutes in normal cats and dogs. In humans this stage can last 20 to 35 minutes and represents the sleep period when most dreams occur.

Sleep is thus a complex CNS and somatic syndrome that normally has an orderly progression. The atonia of REM sleep has the important function of preventing overt movements during the sleep period when the cerebrum is highly active.

SLEEP-ASSOCIATED AGGRESSION

An abnormal behavior that seems to occur relatively commonly is sleep-associated aggression. Owners report that a normally calm and friendly or attacks suddenly if disturbed while sleeping. Although owners may perceive this behavior as unpredictable and unprovoked, these attacks seem to be expressions of aggression—both dominance aggression related to the pet's sense of vulnerability upon arousal and territorial aggression related to defense of the resting place. No cases have been reported or documented in the literature in which animals displayed aggressive behavior directed at their owners while still asleep. Unfortunately, because this behavior is typically episodic and occurs in the home environment, it is difficult to observe directly. However, many or most dogs respond to behavioral approaches to treat aggression.

TRUE SLEEP DISORDERS

In general, true sleep disorders can be classified into two categories: (1) those in which the CNS mechanisms of sleep are normal (Figure 50-1) but other CNS or physiologic abnormalities are unmasked or triggered by sleep and (2) those in which the CNS mechanisms of sleep itself are abnormal. Knowing the physiology of sleep, augmenting a careful history with observation or (preferably) videotapes of behavior, and taking a rational approach to assessing the signs facilitates the differential diagnosis of these problems.

EXACERBATION OR UNMASKING OF ABNORMALITIES WITH SLEEP

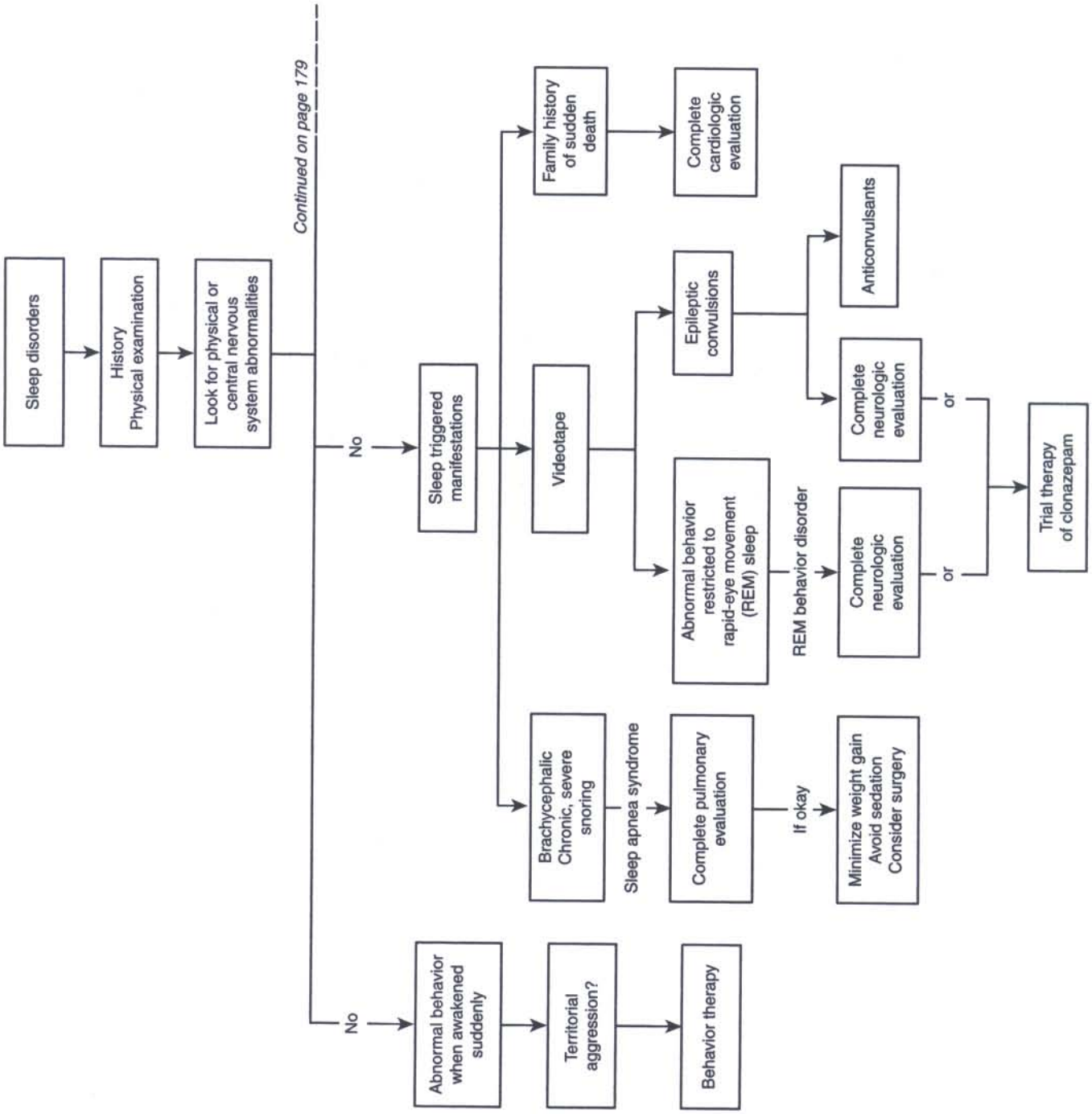
Physiologic Abnormalities

Serious cardiovascular and respiratory disorders associated with sleep have been well documented in the literature and further studied in laboratory colonies of affected animals. Several families of German shepherds with histories of sudden cardiac death in apparently normal pups were identified. These dogs have an inherited predisposition to cardiac arrhythmias that are most common during sleep, especially during the REM stage. Abnormalities during standard clinical cardiac evaluation were relatively subtle, but ventricular tachycardia could be detected if pups were monitored by Holter monitors. Implanted pacemakers appear to have been successful in preventing sudden death in at-risk dogs. The mode of inheritance is complex, apparently either a polygenic or a dominant trait with incomplete penetrance. A colony of these dogs has been established, and studies of the underlying cellular abnormalities are in progress. In addition to the relevance of this basic research, it is significant that several families from widespread geographic regions were found to share a trait that can be transmitted by unaffected carriers. Thus although the syndrome is well described in German shepherds descended from a single common ancestor, the possibility exists that similar abnormalities could occur in other families and in other canine breeds.

Sleep apnea has been described in English bulldogs. Even if they have normal arterial blood gases during waking, virtually all bulldogs exhibit episodes of apnea (pauses in breathing) and hypoxia during sleep, especially in REM sleep. These dogs normally compensate for their narrowed upper airways by augmenting the activity of upper airway dilating muscles during waking and much of non-REM sleep. However, during REM sleep, when muscle activity is reduced by normal atonia and reflexes are intermittently overridden by phasic cerebral influences, intermittent upper airway obstruction occurs. In laboratory studies, these pauses have been documented to occur at rates ranging from six per hour to over 100 per hour. The oxygen saturation can fall as low as 70% but most commonly falls to 85% to 90% from the normal 94% to 95%. As is true for humans with sleep apnea, these dogs are hypersomnolent and exhibit obvious snoring. However, these signs in themselves do not usually present difficulties for owners or pets. Based on other experimental evidence, it is likely that the episodic drops in oxygen saturation lead to hypertension and cardiovascular consequences in both dogs and humans, but the clinical importance of these abnormalities for dogs has not been proved.

Although it is not clear whether sleep apnea alone warrants treatment, surgery is often performed in English bulldogs to relieve waking signs of upper airway obstruction, and this surgery appears to be partially effective in relieving obstructive sleep apnea as well. The usual treatment in humans is to prescribe a face mask to be worn nightly. This constant positive airway pressure mask forces air through the nares to the pharynx to maintain a patent airway; this is obviously not feasible in canine patients. Pharmacotherapy is being investigated, and at present, some approaches that alter serotonin appear to have promise.

As in the case of the sudden cardiac death syndrome of German shepherds, it seems likely that this type of disorder, well described in the laboratory in one breed, may exist in other predisposed animals. Any anatomic narrowing of the upper airway could lead to the same signs. Thus brachycephalic conformation in any cat or dog, or an acquired narrowing caused by tumor or traumatic injury, could predispose to sleep apnea. Owners do not commonly complain of snoring, hypersomnolence, or gasping respiratory patterns in bulldogs; but they often describe these signs in response to direct


Sleep disorders
History
Physical examination
Look for physical or central nervous system abnormalities
Continued on page 179
No
Sleep triggered manifestations
Videotape
Family history of sudden death
Complete cardiologic evaluation
Epileptic convulsions
Anticonvulsants
Abnormal behavior restricted to rapid-eye movement (REM) sleep
REM behavior disorder
Complete neurologic evaluation
Complete neurologic evaluation
or
or
Trial therapy of clonazepam
Brachycephalic Chronic, severe snoring
Sleep apnea syndrome
Complete pulmonary evaluation
If okay
Minimize weight gain
Avoid sedation
Consider surgery
No
Abnormal behavior when awakened suddenly
Territorial aggression?
Behavior therapy

Continued from page 178

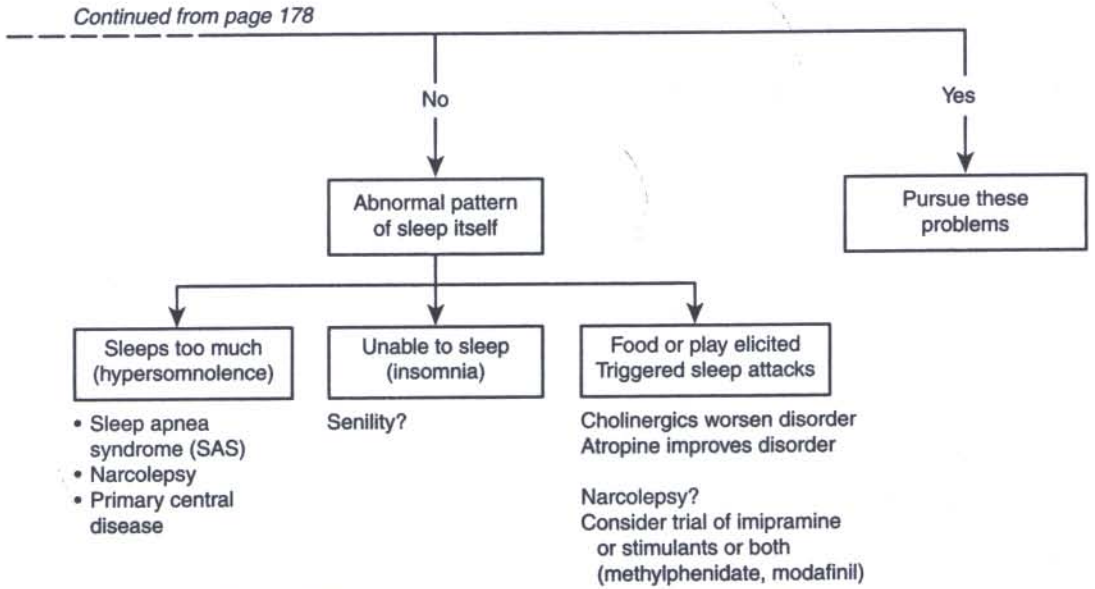


Figure 50-1 Algorithm for clinical evaluation of sleep disorders.

questions. Owners of Shar Peis, pugs, beagles, and an obese, hypothyroid miniature poodle with obvious upper airway narrowing due to fat accumulation have described similar signs. In the latter case, treatment of the hypothyroidism resolved the profound sleepiness and sleep-induced apnea noted by the owners. This anecdotal evidence suggests that sleep apnea exists in several canine breeds. In addition, some owners of brachycephalic cats have described obvious snoring and irregular breathing, but none of these animals has been available for further laboratory assessment.

Diagnosis of sleep apnea requires continuous pulse oximetry and respiratory movement recordings, together with documentation of the sleep stage. This assessment can be noninvasive but is labor-intensive and impractical in a clinical setting. At present, the recommendation to a clinician who sees a pet with signs suggestive of sleep apnea is to treat the animal based largely on its waking signs.

Central Nervous System Abnormalities

Abnormal movements seen during sleep are often evidence of an underlying CNS disorder. The systematic changes in CNS activity that accompany normal sleep can unmask CNS disorders. Epilepsy from any cause, including idiopathic epilepsy, can be triggered by the rhythmic discharges of slow-wave sleep; however, seizures are rarely confined to sleep. Indeed, as part of the diagnostic workup of human epilepsy, the EEG is recorded during slow-wave sleep in an effort to trigger the epileptic charges. During the REM stage, abnormal movements can occur when the inhibitory pathway that normally produces atonia during REM sleep is disrupted. This pathway, which arises in the pons and descends in the spinal cord, can be interrupted by a number of brain stem or spinal cord abnormalities, including traumatic injuries. Interrupting this inhibitory pathway permits the expression of the ongoing cerebral activity. Humans with this disorder (REM behavior disorder [RBD]) report that the observed behaviors represent the motor behavior appropriate to their dream content. Thus a patient may stand up, run, and clutch an invisible object while dreaming of playing football; or a patient may sit up and begin attacking his spouse and later describe that he was defending himself against a dream attacker. Dogs and cats with RBD, which (judging by referrals) appears to be the most common sleep disorder in pets, typically lift their heads and exhibit dramatic but intermittent paddling or locomotor activity during REM sleep. They can easily be aroused from these episodes, which occur during every REM period and can often be recognized by an experienced observer viewing videotapes of the behavior. Although many of these animals are completely normal at all other times, in some cases it is obvious that CNS damage is correlated with the disorder, as in the case of a kitten that suffered a traumatic injury to the cervical spinal cord before the onset of signs. Even individuals that have an unremarkable physical examination may have an underlying CNS disorder. In humans with RBD and no other abnormalities at diagnosis, 38% developed overt Parkinson's disease an average of 3.7 years after the diagnosis of RBD. At the present time, the author has followed two cats with apparent congenital RBD for 10 or more years and observed no progression of signs. One of these cats eventually died and underwent a complete necropsy, and no gross or microscopic CNS abnormalities were identified.

Clonazepam, a benzodiazepine tranquilizer, reduces the level of activity during RBD in the vast majority of humans and was partially effective in the two cats. Routine anticonvulsant agents are not effective because they initially suppress REM sleep, with an eventual rebound of REM and recurrence of the behavior. Even if the disorder is not associated with other evidence of CNS disease, it can be life threatening for cats and dogs because some pets suffer urinary incontinence during the episodes, which is intolerable for some owners. In one cat treated for 10 years with clonazepam, the intensity of the behavior was reduced but not abolished. Withdrawing the clonazepam after the first 6 years resulted in an increase in motor behavior and related urination during REM, which was again partly controlled by reinstituting the treatment. Thus chronic treatment is feasible in pets with this disorder, but no improvement of the underlying abnormality should be expected based on experience to date.

In summary, evidence of abnormal movements during sleep should be assessed in view of the possibility that these movements may reveal otherwise occult CNS disease. However, some individuals (only cats identified to date) appear to have a congenital abnormality of the REM motor inhibitory pathway, perhaps caused by a biochemical change in the neural systems that normally maintain atonia.

DISORDERS OF SLEEP MECHANISMS

Effects of Systemic Disease

Sleep itself is affected by many systemic disorders. Systemic changes in immune function may alter sleep. It is now clear that prostaglandin D and interleukin-1-beta produce the increase in sleep that occurs with many febrile illnesses, accounting for this common symptom. One specific condition that alters sleep in humans is infection with human immunodeficiency virus (HIV), and a recent study documented that cats with feline immunodeficiency virus (FIV) show reduced sleep and disproportionately reduced REM sleep. The only owner complaints the author received regarding reduced sleep, or insomnia, involved elderly dogs who pace throughout the night. These dogs may be like humans with senile dementia, in whom the quantity and pattern of sleep become abnormal in association with increasing dementia. The opposite condition, increased sleep or pathologic hypersomnolence, can occur with sleep apnea and has also been described as an isolated idiopathic abnormality in humans and in one case report of a dog. However, the best-described syndrome in which sleep mechanisms are abnormal is narcolepsy.

Narcolepsy

Narcolepsy is a fascinating but rare disease that is well documented in humans and dogs. It has also been reported in a cat, a bull, and several horses. The abnormality appears to be in the CNS trigger mechanisms of the REM sleep state. The abnormalities that appear are caused by the sudden eruption of components of REM sleep, including unconsciousness, muscle atonia, and dream imagery, into wakefulness. Without the normal temporal insulation of non-REM sleep, such manifestations are disruptive to normal life. In animals, the sudden loss of muscle tone (cataplexy) is almost always the sign noted by owners. However, in one dog, a sleepy appearance led the owners to seek veterinary advice. Although some individual cases of human and canine narcolepsy are caused by organic brain disease, the vast majority has no obvious CNS abnormality. Several subtle changes in CNS pharmacology have been documented in canine narcoleptics. An inherited form of the disease has been best documented in a colony of Doberman pinschers. The gene responsible for inherited narcolepsy in dogs was found to be an abnormality in the receptor for a previously poorly understood neuropeptide named *orexin* or *hypocretin*. The normal function of this neuropeptide is not known, but abnormalities of this system have now been shown to produce narcolepsy in mice, humans, and dogs. This is the first genetic basis of a sleep disorder to be described in any species.

The diagnostic process includes ruling out organic brain disease, and the diagnosis is best made when the behavior can be observed to be triggered by play or by food presentation, as is

typical of canine narcoleptics. Fortunately, the disorder in dogs usually has only a moderate effect on their ability to lead normal lives, and in many cases it may be transient. In a colony of Doberman pinschers, the signs were maximal in pups at 4 to 7 months of age and then waned in severity. One case has been reported, however, in which the food-triggered cataplexy was so severe that complete anorexia resulted in a 20 kg weight loss and long-term treatment was required. The biochemical control of muscle atonia is well characterized, but proven pharmacotherapeutic agents in dogs are limited to imipramine. However, initial reports on treating dogs with orexin, hypocretin, or both suggest that treatments based on this new information hold considerable promise. Arousal-promoting agents can be used to relieve the hypersomnolence if necessary.

CHAPTER 51

Cognitive Dysfunction in Aged Dogs

Elizabeth Head
Gary M. Landsberg

Advanced age in dogs may be associated with behavioral changes including separation anxiety, the onset of new fears and phobias, increasing irritability and aggression, stereotypic disorders, night waking, and house soiling.[1] Some of these behaviors are attributable to existing, possibly age-associated, medical conditions (including other neurologic conditions) and some may be due to primary behavior problems arising from changes in the household. However, once these have been excluded, remaining behavioral signs may be a consequence of pathologic brain aging.

COGNITIVE DYSFUNCTION: CLINICAL SIGNS

Until recently, clinicians had regarded this constellation of behavioral symptoms to indicate senility associated with advanced age. Cognitive dysfunction is not an inevitable consequence of aging in dogs, and striking individual differences are more likely the rule than the exception. Some aged animals show little or mild behavioral decline. However, a subset of aged dogs develops severe cognitive deficits that may disrupt normal function to a level prompting euthanasia. Ruehl and colleagues have identified a more general cognitive dysfunction syndrome (CDS).[2] The clinical signs have been described using a simplified acronym DISHA, which refers to *disorientation, interaction* changes with owners or other pets, *sleep-wake cycle* alterations, *house soiling,* and *activity* changes (which might be increased, stereotypic, or reduced). Additional signs such as increasing agitation and anxiety, altered responsiveness to stimuli (which might be heightened or reduced), altered interest in food (which might be increased or reduced), and decreased ability to perform learned tasks (which might be most obvious in working dogs) may also be seen. The number of dogs affected by CDS has been assessed in a number of survey-based studies. Approximately 48% of pet owners report that their senior dogs (7 years or older) exhibit at least one clinical sign of CDS. However, only 17% of these owners reported these signs to their veterinarian (proprietary market research, 1999; pet owner sample size: 150; data on file, Pfizer Animal Health). In another study, 180 owners of dogs aged 11 to 16 with no identifiable medical problems reported that 28% of the dogs between 11 and 12 years and 68% of the dogs between 15 and 16 years had at least one sign that might be consistent with CDS.[3] Further, CDS may be a progressive disease as aged dogs with impairments in one category were later found to have impairments in 2 or more categories.[4] Thus clinical signs of cognitive dysfunction in senior and geriatric pet dogs occur in a significant number of animals and potentially signals a progressive neurologic disorder.

COGNITIVE DYSFUNCTION: LABORATORY STUDIES

Questionnaire-based tools used in the clinic to identify dogs with CDS provide a measure of global brain dysfunction. However, these behavioral checklists are insensitive to early and subtle changes in learning and memory associated with pathologic aging in dogs. In fact, cognitive dysfunction is generally recognized as a syndrome in dogs 11 years of age and older, and signs may not be apparent until the last 18 to 24 months of a dog's life.[1] At this time no biomarker exists for CDS in aged dogs. An alternative technique to detect cognitive dysfunction in aged dogs involves the use of neuropsychologic tests that provide quantitative measures of cognitive function without reliance on questionnaires.[5] These tests are systematic, standardized, objective and a more sensitive measure of age-related cognitive decline. In fact, they can identify age-related deficits in learning and memory from as early as 7 years of age.[4] Although these tests are too lengthy and complex to be applicable for clinic use, a number of cognitive functions assayed with these laboratory-based tasks are also likely to be contributors to the clinical signs that might be noted by pet owners.

In studies using a battery of reward-motivated neuropsychologic tests, several cognitive domains or functions can be evaluated in aged dogs. These tests involve teaching dogs to use visual information to solve different problems. Simple learning problems include discrimination tasks that involve showing dogs two objects that are different in appearance. Dogs must learn that only one of the two objects covers a food reward. Aged dogs can learn these problems, as can younger dogs. Once dogs have learned this visual discrimination problem, the reward can be switched to the previously incorrect object. This is called *reversal learning* in which dogs must be able to change a previously learned behavior, a type of cognitive ability that depends upon the intact function of the prefrontal cortex. Aged dogs have difficulty learning to switch

to selecting the previously incorrect object, suggesting a lack of ability to modify learned behaviors. These laboratory tests depend on cognitive abilities that would be involved with modifying previously learned behaviors; thus aged dogs may be slower to modify problem behaviors. Other behaviors that are consistent with prefrontal cortex dysfunction include pacing, stereotypic behaviors, and an inability to inhibit behaviors (e.g., house soiling).

The aging process can also significantly affect memory. Spatial memory is defined as the ability of dogs to remember *where* they had last obtained a hidden food reward and is compromised in a subset of aged animals.[6] Functionally this type of memory impairment may be reported in companion animals as disorientation, wandering, and getting lost. Dogs also show age-dependent impairments in their ability to recognize objects seen previously.[7] This type of dysfunction may be reflected in decreased recognition of familiar people or animals.

Age-related differences have also been demonstrated in behavioral reactivity tests. The curiosity test, for example, allows the dogs to examine and play with a variety of toys to assess an animal's reaction to novel objects. In this brief 10-minute test, young dogs show significantly more exploration and contact with novel objects than old dogs, with cognitively impaired aged dogs showing the least object contact. Further, cognitively impaired aged dogs show higher levels of locomotion during a curiosity test than their age-matched unimpaired peers. The curiosity test measures exploratory behavior and is more amenable to clinical use because it requires brief 10-minute testing sessions and a small test area, suggesting that it may be a useful clinical screen for aged animals with cognitive dysfunction.[8]

COGNITIVE DYSFUNCTION: NEUROBIOLOGIC BASIS

Cognitive dysfunction that is not attributable to other systemic or central disease may reflect underlying age-associated neuropathology. A number of morphologic features of aging are found in the canine brain.[9] For example, cortical atrophy and ventricular widening occur with age in dogs.[10] The abnormal accumulation of proteins within and around neurons with age may be toxic to the brain. One form of pathology, the accumulation of diffuse plaques, contains a number of proteins, of which the primary constituent is the β-amyloid peptide (Aβ). The extent and location of Aβ deposition in the aged dog brain is linked to the severity of cognitive deficits.[11,12] For example, aged dogs that are severely impaired on a reversal learning task have the most extensive prefrontal cortex Aβ pathology.[13] Another key feature of the aged canine brain is the progressive accumulation of oxidative damage to proteins and lipids[14] and a reduction in endogenous antioxidant activity. Damaged proteins and lipids can lead to neuronal dysfunction, which may subsequently compromise cognitive function. In support of this hypothesis, a diet rich in antioxidants and mitochondrial cofactors can significantly improve cognitive function in aged but not young dogs.[15]

TREATMENT OPTIONS

Age-dependent cognitive impairments in companion animals, as mentioned previously, may reflect systemic or a CNS disease. Once other contributing factors are eliminated, the appropriate treatment can be implemented. Currently, one pharmaceutical is approved for the treatment of cognitive dysfunction in aged dogs in North America. Anipryl© is a monoamine oxidase B inhibitor that can improve cognitive signs in aged dogs.[16] Its mode of action appears to be to enhance catecholamine transmission, as well as decrease the production and increase the clearance of toxic free radicals. In Europe, two drugs are presently licensed for the treatment of cognitive decline in senior dogs that are purported to enhance cerebral vascular blood flow. Nicergoline is an alpha 1 and alpha 2 adrenergic antagonist, whereas propentofylline may improve blood flow by inhibiting platelet aggregation and thrombus formation. Alternatively, a specially formulated senior canine food is also available (Prescription Diet® Canine b/d™) that contains antioxidants and mitochondrial cofactors that significantly improve cognition in both laboratory and clinical studies.[15]

SUMMARY

Aged dogs, like aged humans, are vulnerable to the development of progressive brain pathology that is associated with clinical signs of cognitive dysfunction. However, it is important to rule out other contributing systemic diseases or other central nervous system (CNS) disorders that can also cause cognitive impairments. Along with behavioral therapy, a variety of medical and dietary treatment options have been licensed; however, availability varies among countries.

CHAPTER 52

Behavioral Disorders

Andrew Luescher

Behavior problems of pets are extremely common. According to a variety of studies the prevalence of behavior problems in dogs and cats lies between 40% and 80%. In an epidemiologic study, approximately 40% of dogs had growled at their owners, and 15% had bitten their owners. Around one third of cats appear to have at least an occasional problem with inappropriate elimination. Behavior problems jeopardize the human-animal bond and are a main cause of relinquishment and euthanasia of healthy dogs and cats. Therefore pet owners, pets, and the veterinary profession benefit from the prevention and treatment of behavior problems in patients.

Behavior services in a small animal practice may include prepurchase counseling, counseling of new pet owners, puppy classes, behavioral intervention, and clinical behavior service. Counseling of new pet owners for problem prevention is a service that is performed routinely, but not always effectively or appropriately, at the first puppy or kitten visit. These first visits set the stage for all future doctor-patient and doctor-client relationships. If handled effectively, they can bond a client and patient to the clinic. Inappropriate actions such as rough handling or frightening ("dominating") the young pet can cause continuous problems with fear or aggression at future visits. Client counseling is best performed with use of a check sheet inserted into the pet's file. Problem prevention includes socialization and exposure to varied environments, house training or litter-box training, consistent interaction and training, encouraging appropriate play, teaching a bite and claw inhibition, and teaching the "leave-it" and "drop-it" commands. To prevent food guarding in puppies, treats should be added to the food while the puppy eats. Puppy and (where available) kitten classes should be recommended. It is advantageous to offer these at the clinic.

Behavioral intervention refers to recognition of a behavior problem that underlies a medical problem. In cases of wounds inflicted by another dog, for example, the aggression between the dogs should be addressed. In cases of self-inflicted wounds, information that relates to possible separation anxiety or panic attacks should be sought. Furthermore, information on management and behavioral issues should be solicited at every yearly visit. For example, it would be important to find out if a dog had been relegated to the garage. This would indicate a high risk of imminent relinquishment, and preventive behavioral intervention would be urgent.

If clinical consults are offered, they should be performed in a methodical way in special appointments. The diagnosis should be based on a minimal medical database (i.e., physical exam with basic neurologic exam, CBC, chemistry profile including a thyroid panel, urinalysis, and additional tests as indicated), a thorough history and direct observation and/or observation from videotapes. The history may involve collection of general information regarding early history; housing, feeding, exercising, and training the pet; the animal's behavior in various situations to assess temperament; and the specific problem. The latter information should include triggers of the behavior; the behavior itself, including body language; and consequences of the behavior. Because behavior problems often change over time, this information should be gathered for the earliest incidents in addition to the most recent few. Observations need to include normal dog-owner interactions. Particular attention should be paid to behavior that results from motivational conflict or frustration.

Treatment modalities include changes in management (housing, feeding, exercise, training methods), behavior modification (e.g., systematic desensitization, counter-conditioning, and response substitution), and pharmacologic treatment.

While behavior modification is being addressed, exposure to the natural stimulus must be avoided. Systematic desensitization involves training the patient to a relaxed down-stay, and exposing the patient to the stimulus at a low intensity. The patient is rewarded for staying relaxed. The stimulus intensity is increased incrementally, and the patient always is rewarded for relaxation. If the dog shows a reaction, the owners have progressed too quickly and need to go back a few steps in the training. Systematic desensitization requires identifying the stimulus, reproducing the stimulus, and having control over the stimulus intensity. If these requirements cannot be met, or the natural stimulus cannot be avoided for the duration of behavior modification, drug desensitization may be necessary. In this case, the patient is put on an effective dose of an appropriate drug and exposed to the natural stimulus as often as possible. He is rewarded for desirable behavior. Over time, the patient is weaned from the drug.

The term *counter-conditioning* is used inconsistently in the literature. This author uses it for a technique based on Pavlovian conditioning. It involves association of a situation that previously evoked fear and/or aggression with something pleasant. The pleasant stimulus can be food or play, for example. It is very unlikely that fear is reinforced by giving food but could easily be reinforced by picking the animal up or sheltering it (avoidance conditioning).

Response substitution is a technique by which an animal is trained to perform an appropriate behavior in a situation in which it used to perform an unacceptable behavior. The animal first needs to be trained to perform the desired behavior on a cue. Then, whenever the animal shows any inclination to perform the unacceptable behavior, the owner distracts it, gives the command, makes the animal do the appropriate behavior, and reinforces that behavior with a reward. They need to either supervise the animal constantly, or put it in a situation in which it will not perform the inappropriate behavior when not supervised. The animals may not be given any chance to perform the inappropriate behavior.

Often these techniques are used in combination. Variations of these techniques are used depending on the situation or problem. The instructions given here are examples, not the only correct form, of behavioral treatment of the specific problem.

CANINE BEHAVIOR PROBLEMS

Aggression

Depending on the author, some dozen different types of canine aggression are recognized, including conflict-related, dominance, possessive, territorial aggression, interdog, play-induced, excitement induced, fear induced, pain-induced, redirected, maternal, and predatory aggression.

They fall into the three major groups of affective aggression, predatory behavior (part of feeding behavior), and play aggression. Redirected and learned aggression are not really diagnoses but imply a mechanism of modification of a type of aggression.

Aggression to Household Members

Aggression to household members is often exhibited in situations in which the dog is threatened or "challenged." This type of aggression has generally been diagnosed as dominance aggression. Dominance aggression would be expected primarily in adult dogs and intact males. Dogs would be expected to have a self-confident personality and show offensive body language when aggressive. However, recent research showed that the majority of cases start at a very young age. Typically, initial aggression is shown in response to discipline or over food within the first 2 months of ownership. The affected dogs have a different disease history (severe early disease, dermatologic disease) than nonaggressive dogs. They are more excitable as puppies and more excitable and fearful (shy of people) as adults. Their body language before and during an attack is ambivalent and indicates a motivational conflict. Frequently, in the initial incidents the dog shows defensive body language, but over time it becomes more and more offensive. There is a breed predisposition; Spaniels, Terriers, and toy breeds are more likely to bite. Dogs most likely to be aggressive are neutered males, neutered females and intact males are less likely, and intact females are least likely to be aggressive (although in small breeds, females are more likely to bite than males). Neutering can make females more aggressive. Dogs that are aggressive to their owners are also likely to be aggressive to strangers, which indicates this aggression is not confined to the dogs' social group.

It appears that the aggressive dogs are in a motivational conflict (approach-withdrawal conflict) relative to people. When a person approaches, aggressive dogs' anxiety level increases and they show aggression. As the person responds by backing off, the threat diminishes. The dogs thus learn that they can resolve their conflict and reduce their anxiety by showing aggression. Thus aggression becomes conditioned through avoidance conditioning; this type of conditioning produces persistent behavior. Based on this putative pathogenesis, we have proposed the term *conflict-related aggression*.

Treatment should address the dog's basic disposition (e.g., fearfulness, hyperexcitability), the way in which the dog is managed, and the cause of conflict (i.e., the inconsistency in the owner-dog interaction).

Recommended management changes include twice daily meal-feeding (as opposed to *ad lib* feeding) and regular twice-daily exercise. The situations in which confrontations are likely should be avoided. This may imply that the dog needs to be confined (e.g., in a separate room or exercise pen) unless being trained. Confinement is also indicated when the owners are afraid of the dog, when smaller children are involved, or when the owner is unable to ignore the dog. A head halter with a leash attached is placed on the dog, so that the owner can control all aggression-inducing situations in a safe, non-confrontational, and consistent way. Toys or other assets that have caused confrontations should be removed. The dog is not to be let on furniture *if* that caused a problem. The dog should be reintroduced to situations in which he showed aggression only in the context of systematic desensitization and response substitution.

Owners are instructed to avoid all casual interaction (i.e., ignore the dog most of the time) and only interact with the dog in a command-response-reward format. This ensures that all interactions with the dog are consistent and thus predictable. Highly structured obedience exercises, especially ones that desensitize the dog to owner-behavior perceived as threatening, are very useful. Clicker training is especially helpful when dealing with these dogs, because it is a hands-off method of training and avoids confrontations between owner and dog. No punishment, choke chain, or scolding are to be used. A head halter assists the owner in training and walking the dog. Punishment or the "alpha roll-over" are *not* appropriate in dealing with aggression. Situations in which the dog still shows aggression are addressed by systematic desensitization, counter-conditioning and response-substitution.

Food guarding can be addressed through management, that is, by feeding the dog in a separate room and calling the dog out of the room once he is finished eating. It can also be treated through systematic desensitization. In the latter case, the dog is tied in a different place than where he is normally fed, and fed from a different food bowl (preferably a saucepan with a long handle). The ration is measured out into yet another dish that is placed out of the dog's reach. The dog is asked to sit and a few kibbles are placed into the food bowl, and the dog is offered the food. This is repeated until all the food is fed, and all meals are fed in this way for about a week. Then, the amount of food given at one time is increased. Next, the amount of food is decreased again to a few kibbles, but the owner lets go of the food bowl while the dog eats. The amount is then increased again. Eventually, a third of the food can be placed into the food bowl, and the owner adds the remainder of the ration gradually with a ladle. Once this goes well, all the food can be placed in the food bowl, and the owner tosses treats into it while the dog eats. This should be done occasionally throughout the dog's life (in very mild cases, this last step is all that needs to be done).

No drugs have been proven effective in the treatment of any type of canine aggression, although there is anecdotal evidence of positive effects with SSRIs.

Possessive Aggression

Guarding of food and objects is a natural but unacceptable canine behavior. It becomes exacerbated if the dog is afraid of a confrontation over the item (it may therefore be regarded as a special case of conflict-related aggression). It can be addressed by management or through training. The latter option includes training "leave-it" and "drop-it" commands, or exchange exercises (a form of systematic desensitization). For exchange exercises, the dog is tied to an immovable object, initially away from where he most commonly shows aggression. The dog is asked to lie down and stay. A toy that the dog does not value much is laid down at some distance from the dog, the leave-it command is given, the toy is picked up, and the dog is rewarded for staying relaxed. At subsequent trials, the distance is reduced. The exercise is repeated with increasingly valuable toys.

Territorial Aggression

Territorial aggression is exhibited to strangers or strange dogs either on the owner's property or in the owner's proximity. It is a normal but unacceptable canine behavior. Treatment involves training the dog to sit near the door and staying while the door is opened, while the doorbell is rung, or while a stranger stands at a distance and progressively closer to the door. It is important to prevent the dog from ever showing aggression until the training program is completed.

The dog should be walked twice daily off the property on head halter and leash. Whenever a person approaches, the owner should go out of the way and keep the dog busy with fast-paced obedience, reinforcing appropriate behavior with ample food treats. Once the other person has passed, they can continue their walk. Each time, the distance to the other person can be reduced (depending on the response of the dog), until the owner can heel the dog by the other person, and then reward the dog for having passed without aggression. This method can also be used with a volunteer who stands still while the owner performs obedience training with the dog at decreasing distance. The dog can also be systematically desensitized to a stranger approaching.

Aggression Between Dogs

Aggression to strange dogs or *interdog aggression* can be status-related, territorial, fear-based, or even predatory. Treatment is similar to that of territorial aggression and includes the same exercises on walks, systematic desensitization to a dog passing by or approaching, response substitution (having a helper with a dog stand still and doing obedience with the patient at decreasing distances, rewarding frequently), and counterconditioning (making the situation when another dog is in sight very pleasant). Punishment is contraindicated with any form of aggression, in this case in part because the patient would learn that the presence of another dog means he will likely get punished.

Aggression between dogs living in the same household, often referred to as "sibling rivalry" (a misnomer because they are not usually siblings), can have various reasons as well but most cases are either status-related or related to owner attachment (sometimes called "alliance aggression"). Fights are usually severe, especially among females.

Status-related aggression may occur between dogs that are close in social status. Fighting may also begin when a younger dog reaches adulthood, or when an older dog is no longer able to maintain his position. Treatment of status-related aggression involves deciding which dog will likely end up dominant and treat him as such (giving attention or food first, giving this dog privileges that the other dog does not have), and treating the other dog as subordinate (ignoring, cutting privileges, possibly confinement, rewarding subordinate behavior). Furthermore, systematic desensitization and response substitution (as for interdog aggression) can be used. The dogs may need to be separated and/or muzzled when exposed to each other. The times the dogs are exposed to each other should be as positive as possible (counterconditioning).

Alliance aggression is aggression to another dog in the same household shown only in the proximity of the owner. It is usually, but not always, the lower-ranking dog that initiates the aggression. The aggressive dog is usually overdependent on the owner and becomes very anxious if the other dog gets close to the owner. He may also feel much more confident in the presence of the owner.

The most important aspect of treatment is to ignore both dogs for 3 to 4 weeks, except when working with them. The dogs should be exposed as much as possible to each other. If there is any indication that the dogs will be aggressive, the owner should distract them with a loud noise (clapping hands, rape alarm) and immediately leave. In some cases the dogs will need to be muzzled when exposed to each other. It should be determined which of the two is the dominant dog (from a videotape taken when they are on their own, without owner present), and that dog should be treated as such.

The aggressive dog can be desensitized to the owner paying attention to the other dog. While the aggressive dog is tied and in a down-stay, the owner interacts with the other dog at decreasing distance and rewards the aggressive dog frequently for staying relaxed. Dogs that exhibit alliance aggression are often not aggressive to each other in other places, or out in the yard. In this case, they can be exposed to each other initially on neutral ground, then kept together in the backyard, and then gradually allowed access to increasing parts of the house.

Predatory Aggression

Predatory aggression is highly genetically controlled and may therefore be difficult to treat. It is a particularly dangerous form of aggression because there is no warning and the bite is not inhibited. Systematic desensitization and response substitution (in combination) can be successful. The owner is instructed to do obedience training at a distance from the "prey" (e.g., horses, cars going by), using a head halter and food rewards. Gradually, the owner reduces the distance. Confinement and control, as well as a muzzle, are useful in managing the behavior. A good recall can help to control dangerous situations. Socialization of the puppy to the species that it should not consider as prey (e.g., children) is essential. Selection of a breed with little predatory behavior helps in prevention.

Separation Anxiety

Separation anxiety is a common problem. Among these cases, dogs obtained from shelters are overrepresented. Affected dogs are usually very friendly and dependent on the owner, and more highly trained than dogs with other behavior problems. Because of their owner attachment, these dogs become anxious when separated form the owner (i.e., when the owner is either not home with the dog, or not accessible to the dog) and express this anxiety in a variety of ways (e.g., by destroying property, barking, salivating, pacing, urinating or defecating, self-mutilation). Diagnostically it is important to note that these behaviors start within a short time of the owner leaving. First line treatment may include two daily walks to reduce anxiety; ignoring the dog for approximately 30 minutes before leaving, and after coming home until the dog settles; giving a hollow toy containing food treats some 5 to 10 minutes before leaving; and ignoring attention-getting behavior at any time. In addition, owners may want to train the dog to a long down-stay and then use that command to prevent the dog from following them all the time, and when doing planned departures (see below). Mixing up the order of predeparture cues makes departure less predictable, and desensitization to these same cues (by presenting them frequently without leaving) will reduce the dog's response to them. Drug treatment concomitant with behavior treatment is often indicated. The drug clomipramine (Clomicalm, Novartis) is the only drug licensed in the United States for the treatment of separation anxiety.

If necessary, the owner can do planned departures, leaving the dog for initially very short and increasingly longer times, while giving the dog a safety cue (e.g., the sound of the radio). If at all possible, dogs with separation anxiety should not be confined when left alone, because usually this makes the anxiety worse. If the owners keep the dog confined and do not want to risk leaving him loose, they may want to use the planned departure technique with the dog loose in the house during practice departures. In this way they can find out without great risk if it is safe to leave the dog loose (if done this way, being loose becomes a safety cue for the dog).

Fear

Fear is a combination of physical, emotional, and physiologic responses to a threatening stimulus or situation that, in the wild, would protect the animal from harm. Fear may become a maladaptive *"phobia"* when the response is out of proportion to the threat. The dog may be afraid of specific stimuli or be globally fearful. The cause of fearfulness may be genetic, or early experience (lack of socialization and exposure before

14 weeks of age, or an adverse experience in the fear period 8 to 10 weeks of age). Specific fears are usually learned.

Learning can exaggerate any fear. Learning is most easily achieved through avoidance or escape conditioning. However, it is very difficult to reinforce fear with food. Giving food to a fearful dog is therefore not contraindicated, but recommended, because it may make the situation more pleasant (counter-conditioning).

Specific fears can usually be treated very effectively with systematic desensitization, counterconditioning, and response substitution. For generalized fear or when fear-evoking stimuli cannot be avoided, or if the stimulus cannot be replicated (e.g., thunderstorms), drug desensitization is indicated. The dog is given a large enough dose of a drug with anxiolytic effects to reduce fear to the point at which the dog is capable of habituation to the stimuli (the above behavior modification techniques should be used simultaneously). Once the dog functions well at that dose, the dose is slightly reduced. When the dog no longer shows fear on the lower dose, the dose is further reduced, and the dog is thus gradually weaned off the drug. Throughout the procedure, the dog should be rewarded for acting confidently. Even after successful treatment, the dog should be periodically exposed to the fear-inducing stimuli and rewarded for not responding fearfully, to prevent spontaneous recovery of the fear response. A fear response is not ever to be punished.

Hyperexcitability

A high level of activity may be normal for a certain breed and age of dog. Although there are various physiologic and environmental reasons for abnormally high activity or excitability, the most common cause is inadvertent conditioning with owner attention. Consequently, the first treatment strategy is to ignore the dog, especially when excitable. Relaxed, calm behavior should be rewarded. Obedience training, especially a long, relaxed down-stay, and regular twice-daily walks will also help in most cases.

Canine House Soiling

Before a diagnosis of house soiling is made, medical causes, urine marking, separation anxiety, and other anxiety-related disorders have to be ruled out. Causes of house soiling include insufficient initial house training, long periods of cage confinement during puppyhood so that the dog learned to soil his bed, and various other factors that can result in the loss of house training.

To treat house soiling, the factors that affect elimination have to be understood. Elimination is most likely after rest, eating, and physical activity. It is also stimulated by the smell of previous elimination. The dog should be fed two to three times a day (depending on his usual number of stools per day) and walked thereafter to the same location. The dog should also be taken to that location when first waking from sleep, after play, and frequently in between. When the dog eliminates at that location, he should be rewarded. If he does not eliminate this time, he can be brought back to the house but should be taken out again within 10 minutes or so. Indoors, the dog should be under constant supervision (crate confinement or on leash with the owner). The soiled areas should be treated with a high-quality enzymatic cleaner and can then be made aversive with bi-weekly application of pine-oil cleaner or citrus-scented liquid, or small amounts (¼ teaspoon) of mothball powder brushed into the pile of the carpet *(mothball crystals are toxic)*.

Canine Urine Marking

Canine urine marking can be a territorial behavior, greatly facilitated by testosterone in intact males (especially in the presence of other intact dogs or bitches in heat), or related to anxiety. It involves deposition of small amounts of urine in specific places, usually on or near vertical objects. The strongest stimulus is environmental competition of other males and freshly voided urine from other dogs.

Stimuli that elicit urine marking should be identified and, if possible, eliminated. If urine marking is anxiety-related, then the cause of the anxiety has to be addressed. The marked areas should be cleaned and deodorized as described for house soiling. Castration reduces leg lifting in the house in about 60% of cases.

Behavior modification involves constant supervision in the house, possibly with the dog tied to the owner with a leash (umbilical cord technique). Whenever the dog shows any signs of wanting to mark a place, the leave-it command (it will have to be taught in advance) or response substitution should be used. Punishment generally does not work as it is usually not applied consistently, and because the dog may learn to lift the leg only when the owner is absent.

Compulsive Disorder in Dogs

Compulsive disorder is expressed as repetitive or sustained, apparently abnormal behaviors performed out of context. Compulsive behaviors could be categorized as related to locomotion, oral activity and grooming, aggression, vocalization, and hallucinatory behaviors. In dogs, locomotory behaviors include circling, tail chasing, pacing, jumping in place, chasing light reflexes, and freezing. Oral behaviors and behaviors related to grooming manifest, among others, as leg or foot chewing, licking, flank sucking, scratching, chewing objects, pica, and snapping in the air ("fly-snapping"). Compulsive behaviors related to aggression include self-directed aggression, attacking the food bowl or other inanimate objects, and possibly unpredictable aggression to people. Vocalization may be rhythmic barking or whining. Hallucinatory behaviors may be staring at "shadows," chasing light reflexes, and startling. Dogs that wake up suddenly without any discernible trigger and jump or are aggressive may suffer from hallucinatory compulsive disorder.

Compulsive behaviors may be considered an expression of stress, frustration, and/or motivational conflict. Frustration refers to the situation in which an animal is motivated to perform a behavior, but prevented from doing so. Motivational conflict results from two opposing, similarly strong motivations (such as approach and withdrawal). Prolonged and particularly repeated frustration and conflict may result in conflict behaviors developing into compulsive disorder. A genetic predisposition is probably present in any case of compulsive disorder. Physical lesions or irritations, such as ones caused by allergy, may trigger CD in some cases by increasing stress and by directing the compulsive behavior towards a particular body site. Owner attention may reinforce existing compulsive behaviors, or condition normal conflict behaviors to the extent that they appear compulsive. Disease that increases stress and/or irritability may contribute to CD, as may other stressful behavioral problems (e.g., interdog aggression or separation anxiety) or certain temperament traits (e.g., fearfulness).

A diagnosis of CD is based primarily on a detailed history and on ruling out other possible behavioral and medical causes for the observed behavior. One aspect of the history that is particularly important for the diagnosis is the development of the problem. In many cases (especially locomotory behaviors), compulsive behaviors are first shown in a specific conflict situation but later may generalize to other contexts in which the animal experiences a high level of arousal. Once established, compulsive behaviors are displayed outside of their natural context and are often excessive. The animal is in full consciousness while performing the behavior and aware of its surroundings (although in some cases they may not respond

to any stimuli in their environment, and may even run into furniture, etc.). The behavior can usually be interrupted, albeit often with difficulty, and the animal does not exhibit a postictal phase. Their performance is not dependent on the owner's presence.

The differential diagnosis has to consider various behavioral, neurologic, dermatologic, and other medical conditions. To exclude other possible causes for the behaviors, a minimal medical database consisting of a physical exam including a basic neurologic exam, and CBC, chemistry profile, thyroid panel, and urinalysis should be obtained. Additional tests may be needed in specific cases.

Behavioral differentials include acute conflict behavior only shown in specific contexts, and conditioned behavior only shown in a person's presence. Neurologic rule-outs are seizures, forebrain and brain stem lesions, lesions of the vestibular system (circling), lumbosacral stenosis (tail chasing), hydrocephalus, sensory neuropathies, and neuromas (self-mutilation).

Any dermatologic lesion, skin-gland disease, or endocrine disease that results in itching or pain can cause licking. Preexisting wounds or pressure point granulomas can also direct compulsive licking towards a particular area.

Treatment is directed at identifying and removing the cause of conflict, frustration, and stress. In cases in which the cause of stress cannot be removed, it may be possible to desensitize the animal to the stressful situation. Casual (i.e., inconsistent) interaction should be avoided and replaced with highly structured interactions in a command-response-reward format. Formal obedience sessions allow for such consistent interaction. Punishment should not be used at all. A consistent feeding and exercise schedule provide for a consistent routine. Sufficient exercise helps reduce anxiety. Rotating toys and providing food-dispensing toys are also recommended.

In most cases, drug therapy may prove necessary or will at least facilitate treatment. Pharmacologic intervention is most likely achieved with serotonin re-uptake inhibitors such as clomipramine (Clomicalm, Novartis Animal Health US, Greensboro, NC) at 3 mg/kg bid, or fluoxetine (Prozac, Eli Lilly, Indianapolis) or paroxetine (Paxil, GlaxoSmithKline, Pittsburgh) at 1 mg/kg sid-bid. It may take more than 4 weeks to see a drug effect. The author usually gives the drug until at least 3 to 6 weeks after the drug appears to have a satisfactory effect and then weans off gradually over at least three weeks, by reducing dose but maintaining dosing frequency. If during the weaning process the behavior reappears, the dose is increased again and maintained at the effective level for some time before resuming weaning. Weaning is important to avoid a rebound effect.

The above behavioral treatment with or without drug treatment is likely to reduce the frequency of the behavior. If the dog still performs the behavior occasionally, consistent response substitution can be highly effective in the treatment of compulsive disorder.

FELINE BEHAVIOR PROBLEMS

Inappropriate Urination and Defecation

Cats that are house-soiling with urine may be differentiated from those that are urine marking by the amount of urine that is released. When marking, a cat eliminates small amounts of urine at a time, usually on vertical objects, whereas a house-soiling cat tends to empty his bladder, which results in a large spot. The exception is cats that mark with full urination and/or defecation on human's concentrated body odor (e.g., beds, bath mats, dirty clothes). In these cases, the cat has a conflict with the person on whose smell he marks with urine or feces.

Cats may stop using their litter-box for a variety of reasons. They may have developed an aversion to the litter, the pan, an odor or the location; they may have developed a preference for certain substrates or locations; they may be under some environmental stress; or they may have underlying disease, most commonly urinary tract infection or cystitis, and in older cats also arthritis or cognitive dysfunction.

The first step in treatment is to identify which cat of a multicat household is the culprit (Figure 52-1). To differentiate disease-related from behavioral house soiling, a physical exam, CBC, profile, urinalysis, and urine culture are indicated. Then litter-box factors need to be addressed. The number of boxes should equal the number of cats plus one. Owners should scoop the box daily and wash it out regularly with warm water only. Many cats do not like covered boxes. Location of boxes is crucial. Laundry rooms and basements are usually not preferred areas, whereas hallways and closets are most suitable. In a multicat household, a core area for each cat should be established, containing food, water, lying area, scratching post and litter-box, in the cats' preferred locations. The most important factor that determines litter acceptance is particle size; most cats prefer small particle size. Litter material should not be scented. A variety of litter materials can be offered. Litter-box liners are often aversive to cats and should not be used. Soiled areas should be cleaned and made aversive as described under canine house soiling.

If cats have established a substrate preference (e.g., for carpet) the cat can be retrained by confining it to a room with different flooring. A piece of carpet is placed in the litter-box. Each day, a somewhat smaller piece of carpet is provided, and a little more litter material is sprinkled on it, until the cat is completely switched over to litter. The cat can then be taken out of the room daily for short and increasingly longer periods of time, under close supervision. It is recommended to feed the cat free choice food and to change its water frequently.

Feline Marking or Spraying

Spraying is a form of territorial marking with small amounts of urine, or rarely, small amounts of feces. It is most common in intact males or males that produce steroids from other sources (check penis for barbs). Among neutered animals, males are twice as likely to spray than are females. Spraying usually occurs in only a few specific areas, most commonly on prominent vertical objects, and often near windows and doors. Spraying is usually related to stress resulting from the presence of other cats, changes in the environment, changes in schedule, food and water restriction, or other factors. Some cats mark with full urination or defecation on concentrations of body odor of a specific person. This usually indicates some conflict related to that person, such as fear or overattachment. The smell of previously soiled areas will compel a cat to re-mark the same area.

In a multicat household it is important to determine which cat is marking. Although disease is not a common cause for urine marking, it should always be ruled out first. Intact animals (especially males) should be neutered. Environmental and social stressors should be addressed. In multicat households, different core areas for the cats, with food, water, lying area, scratching post, and litter-box should be established. Provision of cat trees enables cats to use the third dimension to get out of each other's way. Outside cats may need to be kept away, or the patient needs to be prevented from seeing them. The sprayed areas should be cleaned with a good enzymatic cleaner. Making the sprayed areas aversive is controversial. Application of a feline pheromone analogue (Feliway, Veterinary Products Laboratories, Phoenix), as a spray or by diffuser, may reduce spraying. The temporary use of an anxiolytic drug such as paroxetine (Paxil, GlaxoSmithKline) or clomipramine (Clomicalm, Novartis) may be necessary. It is recommended to offer free-choice food and provide fresh water frequently.

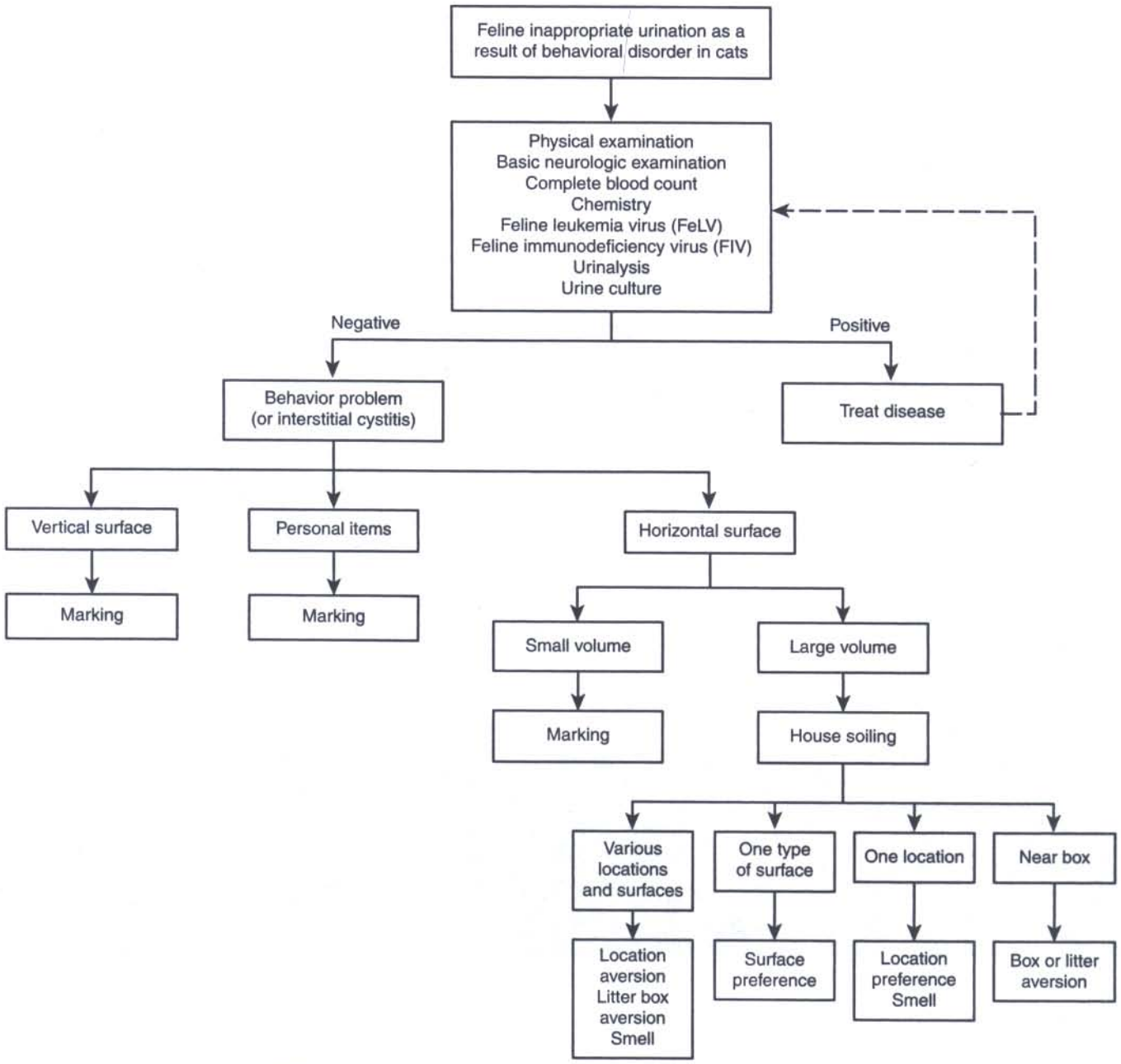


Figure 52-1 Algorithm for diagnosis and treatment of feline inappropriate urination.

Territorial Aggression, Intercat Aggression

This type of aggression is seen most frequently when a new cat is introduced to the household, or when a resident cat is reintroduced after a stay at the veterinary hospital or boarding. One cat may stalk the other cat, and the victim usually shows fear, which increases the probability of an attack.

Letting the cats "fight it out" does not work. Systematic desensitization and counterconditioning are recommended. Cats can be exposed to each other in carriers at a decreasing distance. Each time, the carriers are swapped, so the cats are exposed and take on each other's smell. While exposed to each other, they get their favorite food to eat. They can also be exposed to each other on leashes. While exposed, the owners should play with the cats and give them their favorite treats, gradually reducing the distance. When not systematically exposed to each other, the cats should be separated with only the bare necessities provided, and ignored. The rooms in which the cats are kept can be swapped after each exposure, so the cats are exposed and take on each other's smell. The smell can also be transferred between cats by rubbing a towel alternately on either cat. Drugs are often used on both cats (in the aggressor to reduce aggression, in the victim to reduce fear).

Petting Aggression

Some cats get very aggressive when petted for a prolonged time. The reasons are not well understood. Treatment involves avoiding prolonged petting or systematically desensitizing the cat to tolerate petting.

Redirected Aggression

This is not a diagnosis, but it describes aggression that is redirected to an alternate target, when the intended target is not

accessible. It is often triggered by the view of outside cats. The cat that is indoors redirects its territorial aggression to another resident cat (which results in intercat aggression) or a person.

Play Aggression

Play aggression becomes a problem if the cat delivers uninhibited bites and causes injury. Affected cats are usually young, are living as the only cat in a household, and were taken early from their mothers. Often, owners contribute to the problem by playing roughly with the cat when it is a little kitten, and failing to teach a bite and claw inhibition. Play aggression is not usually preceded by a threat. The cat often hides behind some furniture and waits until a person walks by and then dashes out and attacks the person's ankles. Hands dangling over the armrest of a chair are also favorite targets.

To prevent further injury, the cat should wear a collar with as many bells as possible, so the owner becomes aware when the cat approaches. Some protective device or a canister of compressed air may also be effective. The cat should be distracted with the compressed air, and its behavior can then be redirected by tossing a toy. Teaching a bite and claw inhibition by immediately interrupting play as the cat gets rough is also important. Interesting toys that are rotated daily, and hiding food will keep the cat busy. A companion kitten may also help. The owner should teach the cat appropriate play by engaging it daily in play with interactive toys. They can also train their cat to obey commands and to do tricks.

Compulsive Behavior

In cats, examples of compulsive behavior include overgrooming (psychogenic allopecia), wool-chewing, vocalization, hallucinatory behavior, aggression to self, and many cases of the hyperesthesia syndrome. The diagnostic procedure and differentials are the same as described for dogs. Differentials for neurologic signs include FIV. Dermatologic differentials are particularly important in overgrooming cats. Skin scraping, dermatophyte culture, and trichogram are indicated. The patient should be treated for fleas and mites, undergo a food trial for 8 to 12 weeks, and undergo a trial of corticoid therapy before being treated with an anticompulsive drug.

The treatment is basically the same as in dogs. In multicat households, various core areas with food, water, a litter-box, a soft lying area, and a scratching post should be established, because social tension often contributes to stress. Cat trees allow cats to make better use of the third dimension and get out of each other's way. In some cases, an area needs to be provided where only the patient can go (e.g., electronically controlled cat door in a door). Feeding of dry food should always be ad libitum. It can be distributed around the house so that the cat is kept busy foraging for longer times. A large variety of interesting toys that are rotated may serve as an unspecific means of decreasing arousal. Particularly attractive toys such as food dispensing toys can be given at times when the performance of the compulsive behavior is likely.

Drug therapy is usually necessary as part of the treatment. Response substitution can also be used for cats. The cat is continuously supervised or placed in a situation in which it will not perform the behavior. Every time the cat is about to perform the compulsive behavior, it is distracted (startled), and then its attention reoriented by throwing a toy. If the cat is clicker trained, the same procedures as described above for dogs can be used.

Cardiorespiratory

CHAPTER 53

Coughing

Kelly Anderson-Wessberg

A cough is a sudden, forceful expiration against a closed glottis. Sudden opening of the glottis and turbulent airflow create the noise identified as a cough. Coughing may occur as a conscious action or as a reflex. The coughing reflex is stimulated by mechanical or chemical irritation of the pharynx, larynx, trachea, bronchi, and smaller airways. Less commonly, disease processes involving the pleura, pericardium, diaphragm, nose, nasal sinuses, and mediastinum may also stimulate the coughing reflex.

Coughing may be the first indicator of a serious disease. On the other hand, coughing may be confused with other symptoms such as sneezing, gagging, panting, labored breathing, reverse sneezing, retching, and vomiting. The presence of a terminal retch is often misinterpreted as vomiting. Reverse sneezing has a characteristic sound with audible inspiratory and expiratory components. Failure to differentiate a cough from these other signs results in misdiagnosis and treatment failure.

The causes of coughing in small animals may be divided into the following categories (Box 53-1): inflammatory, neoplastic, cardiovascular, allergic, traumatic and physical factors, parasitic, and fungal.

DIAGNOSTIC APPROACH

Signalment and Historical Findings

The age and breed of the animal will influence the likelihood of certain conditions. Puppies and kittens are more likely to suffer from infectious respiratory diseases. Toy and miniature breeds such as Chihuahuas, Pomeranians, toy poodles,

Box • 53-1

Causes of Coughing in Dogs and Cats

Inflammatory
Pharyngitis
Tonsillitis
Tracheobronchitis
Chronic bronchitis
Bronchiectasis
Pneumonia—bacterial, viral, fungal
Granuloma
Abscess
Chronic pulmonary fibrosis
Collapsed trachea
Hilar lymph node enlargement
Secondary to esophageal dysfunction
Inhalation
Foreign body

Neoplastic
Primary
Mediastinal
Metastatic
Tracheal
Laryngeal
Ribs, sternum, muscle
Lymphoma

Cardiovascular
Left heart failure—pulmonary edema
Cardiomegaly—especially left atrium
Heart failure
Pulmonary emboli
Pulmonary edema—vascular origin

Allergic
Bronchial asthma
Eosinophilic pneumonitis
Eosinophilic pulmonary granulomatosis
Pulmonary infiltrate with eosinophilia (PIE)
Immune disease
Sinusitis (?)
Reverse sneeze (post nasal drip?)

Parasitic
Larval migration (*Toxocara* spp., *Ancylostoma caninum*, *Strongyloides stercoralis*), *Filaroides* spp. (dog), *Aelurostrongylus abstrusis* (feline lungworm), *Paragonimus kellicotti* (dog, cat), *Dirofilaria immitis* (dog, cat), *Capillaria aerophilia* (dog, cat), *Crensoma vulpis* (dog)

Protozoal
Toxoplasmosis (cat)
Pneumocystis (dog)

Fungal
Blastomycosis
Histoplasmosis
Coccidiomycosis
Cryptococcosis
Aspergillosis

Yorkshire terriers, Shih Tzus, and Lhasa apsos are predisposed to collapsed trachea. Lungworm typically occurs in dogs less than 2 years of age, although it may occur in older animals. The history should focus on the general health of the pet, previous medical problems, recent diagnostics performed (heartworm testing, general blood profile, fecal examination, radiographic studies), vaccination status, heartworm prevention, exposure to other animals, and other symptoms the pet is experiencing. The history should include all recent and current medications, dosages, length of treatment, and response to each medication. Environmental history may provide important additional information. Exposure to dog parks, grooming facilities, kennels, and stray animals increases the likelihood of contagious disease. Any changes in the animal's environment should be noted along with the health of the other pets in the household. An accurate travel history should be obtained. Certain respiratory diseases are common in specific geographic areas and unlikely to occur in others. Coughing is a side effect reported in as many as 15% of human patients receiving ACE inhibitors. The cough is due to increased sensitivity of the cough reflex resulting in a dry, nonproductive cough. Increased bradykinin levels are thought to play a role. In dogs, coughing as a side effect from ACE inhibitors does not seem to be a common problem.

Nature of the Cough

A description of the cough provides additional diagnostic clues. Specific questions regarding the cough should include the following: how does the cough sound, is it productive or nonproductive, what stimulates the cough, when does it occur, how often does it occur, is the cough worse at night or during the day, is it stimulated by exercise, is the timing of the cough related to eating or drinking, and does the cough respond to diuretics or other medications? Cardiac disease initially results in nocturnal coughing, but advanced cardiac disease may result in coughing during any time of day or night. Tracheal collapse typically produces a characteristic "goose-honk" sound easily recognized by most owners and experienced clinicians. Coughing due to tracheal collapse or tracheal irritation is stimulated by excitement, drinking water, and by pulling on the collar. A productive cough may be produced by the following conditions: chronic bronchitis/bronchiectasis, pneumonia, pulmonary edema, esophageal dysfunction, and hemoptysis. A nonproductive cough may be produced by the following conditions: bronchitis, early cardiac disease, left atrial enlargement without pulmonary edema, lymphadenopathy, allergic lung disease, and tracheal irritation or collapse. These lists are not meant to be all-inclusive and some diseases may produce both types of cough. Also, some animals may be experiencing more than one disease process at a time, thus having multiple reasons for a cough.

Physical Examination

As with other body systems, a thorough physical examination is required for obvious reasons. Emphasis is placed on the cardiorespiratory system. Careful auscultation will reveal the presence or absence of a murmur, crackles, wheezes, rales, upper airway noises, or evidence of pleural effusion. In the presence of tracheal sensitivity or collapsing trachea, palpation of the extrathoracic trachea may stimulate the coughing response.

Radiographs

Thoracic radiographs may provide information leading to a diagnosis, but they are not necessary in every case. Radiographs should be analyzed for evidence of cardiac enlargement, pulmonary disease, pulmonary edema, and narrowing of the trachea. If pulmonary edema is identified, left heart enlargement is expected. Right heart enlargement alone does not typically result in a cough. It is important to

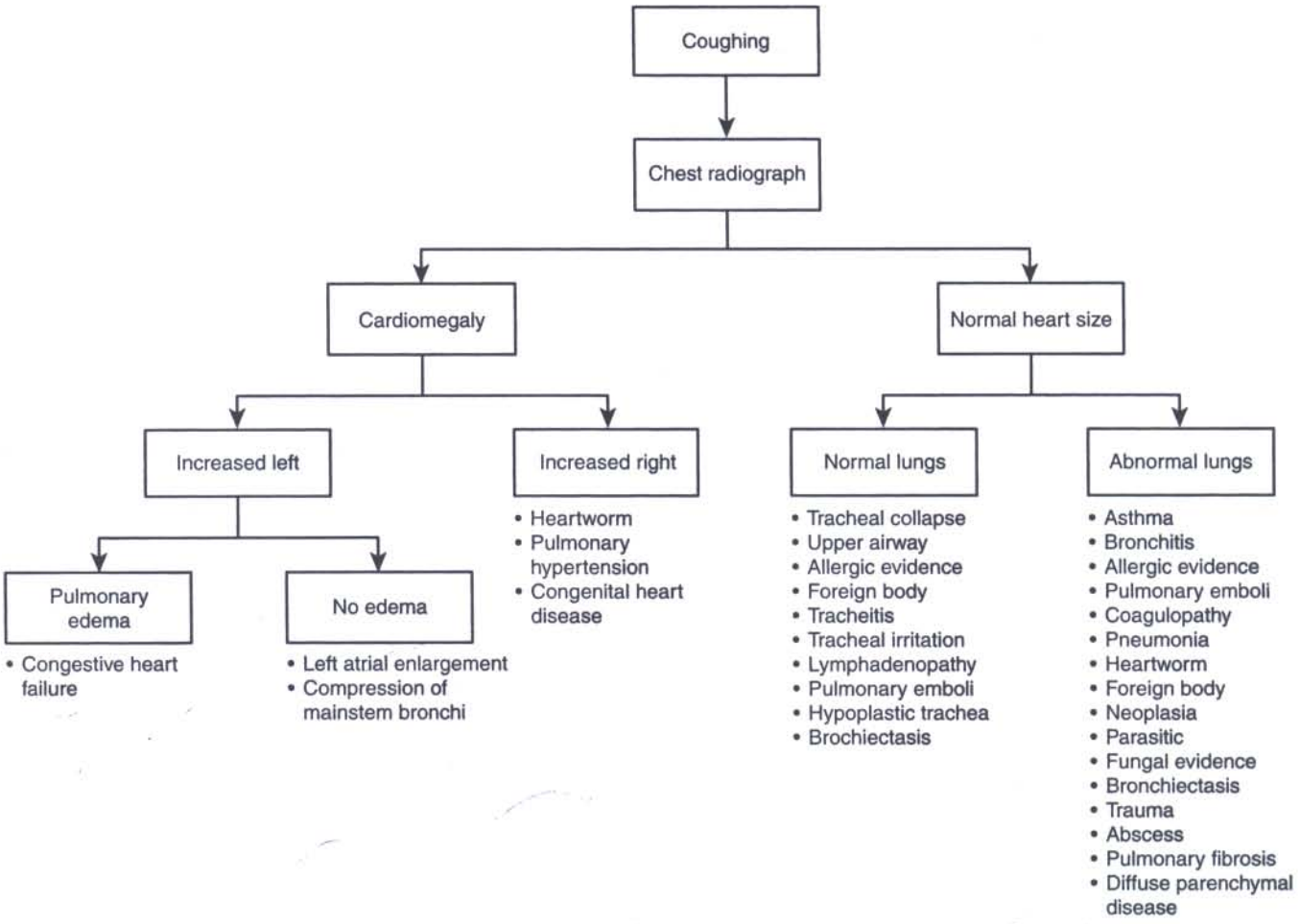


Figure 53-1 Algorithm for interpretation of thoracic radiographs in the presence of a cough.

distinguish coughing due to cardiac enlargement and coughing due to pulmonary edema. Left atrial enlargement may result in compression of the mainstem bronchi. Although some findings may be obvious, it may be impossible to distinguish between neoplasia, fungal infection, and pneumonia on radiographic examination alone. An algorithm for a general approach to interpreting thoracic radiographs in the presence of a cough is presented in Figure 53-1.

Further Diagnostics

In some cases, it may be necessary to perform further diagnostics in an effort to obtain a diagnosis and proper treatment plan. A complete blood cell count, general chemistry profile, fecal examination, and heartworm test (in endemic regions) should precede further diagnostics. Descriptions of further diagnostics involving the cardiac and respiratory systems can be found elsewhere in this textbook.

TREATMENT GOALS

The ideal treatment for a cough is based on a definitive diagnosis and treatment of the underlying problem. However, it is not always possible to obtain a definitive diagnosis, and in such cases, treatment options must be based on clinical assumptions or a preliminary diagnosis. If no specific diagnosis has been made, there is no underlying problem identified, or the cough persists despite treatment of the underlying problem, the use of antitussives should be considered. Table 53-1 outlines commonly used antitussive agents. As a general rule, antitussive agents are contraindicated in cases when suppressing a cough masks important clinical symptoms or when a cough is actually encouraged as part of therapy. Specific treatment of underlying disorders can be found elsewhere in this textbook.

Table • 53-1

Drugs Commonly Used for Canine and Feline Coughing

GENERIC NAME	TRADE NAME	DOSAGE
Bronchodilator		
Aminophylline	Many names	Dog: 10 mg/kg PO, IV tid Cat: 5 mg/kg PO bid
Theophylline	Many names	Dog: 6 mg/kg PO tid
Slow release	Theo-Dur	Dog: 20 mg/kg PO bid
Slow release	Slo-bid	Dog: 25 mg/kg PO bid
Antitussive		
Hydrocodone	Hycodan, Tussigon	Dog: 0.22 mg/kg PO bid-qid
Hydrocodone/Chlorpheniramine	Tussionex	Dog: 0.5 to 1 tsp PO sid-tid
Butorphanol	Torbutrol	Dog: 0.5 mg/kg PO bid-qid
Antiinflammatory		
Prednisone		Dog: 0.5 mg/kg PO bid, then taper dose
Prednisone/trimeprazine	Temaril-P	Dog: 1 tablet/20 lbs PO bid
Expectorant/Antitussive		
Guafenesin/dextromethorphan	Robitussin-DM	Dog: Similar to adult children dosages

CHAPTER • 54

Dyspnea and Tachypnea

Dianne Mawby

Dyspnea is defined as labored or difficult breathing. The human patient is likely to communicate this to the physician as "air hunger." *Respiratory distress* is a similar term. *Tachypnea* is defined as an increased rate of respiration. *Panting* is a method of heat regulation and does not imply respiratory difficulty in the dog; however, panting in the cat usually indicates stress or hyperthermia. *Orthopnea* describes the inability to breathe except in an upright position.

The pathophysiology of respiratory distress usually stems from the lack of oxygen or excess of carbon dioxide in the body. Hypercapnea and acidemia are sensed in the central respiratory center and hypoxia is sensed through the peripheral chemoreceptors located in the carotid and aortic bodies. The body tries to resolve the problem with either increased ventilatory rate or increased ventilatory depth or both.

HISTORICAL FINDINGS

History should include geography and environment, recent exposure to other animals, past illnesses, past injuries, and vaccination and heartworm preventative status. The current complaint should be addressed regarding duration, progression, previous treatment, and response to therapy. The owner can also supply information involving upper respiratory problems such as nasal discharge, sneezing, noisy breathing, abnormal breathing patterns, and recent exposure. Coughing is discussed in Chapter 53. Other relevant history includes exercise intolerance, change in appetite, and general demeanor.

CLINICAL SIGNS

Dyspnea can result from physical obstruction of the nares and upper airways. Animals with complete nasal passage obstruction breathe through the mouth, whereas patients with upper airway obstruction usually have inspiratory dyspnea. Lower airway or bronchial disease is accompanied by expiratory dyspnea because normal expiratory forces increase pressure on diseased airways. Bronchospasm and decreased luminal size due to excretions results in wheezes. Lung parenchymal disease decreases air-blood interaction resulting in dyspnea with increased ventilatory rate and depth. Gas exchange is affected by thickened alveolar-capillary membrane due to inflammatory or neoplastic cells, edema, hemorrhage, or through capillary shunting of blood through unventilated alveolar capillaries. Another cause of ventilation-perfusion

mismatch is pulmonary thromboembolism (PTE), which can also result in severe dyspnea.

Pleural space expansion causes decreased lung compliance and will result in shallow tachypnea. Dyspnea can result when the capacity of the restricted lungs is further challenged, such as with exercise or stress.

Other diseases can be reflected by the respiratory system. With severe acidosis, the body attempts to restore acid-base balance by exhaling carbon dioxide. This can cause tachypnea, which may be interpreted as dyspnea. Infectious, neoplastic, vascular, or traumatic damage to the central nervous system can result in abnormal rate or rhythm of ventilation, which may be mistaken for pulmonary tachypnea or dyspnea.

PHYSICAL FINDINGS

Physical examination of the dyspneic patient can be quick and efficient but should not be pursued until the patient is stable. Oxygen supplementation using a face mask is suggested but, if not tolerated, the oxygen hose alone may prove to be effective. However, the animal may need to recover from the stress of transport and continued stress of handling may be harmful. In these circumstances the patient should be left undisturbed in an oxygen cage.

Body condition and general appearance should be evaluated. The integument is examined for signs of trauma or tumors. Enlarged peripheral lymph nodes can indicate underlying inflammatory, infectious, or neoplastic disease. The musculoskeletal system may also give clues to the cause of respiratory distress if lameness is due to fungal infection or hypertrophic pulmonary osteoarthropathy, or if it indicates trauma (such as fractures). Cats have a propensity for metastasis of primary bronchogenic carcinoma to the digits.

The cardiovascular system is intimately associated with the respiratory system. The mucous membranes can indicate anemia, shock, or cyanosis. The heart is auscultated to evaluate arrhythmias, murmurs, or decreased intensity. Characterization of peripheral pulses indicate perfusion, pulse pressure, and cardiac arrhythmias. Abdominal palpation can reveal abnormal masses, organomegaly, or ascites, which can cause secondary respiratory problems through metastasis or physical compromise. A complete neurologic and ocular examination may reveal diseases that also affect the respiratory system.

The upper airway consists of the nasal passages, pharynx, larynx, and trachea. External nares can be stenotic from cartilage malformation and unilateral or bilateral discharge could indicate upper airway disease. The nasal cavities may not be patent as a result of obstruction with soft tissue or excessive discharge. *Stertor* describes the snoring noise that is made with partial obstruction of the nasal or nasopharyngeal area. The bridge of the nose and the hard and soft palate are examined for abnormalities that may affect the nasal passage. Masses at the back of the throat cause airway obstruction. Everted laryngeal saccules and elongated soft palate occur in the brachiocephalic complex and result in inspiratory dyspnea. The oropharynx may be visualized but examination of the larynx may require heavy sedation or anesthesia. Laryngeal paralysis can cause dyspnea, especially with exercise, excitement/stress, or hyperthermia. The inspiratory dyspnea resulting from upper airway obstruction causes a harsh, high-pitched sound on inspiration, which is called *stridor* (Figure 54-1). Tracheal collapse may cause coughing and may progress to obstruction. The collapse may be in the cervical or intrathoracic trachea and may also involve mainstem bronchi. The characteristic "goose-honk" cough usually historically precedes complete airway collapse.

The lower respiratory tract is examined by observing breathing patterns, palpation, percussion, and auscultation. Breathing patterns may help localize the problem. The obstructive pattern usually has increased rate and depth. Upper airway obstruction results in difficulty with inspiration and lower airway obstruction causes expiratory difficulty. Mixed patterns of increased inspiratory and expiratory effort can occur. Restrictive breathing pattern implies decreased lung compliance, which results in decreased depth and increased rate such as with pleural effusion.

Palpation of the thorax can reveal masses or trauma such as rib fractures. Young cats have an easily compressible thorax, which can be compromised by mediastinal masses or pleural effusion. Feline bronchitis can obstruct outflow of air from the lower airways resulting in a barrel-chested appearance over time.

Percussion of the thoracic wall can help localize areas of increased or decreased resonance. Pneumothorax results in increased resonance on percussion and decreased lung sounds with auscultation. A fluid line may be percussed with pleural effusion when the animal is standing or in sternal recumbency. Fluid or hernias cause decreased resonance with percussion and muffled heart and lung sounds with auscultation.

Normal respiratory sounds with auscultation are termed *bronchovesicular* and are produced by tissue vibration and air movement. Increased bronchovesicular sounds result from increased air flow or turbulence. Upper airway noises can be referred to the thorax due to the direction of air flow; therefore purring, stertor, and stridor can be ausculted in the chest and must be distinguished as such. Abnormal lower airway sounds are termed *continuous* or *discontinuous*. Continuous sounds include rhonchi and wheezes that result from partial obstruction of airways from bronchoconstriction or secretions. Discontinuous sounds usually occur during inspiration and are referred to as *crackles* or *rales*. These sounds result from the opening of alveoli and small airways that are otherwise collapsed or partially filled with fluid. Absence of respiratory sounds may indicate pleural effusions, pneumothorax, diaphragmatic hernia, or masses.

DIAGNOSTIC AND THERAPEUTIC PLAN

To increase oxygen delivery to the dyspneic patient, either mask, nasal tubing, or oxygen cage can be used. Oxygen concentration of 100% can only be tolerated for a few hours before toxicity develops; therefore long-term therapy is usually limited to 40% oxygen. If the animal is dyspneic, cyanotic, and frantic, sedation is essential. Control of upper airway problems may require general anesthesia and placement of an endotracheal tube, during which any obstruction can be visualized and bypassed. If the problem is identified and not readily resolved, a tracheostomy can be performed as a short- or long-term solution.

If the dyspnea is of a mixed or expiratory pattern, then evaluation for lower airway or parenchymal disease is indicated. Crackles heard with auscultation indicate edema or exudate. Wheezes can indicate lower airway disease. Blood can be obtained from the stable patient to determine blood gases and to evaluate for anemia, thrombocytopenia, coagulopathy, and metabolic or infectious causes of disease. A pulse oximeter reading may provide information on hemoglobin saturation. Radiology is an important diagnostic tool for prioritization of differential diagnoses of parenchymal disease, if it can be done without excessive stress. Diuretics are indicated for pulmonary edema. Cardiogenic edema may need to be initially managed with a diuretic plus a venodilator such as topical nitroglycerin. Bronchodilators are used for lower airway and parenchymal disease to increase airflow. If indicated and the patient is stable, transtracheal wash or bronchoalveolar lavage may provide diagnostic information. Fine needle aspiration of diseased lung parenchyma can also be

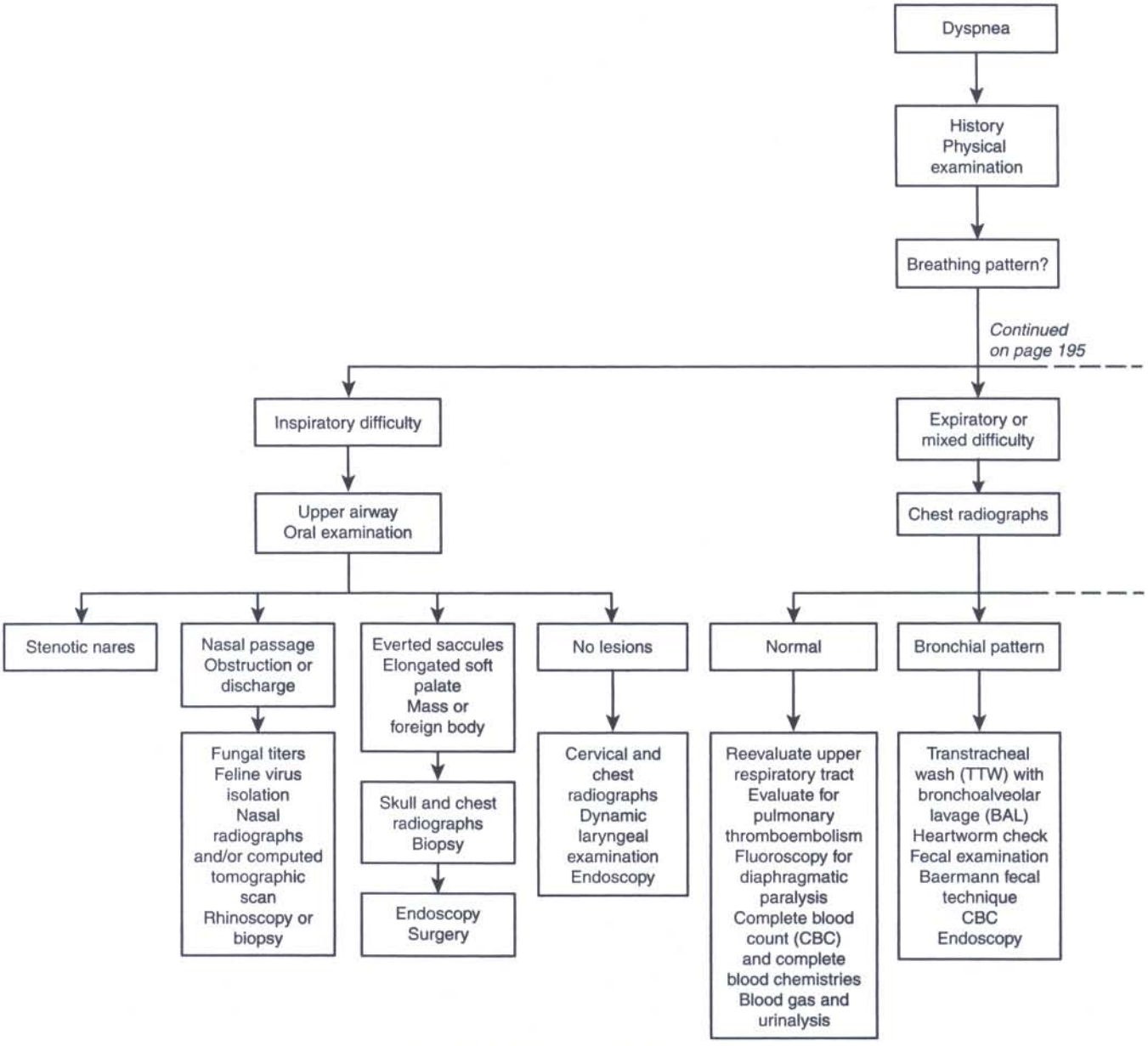


Figure 54-1 Algorithm for inspiratory stridor.

done if inflammatory, infectious, or neoplastic etiologies are suspected. This procedure and complications of FNA are described elsewhere in this text. If an inflammatory process is suspected, corticosteroids are indicated after diagnostic samples are obtained. This may not always be possible with a severely dyspneic animal.

Pulmonary thromboembolism (PTE) patients can be severely dyspneic and have normal radiographs. Definitive diagnosis of PTE involves selective angiography or nuclear medicine scans. Supportive care with efforts directed towards resolution of the underlying disease is the best treatment for PTE. Patients with severe parenchymal disease may benefit from mechanical ventilation, which requires general anesthesia.

Thoracic imaging is useful in identification of problems of the pleural space, but thoracocentesis may be needed first for therapeutic and diagnostic purposes. If air or fluid is obtained, evacuation of the pleural space will resolve the dyspnea and allow radiologic examination for underlying disease. If a diaphragmatic hernia is present, then surgery is necessary for complete resolution.

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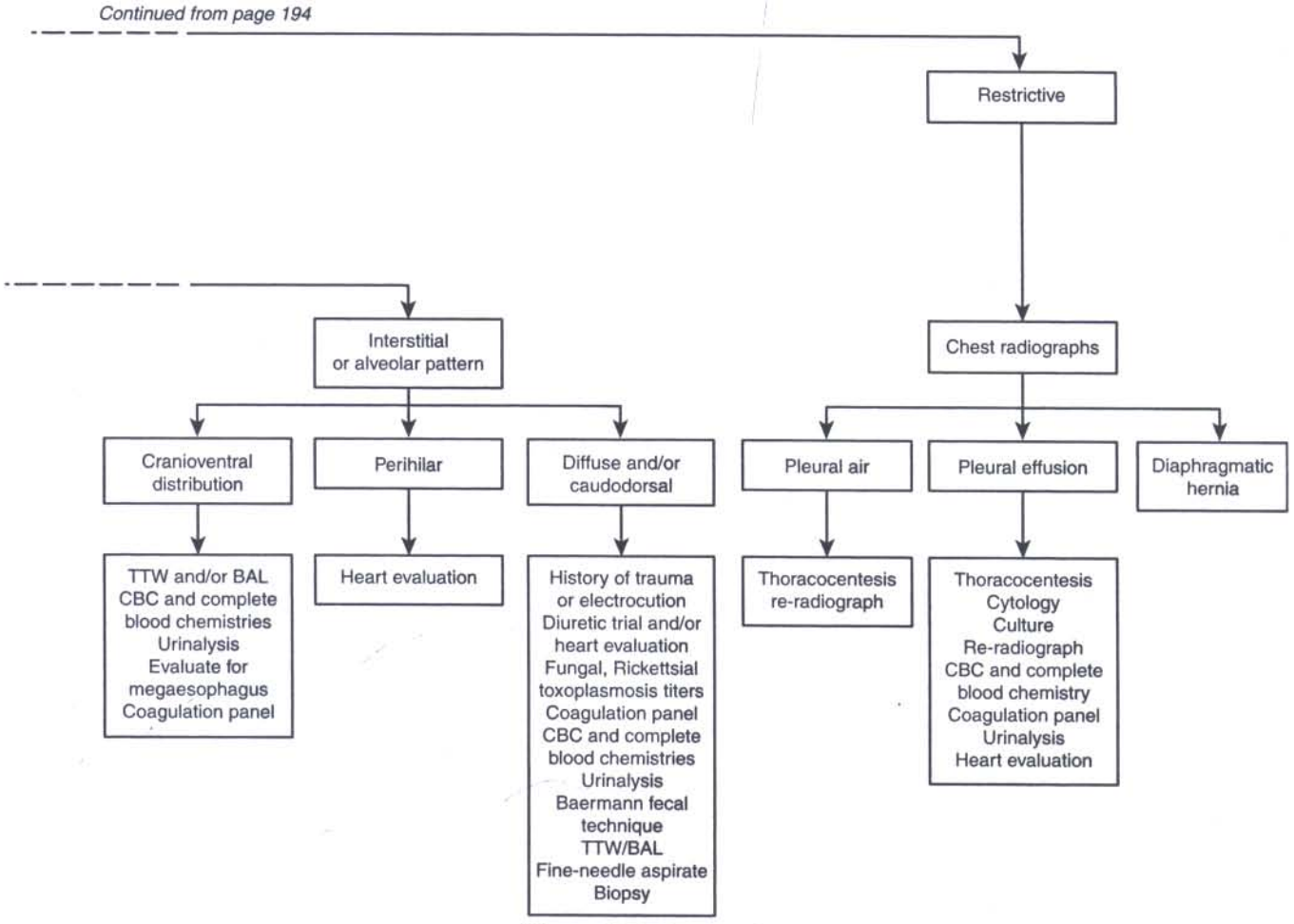

Figure 54-1 Continued.

CHAPTER 55

Abnormal Heart Sounds and Heart Murmurs

Robert Prošek

Cardiac auscultation is an important tool in the clinician's armamentarium. Interpretation of heart and lung sounds is predicated on the clinician's understanding of their genesis in health and a variety of clinical disorders. Cardiovascular sounds of short duration are referred to as *transient heart sounds* and include the normally heard first heart sound (S_1) and second heart sound (S_2). Heart murmurs are auditory vibrations of longer duration created when laminar flow is disrupted.

Implementing good technique with a quality stethoscope is fundamental. During auscultation the animal should be standing or sitting in a quiet environment. Both sides of the thorax should be carefully auscultated with the stethoscope's diaphragm and bell with special attention to the areas overlying the cardiac valves. The clinician should correlate the various heart sounds to the events of the cardiac cycle. A good orientation is the palpation of the precordial impulse (left apex beat) that occurs just after S_1, and the arterial pulse that is felt between S_1 and S_2.

TRANSIENT HEART SOUNDS

The First (S_1) and Second (S_2) Heart Sounds

The first heart sound is associated with closure and tensing of the atrioventricular valves (mitral and tricuspid) at the onset of systole coinciding with the QRS complex on the electrocardiogram. S_1 is longer, louder, and lower pitched than the second heart sound. Causes of increased intensity of S_1 include thin chest wall, tachycardia, high sympathetic tone, systemic

arterial hypertension, and anemia. Diminished intensity of S_1 may be auscultated in animals with obesity, pleural or pericardial effusion, diaphragmatic hernia, dilated cardiomyopathy, hypovolemia, emphysema, or a prolonged P-R interval. Splitting of S_1 is occasionally auscultated at the cardiac apex in healthy, large breed dogs or may result from electrical disturbances (ectopic beats, bundle branch blocks, cardiac pacing) or mechanical factors (tricuspid or mitral stenosis).

The second heart sound is associated with closure of the semilunar valves (aortic and pulmonic) at the end of systole following the T wave on the electrocardiogram. In dogs and cats, pulmonic valve (P_2) closure follows aortic valve (A_2) closure by a very short interval, which causes S_2 to be heard as a single sound. On occasion an audible split second heart sound may be seen in healthy, large breed dogs during inspiration due to a longer right ventricular ejection period. Pathologic splitting of S_2 due to delayed closure of the pulmonic valve is most commonly auscultated in dogs with pulmonary hypertension as occurs with heartworm disease and right-to-left patent ductus arteriosus. Delayed closure of P_2 also occurs with left-to-right intracardiac shunts (atrial septal defects), pulmonic stenosis, right bundle branch block, ectopic beats, and ventricular pacing. Premature A_2 closure can on occasion be noted with mitral insufficiency and mitral stenosis. Paradoxic splitting of S_2 results from delayed closure of the aortic valve and is sometimes audible in dogs with aortic stenosis, left bundle branch block, ectopic beats, and systemic hypertension.

The Third (S_3) and Fourth (S_4) Heart Sounds

The third and fourth heart sounds occur during diastole and are not audible in normal dogs and cats. S_3 and S_4 heart sounds are of lower frequency than S_1 and S_2 and are usually best heard with the bell of the stethoscope. When heard, S_3 or S_4 may sound like the triple cadence of a galloping horse. The term *gallop rhythm* should probably be avoided because the presence of an audible S_3 or S_4 has nothing to do with the heart's underlying electrical rhythm.

Rapid ventricular filling generates the S_3 sound, also known as *S_3 gallop*, *protodiastolic gallop*, or *ventricular gallop*. An audible S_3 is most commonly heard with diastolic volume overloading as in dilated cardiomyopathy, patent ductus arteriosus, and mitral insufficiency. In dogs with mitral insufficiency, the S_3 gallop may be mistaken for the second heart sound if a loud pansystolic murmur extends through the second heart sound. Protodiastolic gallop sounds in cats are most commonly associated with dilated cardiomyopathy, anemia, and hyperthyroidism.

The presystolic gallop, also called *S_4 gallop* or *atrial gallop*, is heard just before S_1 and occurs just after the P wave on the electrocardiogram. This low-frequency sound is generated by blood flow into the ventricles during atrial contraction; hence the absence of S_4 gallops with atrial fibrillation. An audible S_4 in the cat and dog is usually associated with increased ventricular hypertrophy and stiffness and is sometimes audible in animals with third-degree atrioventricular block.

At fast heart rates, rapid ventricular filling and atrial systole transpire very close together, which makes differentiation between S_3 and S_4 impossible. The resulting single accentuated sound is referred to as a *summation gallop*.

Ejection Sounds, Systolic Clicks, Opening Snaps, and Pericardial Knocks

Ejection sounds are left basilar high-frequency sounds generated by opening of the semilunar valves or dilatation of the great vessels during early systole. These sounds are occasionally noted in pulmonic stenosis, aortic stenosis, tetralogy of Fallot, and heartworm disease. Systolic clicks are mid to late high-frequency sounds usually heard best over the mitral valve area. Systolic clicks are occasionally associated with degenerative valvular disease, mitral valve prolapse, and mitral dysplasia. The genesis of the sound in dogs is uncertain but is likely caused by the sudden tensing of redundant valve leaflets or elongated chordae tendineae as they buckle into the left atrium. A systolic click should be differentiated from a split or gallop heart sound. Pericardial knocks are uncommon early diastolic sounds caused by restrictive pericardial disease. Timing of the sound is similar to S_3 and appears to be generated by abrupt restriction to ventricular filling by a diseased pericardium. (See Figure 55-1 for timing of transient heart sounds and description of murmurs.)

CARDIAC MURMURS

Cardiac murmurs represent sounds of longer duration than the transient heart sounds. Cardiac murmurs are caused by turbulent blood flow in the heart or adjacent blood vessels created upon disruption of normal laminar flow. The development of turbulent blood flow can be created by high-velocity flow, flow from narrow restricted area into a larger area, or low blood viscosity. The relationship of cardiac murmurs with flow velocity, vessel size, and blood viscosity is defined by the Reynold's number. When the number reaches a critical high level, blood flow becomes turbulent.

$$\text{Reynold's number} = \frac{(\text{Radius})\ (\text{Velocity})\ (\text{Density})}{\text{Viscosity}}$$

Murmurs can be characterized and described by their timing within the cardiac cycle (systolic, diastolic, portions thereof), location (point of maximal intensity), radiation, intensity (loudness), shape, and frequency (pitch).

Timing

Systolic murmurs may start immediately at the first (S_1) heart sound and last through the second (S_2) heart sound (pansystolic murmur), may start immediately after S_1 and last until S_2 (holosystolic), or may occur in early (protosystolic), mid (mesosystolic), or late (telesystolic) systole. Diastolic murmurs most commonly occur in early diastole (protodiastolic), throughout diastole (holodiastolic), or can occasionally be audible only at the end of diastole (presystolic).

Location and Radiation

The location of a murmur refers to the valve area at which the murmur is heard best (point of maximal intensity). Alternatively, location can be described simply by the terms *apex* or *base* (e.g., left apex or mitral valve area). Some murmurs may also radiate to other areas, yielding important clues as to the source of the murmur. For example, the murmur of subvalvular aortic stenosis (PMI at left heart base) may radiate to the ventral neck area due to turbulence in the carotid arteries and may also be heard on the right cranial thorax.

Intensity (Loudness)

The intensity of the murmur is commonly graded on a 1 to 6 scale, with grade 1 murmur the softest and grade 6 the loudest (Box 55-1). A grade 1 murmur is the faintest murmur and is heard in a quiet environment with particular effort, whereas grade 5 and 6 murmurs are associated with palpable vibrations on the chest wall (palpable thrill). The intensity of the murmur at its origin is determined by blood flow velocity and the rate of flow (velocity × flow = force). The intensity of the murmur at the body surface is affected by direction of the turbulent jet, character of tissue between auscultation area and the turbulent jet, and the frequency of the murmur. Often the intensity of a heart murmur is not directly correlated with the

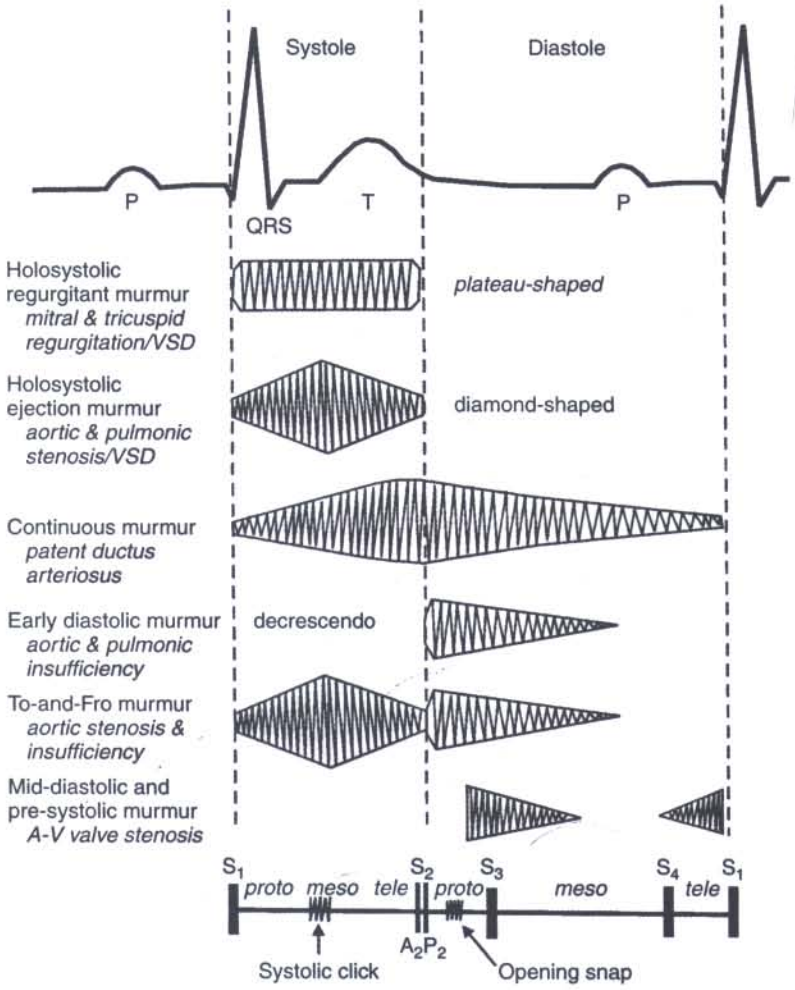

Figure 55-1 Murmur shapes and descriptions with some common examples. Also depicted are normal and abnormal transient heart sounds and their location within the cardiac cycle. *Proto,* Early; *meso,* mid; *tele,* late; A_2, aortic valve closure; P_2, pulmonic valve closure; S_1, first heart sound; S_2, second heart sound; S_3, third heart sound; S_4, fourth heart sound.

severity of a lesion. However, describing the loudness of a murmur is important for serial examinations, and in certain heart diseases at least a rough correlation exists.

Pitch (Frequency)

A murmur's quality and pitch relate to its frequency components, which may be high, medium, low, or of mixed frequency. Most murmurs consist of midrange mixed-frequency sounds. On occasion high-frequency musical tones or low-frequency "honks" are auscultated. Musical murmurs are most commonly identified in dogs with modest mitral valve disease.

Shape

Heart murmurs are often described by their frequency profile within the cardiac cycle in relation to their shape on a phonocardiogram. Terms that are commonly used include *plateau-* or *band-shaped murmurs* for those murmurs of equal intensity throughout their duration; decrescendo for murmurs that gradually taper off from an initial peak; and crescendo decrescendo (diamond-shaped, ejection murmur) for murmurs that build up to a peak intensity and then taper in intensity.

SYSTOLIC HEART MURMURS

Mitral Insufficiency

The murmur of mitral insufficiency is best heard at the left apex (mitral valve area) and commonly radiates dorsally and

Box • 55-1

Grading of Cardiac Murmurs

Grade 1
Very soft, localized murmur detected in a quiet room after intently listening for a few minutes

Grade 2
Soft murmur but easily heard after a few seconds

Grade 3
Moderate intensity murmur

Grade 4
Loud murmur but not accompanied by a palpable thrill (vibration)

Grade 5
Loud murmur accompanied by a palpable thrill

Grade 6
Very loud murmur that produces a palpable thrill still audible after stethoscope is removed from the chest

to the right thorax making reliable diagnosis of tricuspid regurgitation difficult. The characteristic murmur is plateau (band-shaped) and holosystolic; however, in its early stages the murmur may be protosystolic and with mitral valve prolapse the murmur may develop in mid- to late-systole. Mitral insufficiency murmur is typically of mixed frequency and harsh sounding, but it may be high-pitched or musical (whooping) in quality. Mitral insufficiency can be caused by chronic degenerative valvular disease (endocardiosis), endocarditis, hypertrophic obstructive cardiomyopathy, congenital malformations, and diseases that cause left heart enlargement and dilation of the mitral annulus (e.g., patent ductus arteriosus, dilated cardiomyopathy).

Tricuspid Insufficiency

The murmur of tricuspid insufficiency sounds similar to that of mitral insufficiency but is loudest over the right apex (tricuspid valve area). It is often difficult to distinguish tricuspid insufficiency from a radiating murmur of mitral insufficiency. Tricuspid murmurs might be a different pitch compared with a radiating mitral murmur and can be accompanied by jugular pulsations. Tricuspid insufficiency can result from congenital malformations of the valve, chronic degenerative valve disease, or any disorders that cause marked right heart enlargement and valve annulus distention, such as pulmonary hypertension, and arrhythmogenic right ventricular cardiomyopathy). Tricuspid valve endocarditis is extremely rare in dogs and cats.

Aortic Stenosis

Valvular and subvalvular aortic stenosis (SAS) produce a systolic ejection (crescendo-decrescendo) murmur that is usually best heard at the left heart base. The murmur is usually of mixed frequency and harsh, and it sometimes radiates towards the right cranial thorax and up the neck along the carotid arteries. Mild obstructions cause soft murmurs that are difficult to distinguish from innocent or functional murmurs. Murmurs that vary dramatically in intensity with exercise or excitement should prompt consideration of a dynamic left ventricular outflow tract obstruction. Dynamic outflow tract obstruction is the most common type of ejection murmurs in cats with hypertrophic cardiomyopathy and its onset and duration coincide with systolic anterior motion of the mitral valve. Dynamic left ventricular outflow tract obstruction occurs uncommonly in dogs as an isolated abnormality or in association with mitral valve dysplasia or hypertrophy of interventricular septum.

Pulmonic Stenosis

Pulmonic stenosis murmur is typically a high-frequency crescendo-decrescendo (ejection) holosystolic murmur, best heard at the left heart base over the pulmonic valve. The murmur can be very similar to aortic stenosis murmur described above but should not radiate along the carotid arteries. As the pressure gradient between the right ventricle and pulmonary artery increases, the murmur intensity becomes louder and peaks later in systole.

Ventricular Septal Defect

Ventricular septal defects (VSDs) produce murmurs that vary tremendously in shape and quality. Most often the murmur is a harsh, mid- to high-frequency holosystolic murmur best heard on the right cranial thorax. Murmur intensity may be reduced when the VSD is large and as pulmonary hypertension develops. With severe pulmonary hypertension, the murmur may be entirely absent and splitting of the second heart sound is noted.

Atrial Septal Defect

Heart murmurs in dogs and cats with an atrial septal defect (ASD) result from increased flow across the pulmonic valve as a result of the left to right shunting. This murmur resembles that of mild pulmonic stenosis but is often accompanied by a fixed splitting of the second heart sound. Flow across the atrial septal defect is usually not audible.

Physiologic and Innocent Murmurs

Functional (physiologic) murmurs are usually caused by decreased blood viscosity or increased cardiac output. Physiologic murmurs are most often noted in animals with anemia, fever, pregnancy, hyperthyroidism, and increased sympathetic tone. These murmurs usually are proto to mesosystolic, soft to moderate intensity (grade 1/6 to 3/6), and loudest at the left heart base. They tend not to radiate extensively.

Innocent murmurs should disappear as the dog matures and appear to be the result of larger stroke volumes in puppies for the size of their great vessels in comparison with adult dogs. In some cats, turbulent blood flow can be noted in the region of the right ventricular outflow tract, often causing a soft systolic apical sternal murmur ranging in grades from 1 to 3/6, with no evidence of structural heart disease and little clinical consequence.

DIASTOLIC HEART MURMURS

Aortic Insufficiency

The murmur of isolated aortic insufficiency is typically a decrescendo murmur starting at the time of S_2 and extending variably into diastole. In young dogs, aortic insufficiency can occur as an isolated defect or in combination with subaortic stenosis or a ventricular septal defect. Detection of aortic insufficiency in an adult dog or cat should prompt consideration of bacterial endocarditis.

When the regurgitant volume is large, the diastolic murmur is often accompanied by a soft mesosystolic ejection murmur, creating a distinct *"to-and-fro"* murmur. The systolic ejection component tapers off in late systole and allows recognition of S_2 and differentiation from a continuous murmur. Other causes of "to-and-fro" murmurs include ventricular septal defects that cause loss of aortic root support and pulmonic valve stenosis and significant pulmonic insufficiency (rare). Occasionally massive aortic regurgitation causes premature closure of the mitral valve producing functional mitral stenosis and a diastolic murmur referred to as an *Austin Flint murmur.*

Pulmonic Insufficiency

The murmur of pulmonic insufficiency is similar to that of aortic insufficiency; however, clinically significant pulmonic insufficiency is uncommon. It is sometimes detected in animals with pulmonary hypertension, pulmonic valve dysplasia, or idiopathic dilation of the pulmonary artery.

Mitral Stenosis

The diastolic murmur of mitral stenosis is difficult to recognize in dogs and cats. This low-frequency murmur begins in mesodiastole and has presystolic accentuation due to atrial contraction. Mitral stenosis might be accompanied by other cardiac malformations, which causes murmurs such as valvular or subvalvular aortic stenosis. In dogs, mitral stenosis may be more common in breeds that are prone to congenital mitral valve malformations such as the bull terrier breed, in which it is often associated with aortic stenosis.

CONTINUOUS MURMURS

The most common cause of a continuous murmur at the left heart base is patent ductus arteriosus (PDA). This classic "machinery-like" murmur of a PDA is usually audible

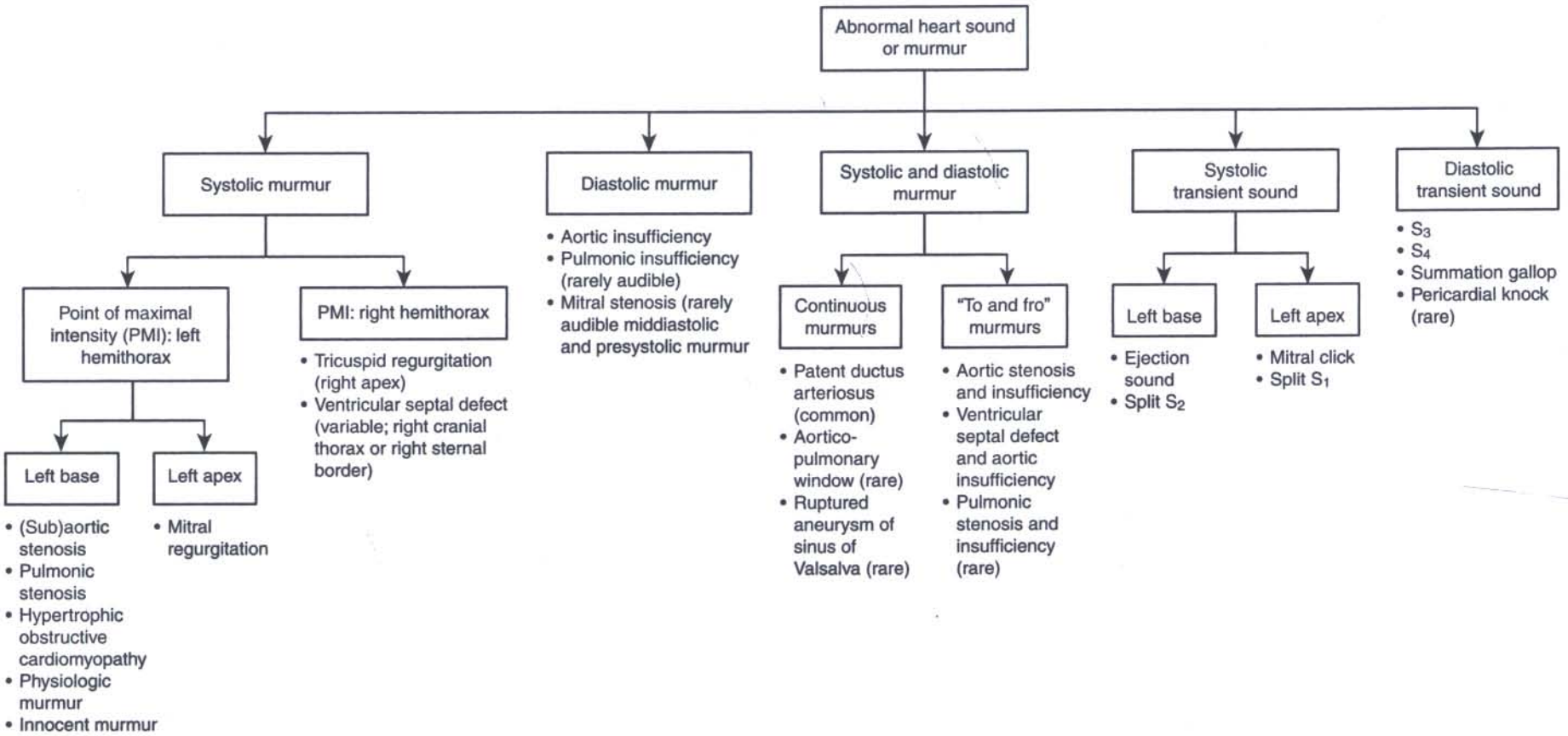

Figure 55-2 Algorithm for differentiating causes of abnormal heart sounds and murmurs. *PMI*, Point of maximal intensity; *PDA*, patent ductus arteriosus; *AP*, aorticopulmonary.

throughout the cardiac cycle with peak intensity near S_2. The intensity of the murmur is diminished in late diastole in dogs with very slow heart rates and the diastolic component can also disappear with the development of pulmonary hypertension. Less common causes of continuous murmurs include aorticopulmonary windows, ruptured aneurysms of sinus of Valsalva, and coronary arteriovenous fistulas.

AUSCULTATION AND BEYOND

Historical findings may suggest underlying heart disease; however, a thorough auscultation with identification and understanding of abnormal heart sounds and their genesis will permit recognition of the most likely cause (see Figure 55-2). As important a tool as cardiac auscultation is, it should be one part of a complete physical exam that integrates evaluation of lung fields, jugular veins, arterial pulses, and peripheral circulation. Increasingly the affordability and availability of next generation electronic stethoscopes will allow the clinician to pick up difficult-to-hear heart sounds and other body sounds.

Additionally, other diagnostic tests might be needed to further classify and define the animal's abnormality, and in some cases differentiate a pathologic from a physiologic murmur (especially cats).

CHAPTER 56

Pulse Alterations

Richard Kienle

Assessment of arterial and venous pulse characteristics is an integral component of the physical examination. However, the findings from these exams should not be used in isolation but integrated with findings from other exams and diagnostic tests. Arterial pulse qualities (rate, rhythm, symmetry, and strength) provide important information regarding the status of the cardiovascular system, specifically cardiac output and perfusion. Evaluation of venous pulse qualities (distention or pulsation) provides insight regarding right-sided cardiac pressures and the status of venous return. Abnormalities of arterial and/or venous pulse characteristics may be present in any cardiovascular disease state and may also be present in other systemic and metabolic states that affect cardiac output and systemic pressure or venous return. Detection of these changes often facilitates selection of additional diagnostics and allows for monitoring of patient status and response to therapy. The clinician should be familiar with the common abnormalities detected and their significance (Figure 56-1).

THE ARTERIAL PULSE

Genesis of the Arterial Pulse

Systolic arterial blood flow and pressure are generated by the contractile force of the left ventricle and to a lesser extent by elastic recoil of the aorta. During systole, aortic pressure rises rapidly as left ventricular pressure exceeds aortic pressure and ventricular ejection begins. Later in systole, as ventricular pressure declines and the blood flows into the distal vasculature, aortic pressure decreases. During ventricular diastole, when left ventricular pressure drops below aortic pressure and the aortic valve closes, diastolic blood pressure is maintained by elastic recoil of the aorta. Diastolic blood pressure gradually decreases as elastic recoil is consumed and blood continues to flow distally.

Assessment of the Arterial Pulse

The femoral pulse should be evaluated carefully in every patient (Figure 56-2). This evaluation is performed preferably with the patient standing but may also be done in recumbent patients. The femoral arteries should be palpated high on the limb so that the artery is palpated within or just below the femoral triangle, where the least amount of fat and muscle overlie the artery. The index finger, the middle finger, or both should be placed over the artery lightly to start. Digital pressure should then be applied with sufficient strength to occlude arterial flow so that no pulsation directly beneath the fingers is identified. Digital pressure should then be gradually decreased until the maximum pulsation is felt. The maximum pulsation occurs when digital pressure is equal to mean arterial blood pressure.

The intensity of the peripheral arterial pulse is determined by the difference between the systolic blood pressure and the diastolic blood pressure, termed the *pulse pressure*. Consequently, absolute blood pressure cannot be determined by digital palpation of artery. In addition to pulse pressure, body condition affects the perceived strength of the arterial pulse. Arterial pulses are usually more prominent in thin animals, whereas they may be difficult to palpate in obese animals. The clinician should take into account the animal's body condition when pulse strength is assessed.

Arterial Pulse Alterations

Pulse pressure can be decreased or increased or it can have an altered configuration (see Figure 56-1). Three physiologic factors are important in determining arterial pulse pressure: (1) heart rate, (2) stroke volume, and (3) peripheral vascular resistance. An increase in heart rate may result in a mild increase in diastolic arterial pressure, as there is less time for diastolic pressure to decline. This will result in a decrease in pulse pressure and an increase in mean arterial pressure generally leading to what is perceived as a weak peripheral pulse. Bradycardias, on the other hand, may lead to excessive run off during diastole as well as a greater strength of contraction due to greater diastolic filling, leading to a stronger than normal pulse.

A decrease in pulse pressure can occur if stroke volume is decreased, as in patients with heart failure or hypovolemia.

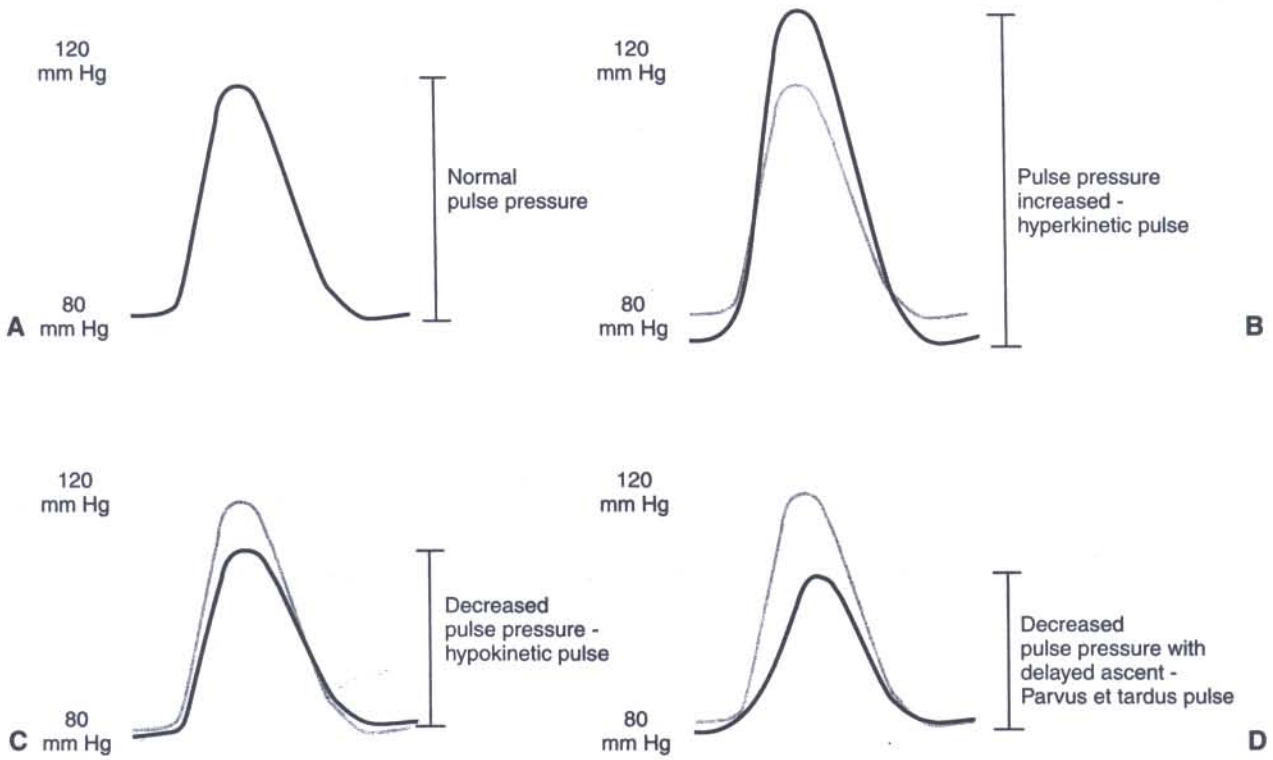

Figure 56-1 Schematic illustration of femoral artery pulse contours. **A,** Normal pulse. There is a rapid rise in pressure followed by a more gradual descent to diastolic pressure. The pulse pressure is indicated by the bar. **B,** Hyperkinetic pulse. Elevation in systolic pressure and decrease in diastolic pressure have widened the pulse pressure, resulting in a strong or hyperkinetic pulse. **C,** Hypokinetic pulse. Pulse pressure is reduced because of decreased systolic pressure. **D,** Parvus et tardus pulse. This is a type of hypokinetic pulse characterized by a slow ascent and is typical for subaortic stenosis.

This is termed a *hypokinetic* pulse. In most patients with a decreased stroke volume, arterial resistance increases and arterial compliance decreases to keep systemic blood pressure within the normal range. Patients with a decreased stroke volume commonly have normal pulses until the stroke volume becomes markedly reduced.

Pulse pressure may also decrease if peripheral vascular resistance (PVR) is decreased or if arterial compliance is increased. Peripheral vascular resistance is a function of vessel tone and arterial wall compliance. When PVR is increased, there is an increase in diastolic blood pressure and a corresponding decrease in pulse pressure. PVR is increased in older animals as a result of loss of arterial wall compliance and in some animals with heart failure.

An increase in pulse pressure, known as a *hyperkinetic* pulse, can occur because of an increase in systolic blood pressure, a decrease in diastolic blood pressure, or both. In cardiovascular disease, an increase in systolic blood pressure is usually caused by an increase in stroke volume. A decrease in diastolic blood pressure is usually due to excessive runoff of blood into some other portion of the cardiovascular system during diastole. Consequently, dogs with shunting lesions such as a patent ductus arteriousus or dogs with aortic insufficiency commonly have a significant increase in pulse pressure, leading to a "bounding" pulse. Bounding pulses can also be felt in patients with arteriovenous fistula, severe bradycardia, thyrotoxicosis, fever, and anemia.

Alterations in pulse conformation may also occur. Dogs with severe subaortic stenosis may have a "weak" pulse or may have a pulse pressure that increases more slowly and peaks later during systole (pulsus parvus et tardus) (see Figure 56-1). This occurs because the velocity of shortening and the ejection time may be longer in severe subaortic stenosis. Dogs with mitral regurgitation, conversely, commonly have a brisk pulse that rises more rapidly in systole and lasts a shorter time because the left ventricle ejects blood at a higher velocity and the ejection time is shorter.

Other pulse abnormalities include pulsus paradoxus, pulse deficits, and pulsus alternans. Pulsus paradoxus is an increase in pulse pressure on expiration and a decrease on inspiration. This occurs normally but is exaggerated in pericardial tamponade. Pulse deficits occur with cardiac tachyarrhythmias in which beats occur so rapidly that the ventricle does not have time to fill enough to result in ejection of blood. Pulsus alternans is alternating strong and weak pulses and is rare. In patients with atrial fibrillation, pulse pressure alternates erratically and pulse deficits are also present.

Systemic thromboembolism, a complication of feline cardiomyopathy, is often characterized by a complete loss of arterial pulsations of the femoral arteries. Systemic thromboembolism may also occur in dogs and cats secondary to hypercoagulable sates such as renal amyloidosis, hyperadrenocorticism, and infective endocarditis.

VENOUS PULSES

Jugular venous pressures correlate with right atrial and ventricular pressures. Because the tricuspid valve is open in diastole and because the tricuspid valve annulus provides very

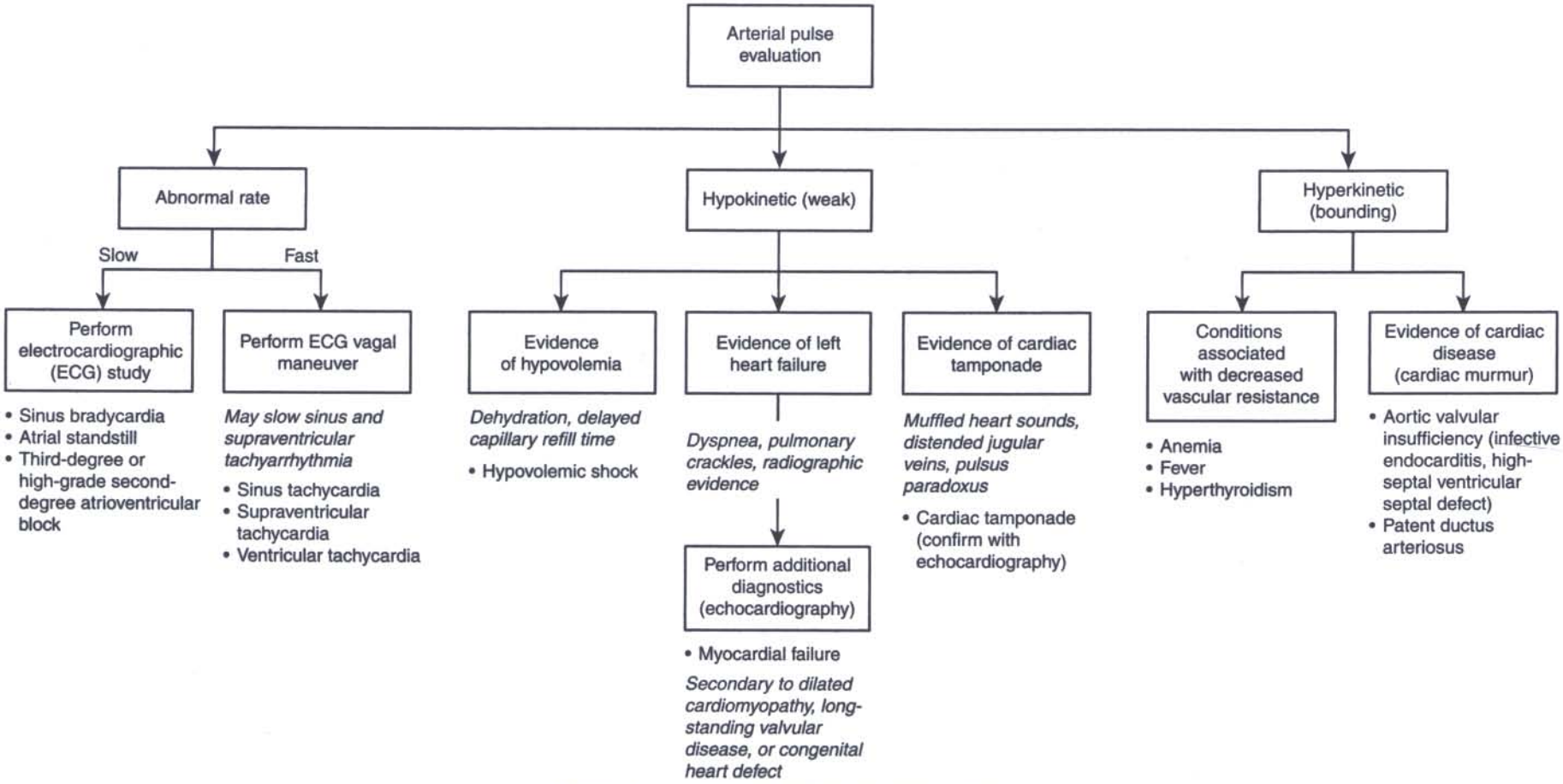

Figure 56-2 Algorithm for arterial pulse evaluation.

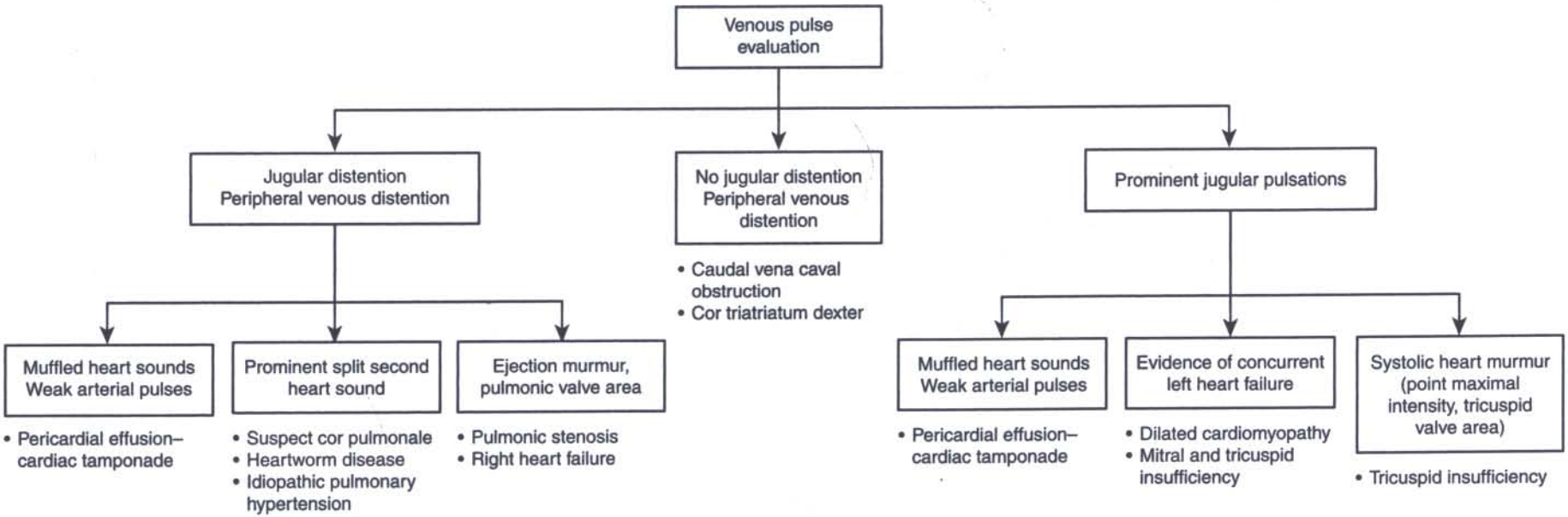

Figure 56-3 Algorithm for venous pulse evaluation.

little resistance, right ventricular diastolic pressure and right atrial pressures are approximately equal. Whatever pressure is present in the right atrium is also present in the systemic veins that are at the same height as the right atrium. The pressure in the vessels higher than the RA will have lesser pressure and the veins will be less distended. Because of this, as right atrial pressure increases, the jugular veins become distended farther and farther up the neck.

Components of the Normal Venous Pulse

When jugular waveforms are analyzed, several components can be detected. The most prominent deflection is the A wave corresponding to right atrial contraction. During right atrial relaxation, a slight dip in pressure is noted (Z point). Immediately following the Z point, a second wave (C wave) corresponding to right ventricular isovolumetric contraction occurs. This wave is produced by bulging of the tricuspid valve into the right atrium and transmission of this pressure into the jugular veins. During right ventricular ejection, the tricuspid valve is displaced downward producing a prominent negative deflection, the X descent. Late in systole, a third positive deflection, the V wave, occurs resulting from increased blood volume and pressure within the right atrium. Immediately following the V wave, right atrial emptying occurs as a result of relaxation of the right ventricle producing a second prominent dip in jugular venous pressure, the Y descent.

Assessment of the Venous (Jugular) Pulse

The jugular veins should be examined carefully in any case suspected of having cardiac disease (Figure 56-3). Neck hair may need to be clipped or wetted to identify the jugular veins in dogs and cats with thick or long neck hair (see Figure 56-3). A jugular vein should be initially identified with the animal in a sitting or standing position with the head moderately extended. In a normal animal the vein should be distended by placement of enough pressure at the thoracic inlet to occlude jugular vein flow, which results in jugular vein distension. Thoracic inlet pressure should then be released and the vein observed to determine the rate of vein collapse. In normal animals, jugular pulsations should not extend more than one third the distance up the neck from the thoracic inlet. Pulsations from the underlying carotid arteries may mimic jugular venous pulsations. If pulsations continue despite occlusion of jugular vein, they are arterial in origin. In an animal with cardiac disease, the vein may be distended or pulsating, in which case the vein should be observed without occlusion. More subtle jugular vein alterations may be detected by performing the hepatojugular or abdominojugular reflux test. This test is performed by application of sustained pressure to the abdomen with one or both hands for 30 to 60 seconds during observation of the jugular veins. This technique results in increased venous return (increased right ventricular preload), which in the presence of underlying right heart disease will elevate right atrial pressure and impede jugular venous return, which leads to distention or pulsation of the jugular veins. This technique is generally accepted as a test for detecting right heart failure. Most likely this test is an indication of increased blood volume in the peripheral venous system and can be positive with either left or right heart failure.

VENOUS (JUGULAR) PULSE ALTERATIONS

Distended jugular veins indicate increased systemic venous pressure or occlusion of the venous system between the jugular veins and the right heart. An increase in systemic venous pressure is most commonly secondary to an increase in right ventricular diastolic pressure.

Jugular vein pulsation may also be observed. Jugular vein pulsation may be due to exaggerated "a" waves, cannon "a" waves, or prominent "v" waves. Exaggerated "a" waves may occur secondary to decreased right ventricular compliance. A decrease in right ventricular compliance may occur with such conditions as right ventricular hypertrophy, restrictive right ventricular disease, and constrictive pericarditis. The deceased right ventricular compliance must be severe to result in jugular vein pulsations and a severe decrease in right ventricular compliance generally results in an overall increase in right ventricular diastolic pressure with resultant jugular vein distension. Cannon "a" waves may occur with A-V dissociation when the atria contract against a closed tricuspid valve, as in third degree A-V block. Prominent "v" waves occur secondary to tricuspid regurgitation. The "v" wave occurs during ventricular systole and is increased in tricuspid regurgitation when the atrial volume is increased by the regurgitation of blood into the right atrium. Patients with overt right heart failure from any cause may have obviously distended jugular veins.

CHAPTER 57

Pleural Effusion

O. Lynne Nelson

DEFINITION OF PLEURAL EFFUSION

The pleura surround the lung lobes (visceral pleura) and line the thoracic cavity (parietal pleura). Normally, the pleural space contains 3 to 5 mL of a low-protein fluid that lubricates the pulmonary tissue for respiratory motion. Normal pleural fluid is in a constant state of flux much like fluid flow across capillary membranes. The same Starling forces that determine fluid movement across capillary walls are responsible for fluid movement in and out of the pleural space. Abnormal accumulations of pleural fluid may occur due to increased capillary hydrostatic pressure or permeability, decreased intravascular oncotic pressure, or impaired lymphatic drainage. The mediastinum of the dog and cat is fenestrated or incomplete, therefore pleural effusions are usually bilateral. Pleural effusion is typically a secondary phenomenon; therefore recognition of

pleural effusion is not analogous to diagnosis of a dog or cat's underlying condition. A thorough investigation should reveal the primary disease (Figure 57-1).

CLINICAL SIGNS OF PLEURAL EFFUSION

Clinical signs associated with pleural effusion are most often related to the respiratory system. Severity of signs is determined by the amount of the effusion and how quickly the effusion developed. The respiratory pattern caused by pleural effusion results from the interference of normal lung expansion. This observed pattern of ventilation is often called *restrictive respiration*. The respiratory effort is characterized by a labored inspiratory phase, often with a pronounced abdominal component, and an easy expiratory phase. The increased inspiratory effort associated with pleural effusion can be difficult to differentiate from the inspiratory effort of airway disease by observation alone. As a general rule, dogs and cats with pleural effusion will have decreased lung sounds, particularly ventrally, on thoracic auscultation. The presence of a fluid line may be determined by auscultation of a definitive point on the chest wall, where respiratory sounds shift from muffled to normal or slightly increased. By contrast, dogs and cats with airway disease often have abnormal inspiratory airway sounds such as crackles and wheezes. Most animals with significant pleural effusion are tachypneic as a compensatory measure

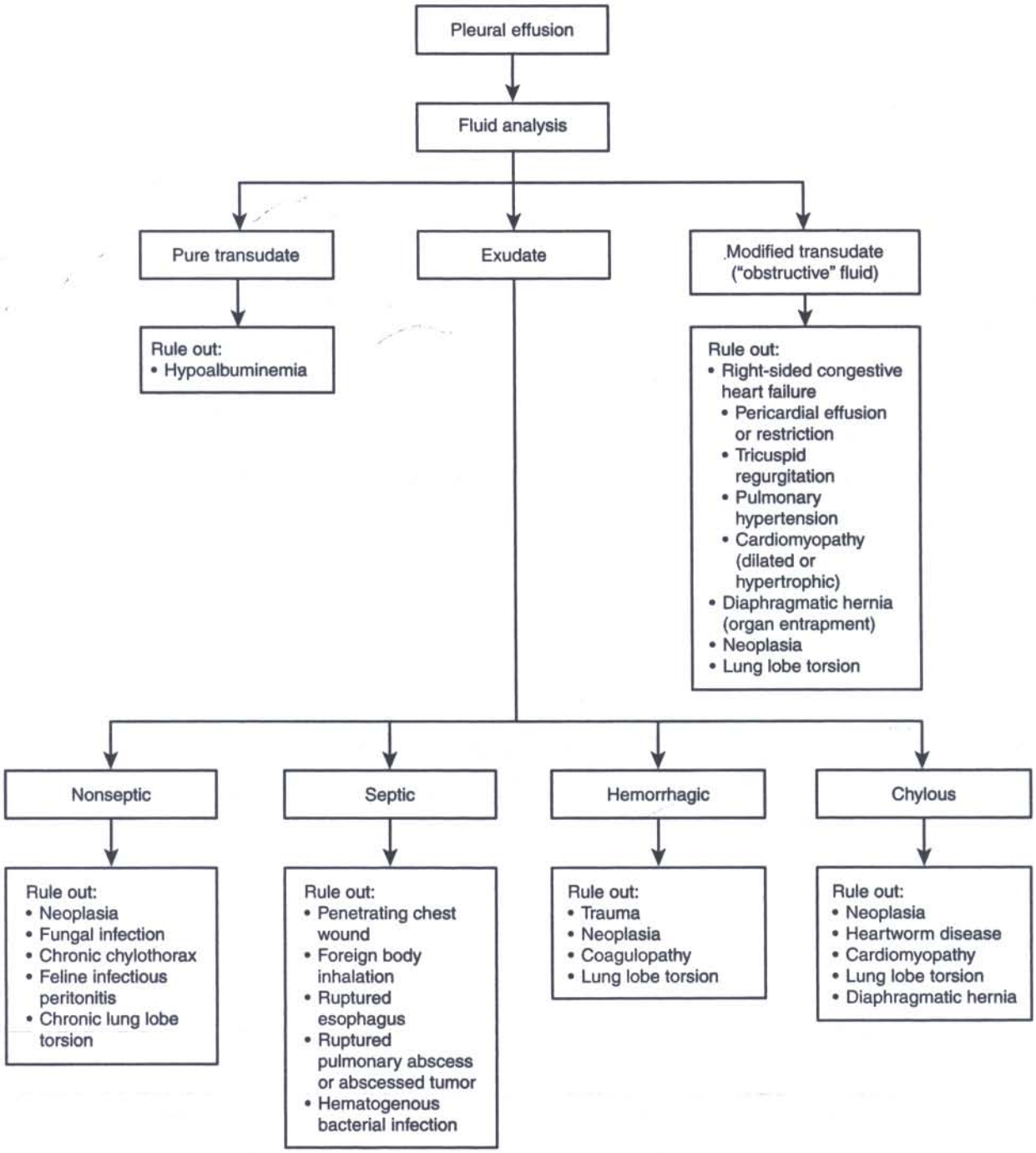

Figure 57-1 Algorithm of differential diagnosis of pleural effusion.

because total lung capacity is reduced (secondary to reduced inspiratory capacity). Coughing is occasionally noted.

DIAGNOSTIC EVALUATION OF PLEURAL EFFUSION

A thorough physical examination often provides clues to the underlying cause of pleural effusion. For example, the presence of uveitis may alert the clinician to possible systemic inflammatory conditions such as viral disease (e.g., feline infectious peritonitis), rickettsial disease, fungal infection, or sepsis or systemic neoplasia (e.g., lymphosarcoma). Lymphadenopathy may suggest systemic inflammatory process or lymphosarcoma. Jugular distension and pulsation suggests increased right heart filling pressures that may be associated with cardiomyopathy, pericardial effusion, tricuspid regurgitation, pulmonic stenosis, or any of the many causes of pulmonary hypertension (e.g., heartworm disease, thromboembolic disease). Jugular distension without pulsation is more likely to be associated with occlusion of right heart inflow, due to mediastinal masses or severely increased intrapericardial pressues. Many cats with large mediastinal masses will have decreased compressibility of the anterior thorax. A thorough palpation of the skeleton and the abdomen may uncover masses or painful regions associated with inflammatory disease.

Dogs and cats with severe respiratory distress from pleural effusion may be quite fragile. Unnecessary handling should be avoided until the animal is sufficiently stable. In these cases, oxygen therapy may be provided and thoracocentesis should be performed before additional diagnostics are planned. Although thoracocentesis is invasive, the potential therapeutic benefit far outweighs the small chance of complications. Patients that present in stable condition may have chest radiographs taken to confirm presence of pleural effusion before thoracocentesis.

Thoracic radiography can confirm pleural effusion and often identifies the underlying cause (i.e., cardiac disease, mediastinal mass). In many cases, critical evaluation of the chest cannot be performed because the fluid silhouettes with the normal thoracic structures, which obscures their borders. Repeating chest radiographs after thoracocentesis may aid in identification of thoracic pathology.

Fifty to 100 milliliters of fluid must be present for pleural effusion to be recognized radiographically. A minute amount of effusion may be detected as pleural fissure lines on the radiograph. These radio-opaque lines arc from the periphery toward the hilar region and outline individual lung margins. As effusions progress, lung lobes retract from the chest wall and lung borders become rounded. With large volumes of effusion, the lungs appear to float on the fluid line and the trachea is displaced dorsally, which mimics cardiomegaly or cranial mediastinal mass. The fluid often obscures cardiac margins interfering with cardiac size interpretation. The cardiac silhouette may not be visualized at all on the dorsoventral radiograph. Lung lobes may appear abnormally dense due to incomplete expansion, collapse, or lung lobe torsion. Pockets of fluid accumulation or unilateral effusions should alert the clinician to the possibility of inflammatory lesions and pleural adhesions.

Analysis of the pleural fluid obtained by thoracocentesis provides important clues in determination of the cause. The thoracocentesis technique is described in detail elsewhere in this text. Samples should be placed into anticoagulant tubes (EDTA) for cell counts, clot tubes for possible biochemical analysis, and culture devices in the event septic processes are identified by cytologic evaluation. Measurement of protein concentration, a total cell count, and cytologic analysis may reveal a specific diagnosis or at minimum, assist in formulating a diagnostic plan. Pleural effusions can generally be categorized as transudates and modified transudates; septic and nonseptic exudates; or chylous, hemorrhagic, or neoplastic effusions.

TRANSUDATES AND MODIFIED TRANSUDATES

Pure transudates are fluids characterized by low protein concentration (less than 3 gm/dl) and low nucleated cell counts (less than 1000/μl). Macrophages, lymphocytes, and mesothelial cells are the primary cell types. Modified transudates have slightly higher protein concentration of up to 3.5 gm/dL and cell counts of up to 5000/μl. In addition to the above cell types, neutrophils are a common finding. Pure transudates are classically transparent, whereas modified transudates may have very slight turbidity.

The most common cause of a pure transudate is decreased oncotic pressure from hypoalbuminemia. The finding of a pure transudate should alert the clinician to assess serum albumin concentration and to screen for underlying causes of hypoalbuminemia (impaired hepatic production, or albumin loss via gastrointestinal or renal lesions). Occasionally, pleural effusions of hypoalbuminemia will be modified transudates in long-standing cases.

The most common cause of modified transudates is increased hydrostatic pressure of the vascular system or lymphatics. Pleural effusion due to increased intravascular hydrostatic pressure is typically referred to as *right-sided congestive heart failure*. Cardiomyopathy (dilated and hypertrophic), severe tricuspid regurgitation, pulmonary hypertension, and pericardial effusion or restriction are some common examples of diseases that may result in right heart failure. Pleural effusion from lymphatic obstruction can be caused by neoplasia or strangulation of intrathoracic tissue such as with diaphragmatic hernia or lung lobe torsion.

SEPTIC AND NONSEPTIC EXUDATES

Exudates are usually the result of inflammation and increased vascular permeability. Exudates have a higher protein content and cell count than transudates. Protein concentrations are classically greater than 3 gm/dL and cell counts are greater than 5000/μl. These fluids appear turbid as a result of the higher cellular content. The cell types are similar for septic and nonseptic exudates (neutrophils, macrophages, eosinophils, lymphocytes), but septic processes usually have extremely high nucleated cell counts, that is, greater than 50,000/μl. In septic exudates, degenerate neutrophils predominate and bacteria can also be observed within the neutrophils or free fluid. However, the absence of bacteria does not rule out an infectious process and all exudative fluids should be submitted for gram stain and aerobic/anaerobic culture. Prior antibiotic therapy can alter the cellular concentration of the pleural fluid and diminish bacterial numbers; therefore cytology (and culture) should ideally be performed prior to initiation of treatment. In some cases the septic exudates will have a foul odor. Septic pleural effusions are also called *pyothorax*. Penetrating chest wounds, penetrating esophageal or airway lesions, migrating foreign material such as grass awns, and extension of bacterial pneumonia are relatively common causes of pyothorax in the dog and cat.

Nonseptic exudates may be difficult to differentiate from septic processes. The cell count is usually lower for nonseptic effusions. Although macrophages and lymphocytes may appear activated, neutrophils are typically nondegenerate. As stated earlier, the absence of obvious bacteria in fluid does not guarantee a nonseptic process. Culture and sensitivity testing should be performed. Differential diagnoses for patients with nonseptic exudates include neoplasia, resolving sepsis, chronic diaphragmatic hernia and lung lobe torsion, fungal infection, feline infectious peritonitis, and long-standing chylothorax.

HEMORRHAGIC EFFUSIONS

Hemorrhagic effusions are grossly red with red blood cells and may appear similar to frank blood. A packed cell volume (PCV) should be determined on the fluid and compared with a peripheral blood sample. PCV of similar values suggest active bleeding into the chest cavity, whereas effusions with lower PCV than the peripheral blood suggest other factors are responsible for the bloody effusion. Hemorrhagic effusions due to active inflammatory causes often have increased numbers of neutrophils and macophages compared with the peripheral blood sample, and erythorphagocytosis is commonly present. Hemorrhagic effusions may result from trauma, neoplasia, lung lobe torsion, and systemic coagulopathies such as rodenticide ingestion.

CHYLOUS EFFUSIONS

Chylous pleural effusion (chylothorax) results from leakage of material from the thoracic duct. These effusions may occur from increased lymphatic hydrostatic pressure or obstruction. Common causes include cardiac disease, pericardial disease, dirofilariasis and pulmonary hypertension, lung lobe torsion, diaphragmatic hernia, neoplasia, and trauma. Idiopathic cases of chylothorax are suspected to be secondary congenital or acquired defects of the thoracic duct.

Chylous effusion is usually milky white due to the presence of chylomicrons, but it may be clear if the animal has fasted. Occasionally, the effusions are blood-tinged and resemble tomato soup. These fluids must be differentiated from exudative processes, as protein concentration and cell counts are similar. The predominant cell type in chylous effusion is the mature lymphocyte. With chronic effusions, increasing numbers of nondegenerate neutrophils and macrophages may be seen. A definitive diagnosis of chylothorax may also be made by comparing the triglyceride content of the effusion to that of serum. The triglyceride content of chyle is classically greater. Occasionally, this test may need to be repeated if an animal has been anorectic.

NEOPLASTIC EFFUSIONS

Thoracic neoplasia can cause any type of pleural effusion with the possible exception of pure transudates. Neoplastic cells may or may not exfoliate into the effusion for cytologic identification. Repeat thoracic radiography after thoracocentesis (particularly with mediastinal neoplasia), thoracic ultrasonography or computed tomography may uncover masses, but definitive diagnosis requires fine needle aspiration or biopsy.

TREATMENT AND PROGNOSIS OF PLEURAL EFFUSION

Recognition of pleural effusion is not analogous to diagnosis of the patient's underlying condition. A thorough investigation should reveal the primary disease process. Initial treatment for patients with respiratory distress from pleural effusion is thoracocentesis. Thoracocentesis provides therapeutic as well as diagnostic benefit. The prognosis for pleural effusion is directly related to the underlying condition.

CHAPTER 58

Sneezing and Nasal Discharge

Kirsten Cooke

Sneezing and nasal discharge are common problems in companion animals. Nasal discharge may result from nasal or paranasal (sinus) disorders or from systemic disease (Box 58-1). Sneezing and reverse sneezing localize the problem to the nasal cavity or nasopharynx. Although increased frequency of sneezing is often readily apparent, many owners may not notice nasal discharge immediately because most animals clear these secretions by licking. However, clients may report other clinical signs associated with nasal disease, including increased respiratory sounds, increased respiratory effort, gagging, epiphora, and/or nasal deformity. Alternatively, they may notice signs of systemic disease such as lethargy and weight loss.

Signalment, history, and physical exam including characterization of the nasal discharge can help narrow the list of differential diagnoses and thus the diagnostic focus.

DIAGNOSTIC APPROACH

Signalment

Younger animals are more likely to have congenital, infectious, or toxicity-related disorders, whereas nasal discharge in older animals is more likely to be due to neoplasia, metabolic, or dental disease.

History

Acute disease results most commonly from trauma, foreign body, acute viral infections, and coagulopathies. If other pets in the household are affected, an infectious process should be suspected. Chronic disease is usually caused by neoplasia, fungal infection, dental disease, or chronic foreign bodies. Outdoor pets are prone to trauma and foreign bodies in addition to parasitic and fungal infections. Owners should also be questioned about clinical signs such as polyuria, polydipsia, or melena that may support systemic disease. Environment and travel history should be determined as both rickettsial and fungal infections have regional predilections.

Physical Exam

A complete physical exam should be performed to try to differentiate nasal disease from systemic disease (Table 58-1). Patency of each nostril should be evaluated with the use of a glass slide to look for condensation or a wisp of cotton and looking for movement with respiration. Cats with polyps may

Box • 58-1

Causes of Sneezing and Nasal Discharge

Nasal and Paranasal Diseases

- Congenital
  - Cleft palate
  - Ciliary dyskinesia
- Foreign body
- Dental disease
  - Tooth root abscess
  - Oronasal fistula
- Neoplasia
  - Carcinoma (adeno-, squamous cell)
  - Sarcoma (fibro-, osteo-, chondro-)
  - Round cell (lymphoma, transmissible venereal tumor)
- Infectious
  - Viral
    - Herpesvirus (C)
    - Calicivirus (C)
  - Fungal
    - *Aspergillus* (D)
    - *Penicillium* (D)
    - *Rhinosporidium* (D)
    - *Cryptococcus* (C)
  - Parasites
    - *Pneumonyssus caninum* (nasal mite) (C)
    - *Eucoleus böehmi* (formerly *Capillaria* sp.) (C, D)
    - *Cuterebra* sp. (C, D)
  - Inflammatory
    - Lymphocytic-plasmacytic rhinitis
    - Allergic rhinitis
    - Acquired nasopharyngeal stenosis
    - Nasopharyngeal polyps (C)
  - Trauma

Systemic Disease

- Hypertension
  - Hyperthyroidism
  - Hyperadrenocorticism
  - Renal disease
  - Pheochromocytoma
- Infectious
  - Canine infectious tracheobronchitis (kennel cough)
  - Canine distemper
  - Pneumonia
- Coagulopathy
  - Thrombocytopenia
  - Vitamin K rodenticide toxicity
  - DIC
- Vasculitis
  - *Ehrlichia*
  - Rocky Mountain spotted fever
- Hyperviscosity
  - Multiple myeloma
  - Lymphoma

D, Dogs; C, cats.

have a head tilt, nystagmus, or otic discharge. Systemic disease is associated with clinical signs that involve other organs such as ocular lesions (hypertension) or petechia (coagulopathy).

A thorough oral exam to evaluate the teeth, gums, palate, and tonsils is essential. However, this may be difficult or impossible in the conscious animal. A cursory exam may be done during the initial physical and a more complete exam done under sedation or anesthesia prior to other, more invasive, diagnostics.

Characterization of Nasal Discharge

Unilateral nasal discharge is usually indicative of intranasal rather than systemic disease. Neoplasia, fungal infection, foreign bodies, and dental disease often present with unilateral nasal discharge. However, the discharge may become bilateral as the disease progresses. Therefore establishing whether bilateral nasal discharge began as unilateral discharge can be an important piece of historical information.

Bilateral nasal discharge can be due to lymphocytic-plasmacytic rhinitis, allergic rhinitis, and chronic fungal or neoplastic diseases. Systemic diseases such as hypertension, coagulopathy, or infectious diseases usually result in bilateral nasal discharge as well. However, systemic diseases such as coagulopathies can occasionally be associated with unilateral nasal discharge.

Nasal discharge can be characterized as serous, mucoid, purulent, or hemorrhagic (or a combination of types). The character of the discharge may change as acute disease becomes chronic. For example, a serous discharge may become purulent as the result of a secondary bacterial infection.

Serous discharge is clear and often intermittent. It is most commonly associated with allergic rhinitis, lymphocytic-plasmacytic rhinitis, nasal parasites, foreign bodies, and early viral infections. If the disease is associated with paroxysmal sneezing, the discharge may become blood-tinged.

Purulent nasal discharge is thick, opaque, and yellow to green and is associated with bacterial infection. However, bacterial infections are almost always secondary to some other disease that has damaged the nasal mucosa. Mucopurulent nasal discharge can also be seen in patients with bacterial pneumonia. As with a serous discharge, it is not uncommon for purulent discharge to be tinged with blood due to mucosal irritation.

Systemic diseases, including coagulopathies or vasculitis, can lead to epistaxis or hemorrhagic nasal discharge. Intranasal diseases that erode major blood vessels (neoplasia, fungal disease) should also be included on the list of differential diagnoses for epistaxis. Hemorrhagic nasal discharge can be differentiated from blood-tinged nasal discharge by the volume. Epistaxis is generally copious and has a hematocrit similar to peripheral blood.

Mucoid nasal discharge is clear and gel-like. It may be copious and may be blood tinged. It is uncommon but when seen, is most commonly associated with nasal adenocarcinoma.

Table • 58-1

Physical Exam Findings Associated with Sneezing

LOCATION	FINDINGS	DIFFERENTIAL DIAGNOSIS
Face	Asymmetry (swelling, deformity)	Neoplasia
		Fungal rhinitis
		Tooth root abscess
Nose	↓ Air movement	Neoplasia
	Depigmentation	Fungal rhinitis
	Mass	
Submandibular lymph nodes	Enlargement	Neoplasia
		Infection
		Dental disease
Oral cavity	Dental disease	Oronasal fistula
	Cleft palate	Tooth root abscess
	Swelling	Neoplasia
Eyes	Exophthalmos	Neoplasia
		Trauma
		Abscess
	Retinal hemorrhage/detachment	Vasculitis
	Tortuous vessels	Hypertension
		Coagulopathy
	Ocular discharge	Viral infection
		Lacrimal duct obstruction (neoplasia)
Skin	Petechia	Vasculitis
Mucous membranes	Ecchymoses	Coagulopathy
Thoracic auscultation	Crackles	Pneumonia

The presence of food particles in nasal discharge suggests a cleft palate in a young animal or an oronasal fistula in an adult.

DIAGNOSTIC PLAN

Evaluation of the signalment, history and physical exam findings should allow initial prioritization of differential diagnoses and selection of the most appropriate diagnostic tests (Figure 58-1).

Routine laboratory evaluation (CBC, chemistry profile, urinalysis) is unlikely to establish a diagnosis for intranasal disease. However, these tests may support a systemic cause of nasal discharge and prompt investigation along these lines. Additionally, these values may provide information on the patient's overall health prior to general anesthesia, which may be required to arrive at a definitive diagnosis.

Indirect blood pressure can be measured to determine if the patient is hypertensive. If vasculitis is suspected, serology for *Ehrlichia* species and Rocky Mountain spotted fever should be done. A platelet count, buccal mucosal bleeding time, prothrombin time, and partial thromboplastin time are indicated to rule out a coagulopathy in a patient with epistaxis. It is also a good idea to assess coagulation parameters prior to nasal biopsy.

Fungal serology for aspergillosis, penicilliosis, and cryptococcosis may be evaluated. Both false positive and false negative results occur. Results are interpreted in light of other findings, including imaging, rhinoscopy, histopathology, and fungal culture.

Cytology of nasal secretions or tissue specimens is of limited value. Neutrophils, bacteria, and even fungal elements may be present in normal animals or as part of a secondary infection and are not diagnostic of a primary bacterial or fungal rhinitis. Cytology can be useful in the diagnosis of cryptococcal rhinitis as well as nasal lymphoma.

Imaging

Imaging of the nasal cavity, whether via conventional radiography, computed tomography, or magnetic resonance imaging, requires general anesthesia to provide the most accurate study. Imaging should be done *prior* to invasive diagnostic procedures such as rhinoscopy, nasal flushing, or nasal biopsy. These procedures can lead to hemorrhage in addition to alterations in bony and soft tissue structures, which can obscure subtle pathologic lesions and make it difficult to determine if abnormalities are pathologic or iatrogenic.

Immediately following induction of anesthesia for imaging studies is the perfect time to complete the oral exam. Palpation of the hard and soft palate and evaluation of the tonsils, teeth, and gums, including periodontal probing, should be done at this time.

Radiography

Radiography of the nasal cavity and sinuses can be useful for determining the location and extent of disease. Radiographs should be evaluated for changes in soft tissue opacity in addition to osteolytic or osteoproductive changes. Nasal and sinus films can be challenging to interpret under the best of circumstances due to the complexity of the anatomy as well as superimposition of overlying structures. Proper positioning requires general anesthesia and is critical to obtaining diagnostic films.

Computed Tomography

Computed tomography (CT) allows a more complete examination of the nasal cavity and sinuses than conventional radiography. Because cross-sectional images are obtained, superimposition of structures is eliminated. Where available, it has largely replaced radiography for evaluation of nasal disease.

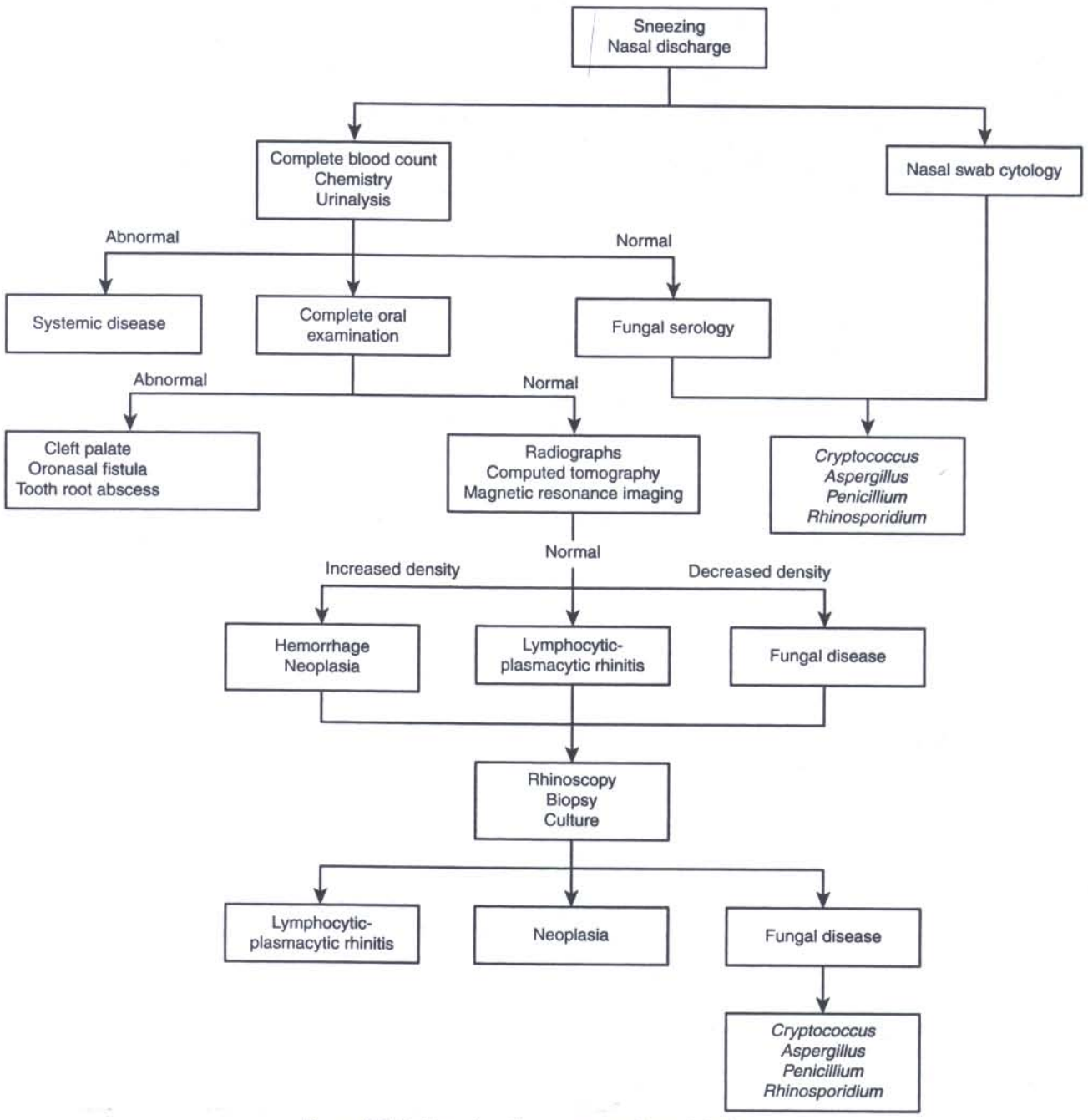

Figure 58-1 Algorithm for sneezing and nasal discharge.

The use of contrast agents can help to distinguish vascularized tumors from mucous accumulation. The ability of CT to localize nasal lesions can help direct other procedures, including rhinoscopy and biopsy.

Although imaging provides information regarding the location, extent, and character of a nasal lesion, it generally does not provide a definitive diagnosis.

Rhinoscopy

Rhinoscopy provides direct visualization of the anterior nasal cavity, the nasopharynx, and the choanae. It allows sample collection directly from visible lesions and foreign body removal in addition to diagnosis of nasal mites and nasopharyngeal polyps. Tissue samples should be submitted for histopathology and fungal culture.

Histopathology

Histopathology remains the gold standard in the diagnosis of most cases of nasal disease. Biopsies are obtained rhinoscopically. Alternatively, "blind" biopsies can be obtained with or without the use of radiography or CT to localize the lesion. It is extremely important that the biopsy instrument be passed no further than the distance from the tip of the nose to the medial canthus of the eye to avoid penetration of the cribriform plate.

Treatment and Outcome

Successful treatment of sneezing and nasal discharge hinges on the determination of a definitive diagnosis. Although antibiotic therapy may lead to some improvement, clinical signs will return unless the underlying problem can be resolved.

Hematologic/Chemical

CHAPTER • 59

Pallor

Wallace B. Morrison

The term *pallor* is defined as the absence of skin color. Clinically, the term *pallor* is most associated with paleness of mucous membranes. Pale mucous membranes originate from either shock or anemia (Figure 59-1). A severely anemic patient may progress to shock as an end-stage event. A patient experiencing shock will be anemic only if blood loss is a part of the clinical disorder. However, severe blood loss may lead to both shock and anemia. Neutrophil and platelet counts are unaffected by shock and many causes of anemia. Anemia with other and concurrent cytopenias is common. Anemic patients that are not in shock should have a normal capillary refill time (CRT) of 1 to 2 seconds. Patients in shock will have a prolonged CRT; however, unless blood loss is also present, they should have a normal packed cell volume (PCV). Evaluation of mucous membrane color and CRT becomes progressively more difficult as the PCV falls below about 20% because not enough hemoglobin is present to impart any color through mucous membranes to make evaluation of these parameters possible.

Metabolically and biochemically, shock is a complex event characterized by poor tissue perfusion that leads to decreased or uneven O_2 delivery to tissues, altered cell metabolism that may in turn result in cell death, organ failure, or a combination. Shock usually has a readily apparent cause and either responds to intervention or results in death. Shock is a peracute state. It is not a chronic condition, although the primary disorder that ultimately culminated in shock may itself have been chronic in duration.

Causes of shock include hypovolemia and disruptions in blood flow (noncardiogenic shock), as well as poor cardiac activity (cardiogenic shock). The primary causes of shock are trauma, hypovolemia, hypotension, severe acute blood loss (internal or external), severe chronic blood loss (flea infestation, gastrointestinal loss), severe heart disease causing underperfusion of peripheral tissues, and sepsis. Most cardiac conditions that result in shock are secondary to decreased myodynamic ventricular function, conditions that compromise ventricular filling, disruption of valve structures that result in severe regurgitation of blood, severe arrhythmias, or conditions that block outflow of blood from the heart (Table 59-1). The physical consequences of inadequate tissue perfusion relate directly to the production of proinflammatory mediators as a result of cellular ischemia and inadequate oxygen delivery to tissues. The origins and clinical consequences of proinflammatory mediators in shock are listed in Table 59-2.

Anemia has many origins and is initially classified as either being regenerative or nonregenerative (see Figure 59-1). Anemia can be further characterized with erythrocyte indices. The terms *normocytic*, *microcytic*, and *macrocytic* characterize the size of red blood cells (RBCs). The terms *normochromic* and *hypochromic* characterize the hemoglobin-related properties of RBCs.

Nonregenerative anemia lacks a normal reticulocyte response (reticulocyte count <60,000/μL). It occurs when selective erythropoietic depression, decreased RBC survival time from an extramarrow chronic disease, or insufficient erythropoietin release (or a combination of these factors) exist, as well as if the bone marrow fails to respond to normal or increased amounts of erythropoietin. Simple, nonregenerative anemia that is due to hyporesponsiveness of bone marrow to erythropoietin alone will have normal platelet and leukocyte production. Bone marrow disorders affecting more than erythrocytes will have other and concurrent cytopenias (Table 59-3). Nonregenerative anemias are usually normocytic and normochromic.

A regenerative anemia is usually the result of blood loss (bleeding) or hemolytic disease (Table 59-4). A regenerative anemia has a normal bone marrow response to erythropoietin in an effort to replace the lost red cells. A regenerative anemia is characterized by a reticulocytosis (reticulocyte count >60,000/μL), polychromasia, and perhaps the presence of nucleated RBCs. It takes 5 to 7 days from the time of the

Table • 59-1

Classification and Examples of Causes of Shock

CARDIOGENIC	NONCARDIOGENIC
Decreased myodynamic ventricular function	Trauma
Dilated cardiomyopathy	
Myocarditis	
Myocardial infarction	
Compromised ventricular filling	Hypovolemia
Cardiac tamponade	Severe blood loss
Hypertrophic cardiomyopathy	Severe dehydration
	Hypoadrenocorticism
Disruption in valvular function	Disruptions in blood flow
Severe endocardiosis	Sepsis and endotoxemia
	Hypotension
Outflow obstruction	
Intracardiac tumors	
Aortic stenosis	
Hypertrophic obstructive cardiomyopathy	
Heartworm disease	
Thrombosis	
Severe arrhythmia	

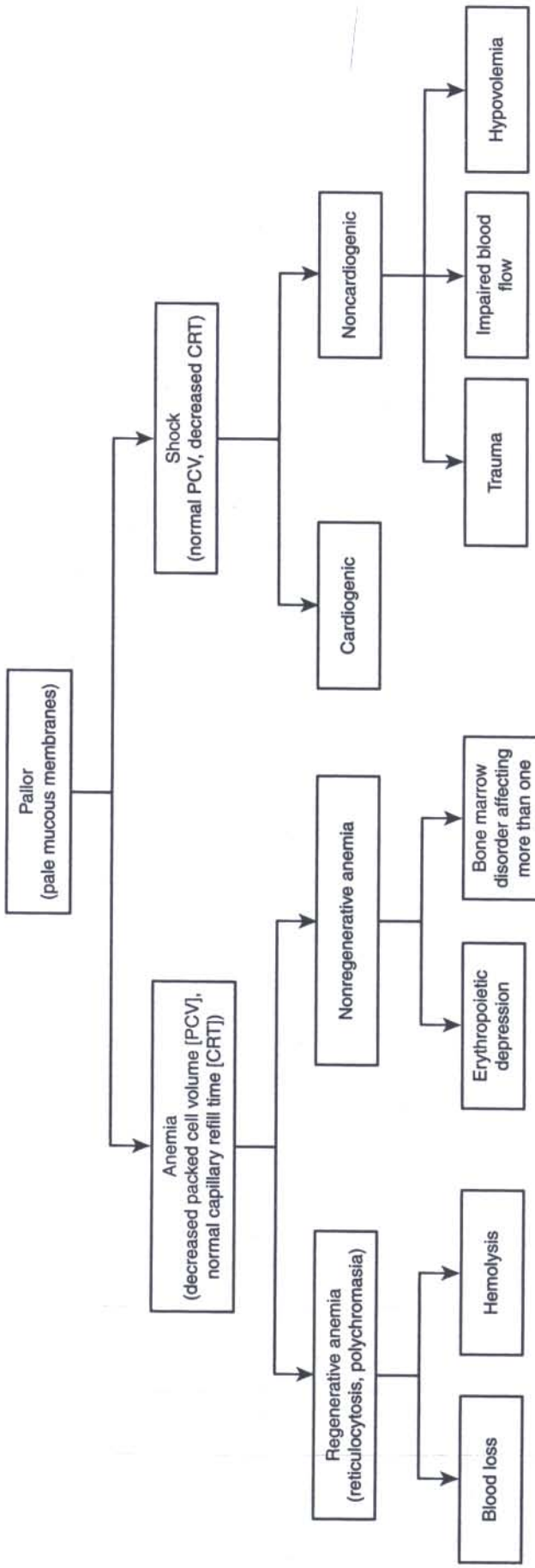

Figure 59-1 Algorithm for pallor.

Table • 59-2

Cytokine and Chemical Mediators of Shock

CYTOKINE OR CHEMICAL MEDIATOR	CLINICAL CONSEQUENCES
Histamine	Released from mast cells and results in vasodilation, increased capillary permeability, and bronchoconstriction
Bradykinin	Released from many cells and kallikrein; it causes pain, vasodilation, and edema; it also stimulates prostacyclin production
Serotonin	Causes bronchoconstriction, platelet aggregation, and increased vascular permeability
Prostaglandins	Prostaglandin E_2 results in vasodilation, erythema, hyperalgesia, and edema; prostaglandin F_2 results in vasoconstriction
Thromboxane A_2	Causes vasoconstriction, platelet aggregation, and leakage of lysosomal enzymes
Leukotrienes C_4, D_4, and E_4	Causes bronchoconstriction, vasodilation, increased vascular permeability, and cardiodepression
Tumor necrosis factor	Stimulates the production of many inflammatory mediators and cytokines; it promotes the production of adrenomedullin, vasodilation, myocardial depression, increased capillary permeability, edema and disseminated intravascular coagulation
Platelet-activating factor	Produced by most inflammatory cells, the endothelium, and platelets; it can result in vasodilation and increased capillary permeability
Endothelins	Causes vasoconstriction and increased capillary permeability
Nitric oxide	Causes vasodilation, increased capillary permeability, hypotension, and the production of oxygen free radicals
Oxygen free radicals (O_2^-, H_2O_2, OH^-)	Free radicals promote production of peroxynitrite and peroxynitrous acid, destroy cell membranes, and cause cell lysis

Modified from Muir WW: Shock, *Compend Cont Ed* 20:549, 1998.

Table • 59-3

Nonregenerative Anemia

CAUSE	KEY POINTS
Erythropoietic Depression	
Anemia of chronic disease	This is a poorly understood disorder that accompanies many chronic diseases. It is normochromic and normocytic, the survival time of red blood cells (RBCs) is decreased, increased tissue iron stores exist, and apparent bone marrow hyporesponsiveness to erythropoietin occurs. Packed cell volume (PCV) is usually only mildly depressed and rarely requires treatment. Neutrophil and platelet counts are unaffected.
Anemia with renal failure	Common in dogs and cats in chronic renal failure. It is due to inadequate renal erythropoietin release and a shortened survival of RBCs. It may be mild to severe in magnitude. Neutrophil and platelet counts are unaffected.
Feline leukemia virus (FeLV)—associated	Approximately 70% of anemic cats will test positive for FeLV. Nonregenerative anemia may be due to simple erythropoietic depression and/or associated hemolysis, but concurrent neutropenia and/or thrombocytopenia often result from the myelodysplasic, myeloproliferative, or myeloaplastic effects of infection with FeLV.
Endocrine	Mild anemia is often associated with hypothyroidism and hypoadrenocorticism in dogs, but the mechanisms are poorly characterized.
Bone Marrow Disorders	
Myeloaplasia (aplastic anemia)	Characterized by severe bone marrow cell depopulation and peripheral cytopenias. Because bone marrow aspirates are often diluted with blood and therefore difficult to interpret, it is advisable to collect a bone marrow core biopsy for histologic examination to establish a diagnosis. Myeloaplasia can be associated with FeLV infection, ehrlichiosis, trimethoprim-sulfadiazine use, estrogen toxicity, phenylbutazone toxicity, chemotherapy, and chloramphenicol toxicity. It occasionally occurs without a known cause.
Myelodysplasia	Bone marrow of affected individuals is often normal or hypercellular, but associated maturation defects result in cytopenias. Myelodysplasic anemia is most recognized in cats where the anemia is attributed to maturation defects in RBCs.
Myeloproliferative and lymphoproliferative disorders	This disorder is characterized by the proliferation of abnormal cells within bone marrow at the expense of normal hematopoiesis. If the anemia appears to be regenerative, a low-grade hemolytic process may be occurring concurrently.
Myelofibrosis and osteosclerosis	These disorders may be terminal lesions in myeloproliferative disorders or a response to bone marrow injury. Myelofibrosis can be a consequence of pyruvate kinase (PK) deficiency in dogs.

Table • 59-4

Regenerative Anemia

CAUSE	KEY POINTS
Hemolysis Immune mediated Extravascular Intravascular	An absolute reticulocytosis is not present in up to 30% of cases. Spherocytosis is expected in dogs. Cats rarely show spherocytosis with immune-mediated hemolytic anemia because they have relatively small red blood cells (RBCs) and lack central pallor when compared with dogs.
Parasites of Erythrocytes	These organisms are known to cause hemolytic disease and include *Hemobartonella*, *Babesia*, and *Cytauxzoon* spp.
Fragmentation (Microangiopathic)	Fragmentation anemia may occur with disorders like disseminated intravascular coagulation, heartworm disease, hemangiosarcoma, vasculitis, hemolytic-uremic syndrome, and diabetes mellitus. Anemia results from mechanical shearing of red cells by intravascular strands of fibrin across small vessel lumina. Often the rate of hemolysis is subclinical. RBC fragments are called schistocytes.
Hereditary Nonspherocytic Hemolytic Anemia	Hereditary nonspherocytic hemolytic anemia has been reported in poodle and beagle dogs, but it may not be the same disease in each breed. It is very rare.
Pyruvate Kinase (PK) Deficiency	Lack of normal red cell PK activity impairs normal adenosine triphosphate (ATP) generation from glucose. The result is chronic, severe hemolysis without spherocytosis. PK deficiency affects basenjis and beagles and is very rare.
Phosphofructokinase (PFK) Deficiency	This is intravascular hemolysis as a result of vigorous exercise or panting from overheating. It involves erythrocyte fragility to alkaline pH caused by impaired synthesis of 2,3,diphosphoglycerate (2,3,DPG). Spherocytosis is absent. It is very rare.
Feline Porphyria	This is a rare autosomal dominant disorder of Siamese cats that is characterized by porphyrin accumulation that causes reddish discoloration of teeth and bones, fluorescence with ultraviolet light, and mild-to-severe anemia.
Hemolysis in Abyssinian and Somali Cats	This is a very rare hereditary hemolytic anemia secondary to severe increased osmotic fragility of erythrocytes.
Copper Toxicity	Intravascular hemolysis has been rarely associated with hepatic necrosis in Bedlington terriers.
Neonatal Isoerythrolysis	Although rare in dogs and cats, this results from colostrum passage of an antibody capable of lysing RBCs.
Oxidative Injury (Heinz Body) Onion ingestion (usually dogs) Acetaminophen ingestion (usually cats) Zinc ingestion (pennies minted post-1982, zinc oxide ointment, zinc-plated bolts and screws) Benzocaine ingestion vitamin K3 (dogs) D-L methionine ingestion (cats) Phenolic compounds (moth balls) Phenazopyridine (cats)	A variety of agents will cause oxidative injury to hemoglobin. Exposure to oxidants can denature hemoglobin into aggregates known as *Heinz bodies*. Cats are more sensitive to Heinz body formation than are dogs. Eccentrocytes may form in dog RBCs after oxidant-induced membrane fusion that causes hemoglobin to shift to one side of the cell, lack of central pallor, and a clear zone outlined by a membrane. They are associated with Heinz body formation in dogs. Oxidant damage to hemoglobin can also result in methemoglobin formation.
Blood Loss Anemia External blood loss Blood loss to a body cavity Coagulopathy (factors, platelets, disseminated intravascular coagulopathy [DIC]) Endoparasites GI loss	Occult GI loss of blood may not be obvious. Body iron is stored as hemoglobin, and iron deficiency anemia is a late feature of chronic blood loss. Iron deficiency anemia is usually characterized as being microcytic and hypochromic. Red cell fragmentation may be seen after microcytosis is well established owing to increased stiffness of the RBC membrane and increased membrane fragility to normal intravascular trauma.

blood loss for the maturation process of red cells to develop such that polychromasia and reticulocytosis is detectable.

Hemolysis can be triggered by immune-mediated and nonimmune-mediated mechanisms. Immune-mediated hemolytic anemia is often highly regenerative. However, in up to 30% of cases, the anemia is not regenerative because it is either too acute and the bone marrow has not yet had time to respond or because there may be antibodies also directed at bone marrow stem cells that inhibit the normal regenerative response. Primary immune-mediated hemolytic anemia occurs when immunoglobulins (usually IgG or IgM) develop against normal or altered RBC membrane antigens. Primary immune-mediated hemolytic anemia is common in dogs but rare in cats. Infectious agents like *Ehrlichia, Hemobartonella, Babesia,* and *Leptospira* organisms and feline leukemia virus (FeLV) can alter normal surface antigens on RBCs and result in secondary immune-mediated hemolytic disease. Adsorbed immunoglobulins on RBC membranes cause intravascular hemolysis, extravascular hemolysis, or both. Extravascular hemolysis occurs when RBCs are removed by macrophages of the reticuloendothelial system (primarily in the spleen and liver) at an accelerated rate. Intravascular hemolysis occurs when adsorbed immunoglobulins activate complement and the cells spontaneously lyse. Some immunoglobulins (IgM) have greatest activity below normal body temperature and cause intravascular agglutination at cold temperatures (cold-agglutinin disease). Clinical effects may first be noticed in devitalized areas of the ear tips, feet, and tip of the tail after exposure to cold temperatures has caused plugging of small vessels and capillaries with agglutinated RBCs.

Nonimmune-mediated mechanisms of hemolysis include Heinz body formation after oxidative damage to hemoglobin, congenital defects in erythrocyte metabolism, intracellular parasites of erythrocytes, fragmentation across intravascular strands of fibrin, and copper toxicity. Common causes of blood loss include trauma, external blood loss, blood loss to a body cavity, coagulopathy, endoparasites and ectoparasites that suck blood, and gastrointestinal loss from nonparasite causes.

Clinical signs of severe anemia and shock may be similar and may include pallor (pale mucous membranes), cool mucous membranes, polypnea, tachycardia, weakness, and signs referable to the primary disease. Distinguishing shock from anemia should be uncomplicated. A patient in shock will usually have a history of trauma or a preexisting and serious systemic disease. Previously nonanemic patients with shock from any acute cause (including acute bleeding) should have a normal PCV. A time delay exists for acute blood loss to be reflected as a lower PCV because it takes several hours to complete fluid shifting from the extravascular space to the intravascular space to compensate for lost blood volume. Patients with shock and anemia will have a low PCV, but a careful history and physical examination and other diagnostic texts should reveal the underlying disorder.

An anemic patient will have a PCV below the reference range and will either be unstable if the blood loss is acute and severe or stable if the blood loss is mild, moderate, or of slow onset over a prolonged period of time (up to a critical end point). Patients with sudden blood loss will become unstable because of hypovolemia and the reduced oxygen carrying capacity of blood. Anemia that develops slowly over time allows for each red cell to increase the relative amounts of oxygen it carries in hemoglobin through increases in intracellular 2,3,diphosphoglycerate (2,3,DPG). Increases in 2,3,DPG increases the amount of oxygen that hemoglobin can carry so that the clinical manifestations of a decreased red cell mass are minimized. The speed of the blood loss will in part determine how stable the anemic patient is relative to the degree of anemia present (Table 59-5). The detection of anemia after acute blood loss cannot be done until several hours has passed and the normal circulating blood volume is reestablished.

Table • 59-5

Guidelines for Interpreting Anemia

CRITERIA	PCV DOG	PCV CAT
Normal	40%–50%	30%–40%
Mild anemia	35%–39%	25%–29%
Moderate anemia	20%–34%	20%–24%
Severe anemia	<20%	<20%

PCV, Packed cell volume.

CHAPTER • 60

Polycythemia

Andreas H. Hasler

DEFINITIONS AND PATHOPHYSIOLOGY

Polycythemia denotes the finding of an elevated cell count in the blood and is a medical composite term of the Greek words *polys* (many), *cytos* (cell), and *haima* (blood). In veterinary medicine most often only the erythrocyte number is increased, whereas the other cell lines (leukocytes, thrombocytes) are not. Some authors prefer the term *erythrocytosis,* but the term *polycythemia* is historically well established.

It is important to recognize that normal upper values of erythrocyte parameters for dogs are different from those for cats. Upper limits for dogs versus cats are packed cell volume (PCV) of 55% versus 45%, red blood cell (RBC) count of $8.5 \times 10^6/\mu L$ versus $10 \times 10^6/\mu L$, and hemoglobin concentration (Hb) of 18 versus 14 g/dl. Certain breeds such as

greyhounds and dachshunds generally have higher PCV values than other breeds.

PATHOPHYSIOLOGY

Polycythemia is classified as relative or absolute (Figure 60-1). Relative polycythemia is defined as an increased PCV with a normal total RBC mass resulting from a decrease in plasma volume. The most common causes of relative polycythemia are external losses of body fluids such as in diarrhea or burns. Less common causes are shifting of body fluids from the vascular space into the interstitial space or inadequate fluid intake (water deprivation). Signs of dehydration are usually present. Splenic contraction can lead to a temporary increase of circulating red cells in dogs but not in cats.

An increase in total RBC mass defines the absolute polycythemias. Absolute polycythemia is further divided into primary and secondary polycythemia, and the latter is further classified as physiologically appropriate or inappropriate (see Figure 60-1).

Under normal circumstances, the erythropoiesis and hence red cell mass is tightly regulated. The principal hormone that regulates erythropoiesis is erythropoietin (EPO). Renal hypoxia, but not the number or mass of circulating red cells, mediates the production of the hypoxia-inducible factor-1 (HIF-1). HIF-1 is a physiologic factor and the major factor of EPO gene transcriptional activation. The cellular site of EPO production in the kidney has been localized to interstitial renal cells in the inner cortex lying in immediate proximity to the proximal tubules. The number of cells that are recruited parallels the degree of hypoxia. As a consequence, EPO is released and its plasma level increases. The interaction of EPO with the EPO receptor results in stimulation of mitosis, differentiation, and prevention of apoptosis of erythroid progenitor cells. The resulting increase in circulating red cells enhances the oxygen-carrying capacity and, as a consequence, improves renal oxygenation. The oxygen sensor is turned off, HIF-1 and EPO levels decrease, and the regulatory loop is complete. The classification of absolute polycythemia is based on this physiology. In primary polycythemia an autonomous (i.e., EPO independent) production of red cells takes place, whereas in secondary polycythemia the red cell production is EPO dependent.

In veterinary medicine the term *primary polycythemia* is used synonymously with polycythemia vera. To the author's knowledge no attempts have been published to further characterize primary polycythemia in dogs or cats. Conversely, in human medicine polycythemia vera is one of several forms of primary polycythemia. The underlying molecular basis of polycythemia vera has yet to be determined. Despite being considered a myeloproliferative disorder, the erythroid precursors mature into normal RBCs.

Secondary appropriate polycythemia is a consequence of persistent hypoxia. This may be a physiologic response to living at high altitude. The most common cause of appropriate polycythemia is congenital heart defect with right-to-left shunting of blood. The mixing of venous and arterial blood causes systemic hypoxemia and activation of EPO production. Lung disease may cause hypoxia due to abnormal ventilation or ventilation-perfusion mismatch. The author is aware of one case of eosinophilic bronchitis in a cat with a PCV of 55% and mildly elevated serum EPO levels, but in general, respiratory disease causes mild polycythemia.

Hemoglobin function abnormalities that cause polycythemia are extremely rare in cats and in dogs. One cat with methemoglobinemia due to methemoglobin-reductase deficiency was noted to have moderate polycythemia (PCV 55%). Alterations of hemoglobin structure or decreases in 2,3-biphosphoglycerol that lead to polycythemia have been described in humans but not in cats or dogs.

Secondary inappropriate polycythemia refers to disease processes leading to elevated serum EPO levels without systemic hypoxia. Malignancies can produce EPO as a paraneoplastic syndrome; in a case of cecal leiomyosarcoma, immunohistochemistry and mRNA assays found the neoplastic cells to be the source of EPO origin. Renal disease (e.g., renal neoplasia, amyloidosis, infection, inflammation) may cause local hypoxia and trigger EPO synthesis.

Regardless of the cause, the consequence of an increased PCV is an increase in viscosity. As the red cells occupy the largest fraction of volume, hematocrit is a major determinant of blood viscosity. The rise in viscosity is not linear and becomes more pronounced above a PCV value of 50% to 60% (for dogs). Viscosity is elevated about twofold at a PCV of 70%. Depending on the degree of viscosity and local or systemic vascular hindrance, microcirculation decreases and may lead to local hypoxia or thrombosis. Most likely the neurologic symptoms seen in patients with absolute polycythemia are caused by impaired microcirculation in the brain. Thrombosis of cortical arteries associated with seizures and secondary polycythemia has been reported in a dog.

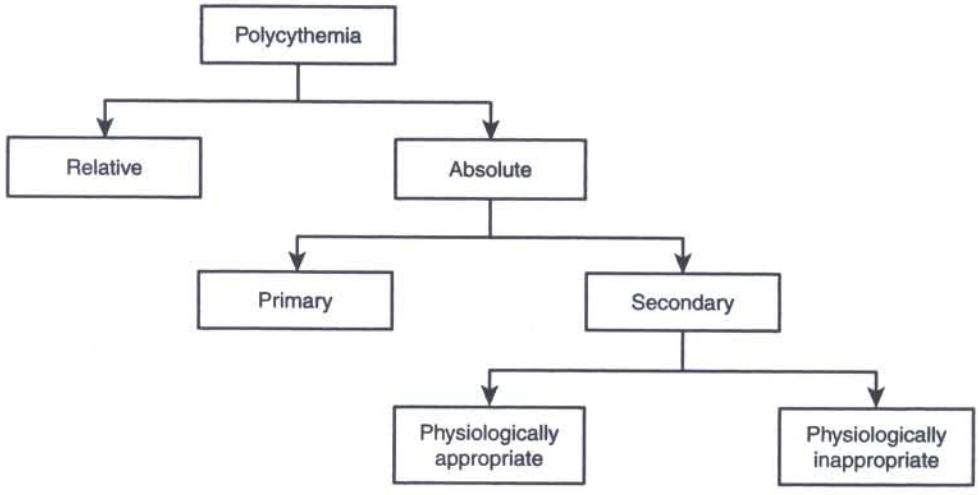

Figure 60-1 Classification of polycythemia.

PRESENTING COMPLAINT AND PHYSICAL FINDINGS

The signs of relative polycythemia are usually obvious and depend on the severity of dehydration and the underlying disease process. The hematocrit generally is mildly increased (i.e., in dogs 55% to 65%) and returns to normal with fluid therapy. Depending on the amount of concomitant protein loss or shift, the plasma protein concentration will be low, normal, or high. Patients with absolute primary polycythemia have mainly signs related to hyperviscosity. More than half of the cases with primary polycythemia are presented for neurologic complaints such as seizures, ataxia, blindness, tremor, or behavior changes.

Animals with secondary polycythemia can have signs referable to hyperviscosity, to the underlying disease process, or both. Mucous membranes are typically hyperemic, and differentiation from cyanosis can be difficult.

DIAGNOSTIC PLAN

Treatment of a polycythemic animal is dependent on the cause; hence the type of polycythemia should be determined. Primary polycythemia is a diagnosis by exclusion; therefore all diagnostic steps are used to identify a relative or secondary cause of polycythemia (Figure 60-2).

Minimal Data Base

A complete blood count (CBC), a chemistry panel, and urinalysis are the minimal data base. This enables the clinician to distinguish absolute from relative polycythemia, to assess the degree of polycythemia, and to determine therapeutic success. In clinical practice it is rarely necessary or feasible to determine total red cell mass. On the other a hand, an absolute reticulocyte count is an inexpensive method to gauge the erythropoietic activity.

Appropriate polycythemia will show signs of dyspnea or cyanosis. In the latter case, signs might be restricted to caudal body parts, as seen with reversed patent ductus arteriosus (rPDA). Although an arterial blood gas (ABG) value should detect systemic hypoxia, the high viscosity can hamper sampling and reading. Hence it is recommended to stabilize the patient first (phlebotomy). Normal values are expected in all but appropriate polycythemia (exception: hemoglobinopathies where pO_2 is normal). If hypoxia is the cause of polycythemia, the changes are usually marked. Pulse oximetry can be used if ABG determination is not available. A low saturation (<80%) with a reliable recording and repeatability suggests hypoxia.

Abdominal ultrasound is used to detect renal disease, abdominal neoplasia, or both. Unspecific signs such as hyperechoic kidneys may be found in primary polycythemia. Splenomegaly is detected in up to 25% of cats and about 10% of dogs with primary polycythemia and might suggest primary polycythemia.

Thoracic radiographs and cardiac ultrasound examinations are directed toward identifying pulmonary and cardiac abnormalities. Mild changes such as myocardial hypertrophy or bronchointerstitial changes can be found in primary polycythemia and may be the result of hyperviscosity.

Routine bone marrow examination cannot distinguish primary from secondary polycythemia and hence are not useful. In either case the myeloid-erythroid ratio is normal or decreased. Growth performance of erythroid precursors in EPO-free culture medium can be helpful because erythroid cells of patients with polycythemia vera show normal growth, whereas erythropoiesis in secondary polycythemia is EPO dependent. However, this method is restricted to research laboratories, and few cases have been published in veterinary medicine.

As primary and secondary polycythemia are EPO independent and EPO dependent respectively, it would appear that measurement of serum EPO levels is an appropriate test to differentiate the two forms. Several human test kits using either an enzyme-linked immunosorbent assay (ELISA) or radioimmune assay (RIA) method have been validated for animals. Although an increased serum EPO level is diagnostic for secondary polycythemia and values up to fiftyfold elevation have been found in secondary polycythemia, a low or normal serum EPO value occurs in about 50% of secondary polycythemia. This finding reduces the diagnostic accuracy of serum EPO level's determination.

Treatment and Prognosis

Relative polycythemia is treated with intravenous fluids and addressing the underlying cause. Phlebotomy is contraindicated in cases of relative polycythemia. Independent of the cause, absolute polycythemia is treated initially with bloodletting. This can be done by phlebotomy or by leeching. The latter has been used successfully in a cat as initial treatment when phlebotomy was not feasible. Four leeches reduced the hematocrit from 79% to 56% within 48 hours. Serial phlebotomies of 10 to 20 mL/kg blood are withdrawn until clinical symptoms have resolved or the target hematocrit is reached. In primary polycythemia the target hematocrit is below 55% for dogs and below 50% for cats. In cases of secondary appropriate polycythemia such as in rPDA the aim of treatment is resolving clinical signs of polycythemia and a higher hematocrit (60% to 70%) can be acceptable. A higher hematocrit might provide higher oxygen carrying capacity without causing hyperviscosity problems. If blood letting is inadequate, the myelosuppressing drug hydroxyurea is the treatment of choice. Multiple-dose regimens have been suggested in the literature. Some regimens use a loading dose starting with 30 to 50 mg/kg orally once a day; after 1 week the dose is reduced to 15 mg/kg/d, then titrated to effect. Other regimens propose using a maintenance dose such as 50 mg/kg every other day and titrating to effect. Side effects are reversible and include myelosuppression (thrombocytopenia), hair loss, and gastrointestinal (GI) upsets.

The prognosis for primary polycythemia is guarded, but survival for more than 6 years has been achieved in treated animals. The prognosis for secondary polycythemia depends on the cause. In cases of rPDA, survival of more than 4 years has been reported.

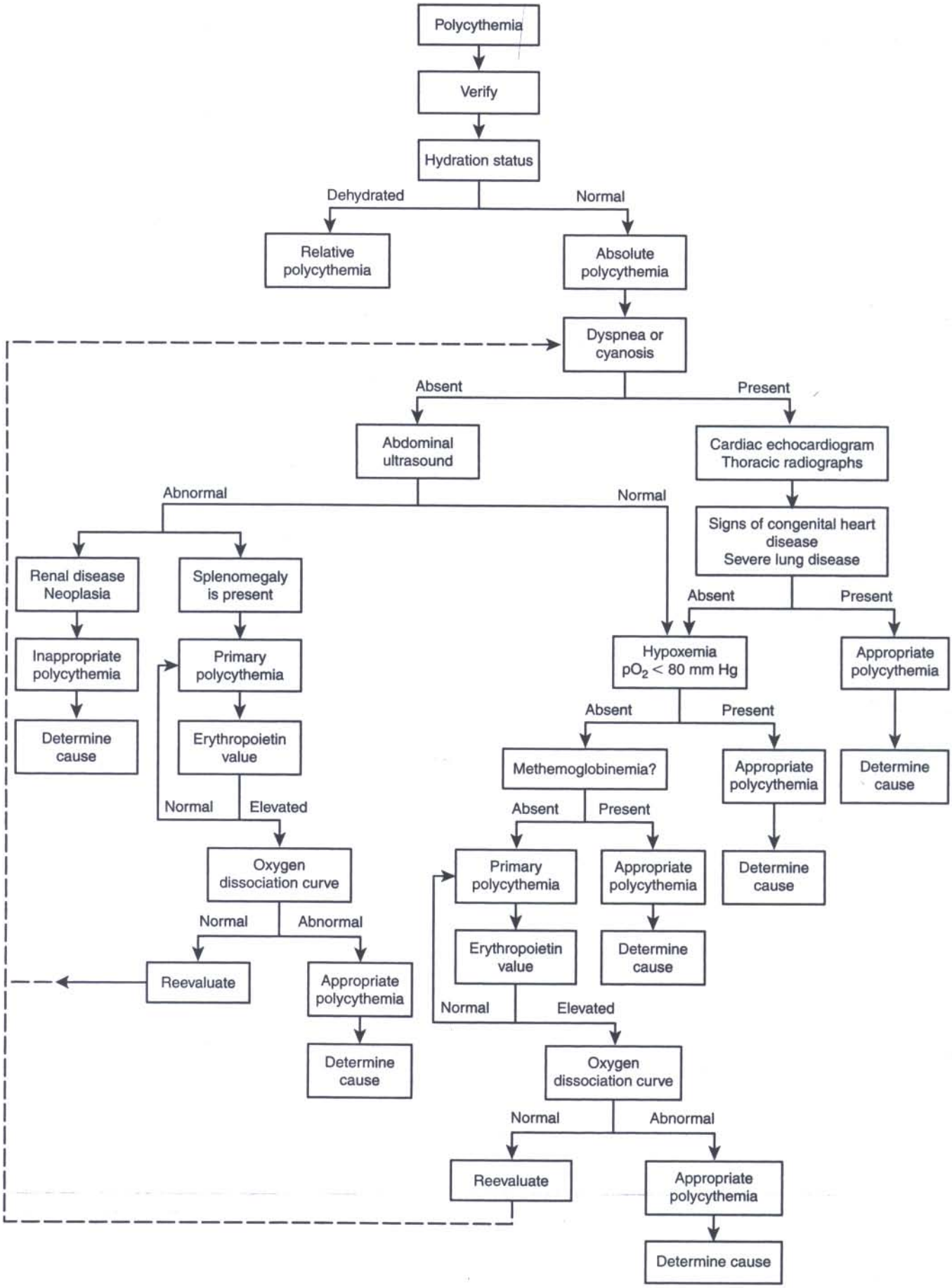

Figure 60-2 Algorithm for diagnostic approach to polycythemia.

CHAPTER 61

Cyanosis

Jean-Paul Petrie

Cyanosis is a bluish discoloration of the skin and mucous membranes. It occurs due to an increased amount of reduced hemoglobin (RHb) within the erythrocytes and can be broken down into *central* and *peripheral* causes. In central cyanosis an unsaturation of arterial blood or the presence of a hemoglobin (Hb) derivative is seen. Peripheral cyanosis is a desaturation of blood due to a regional reduction in blood flow. It is not a sensitive indicator of the state of oxygenation, often not being recognized until the percent saturation of Hb in arterial blood (SaO_2) falls below 80%. Cyanosis is an emergency condition necessitating early recognition and careful diagnostic planning.

PATHOPHYSIOLOGY

Cyanosis can usually be detected when the mean capillary concentration of RHb is greater than 5 g/100 mL. An animal with a normal packed cell volume (PCV) must have an SaO_2 between 73% and 78%, or an arterial oxygen tension (PaO_2) of 39 to 44 mm Hg to have clinically detectable cyanosis. In general, the lower the total Hb concentration, the more SaO_2 may fall before the detection of cyanosis. An animal with a PCV of 18% (total Hb 6 g/dl) must have a PaO_2 of less than 30 mm Hg before cyanosis is detectable. This degree of arterial saturation is not compatible with life; therefore cyanosis is only detectable in this patient after death!

Secondary polycythemia is frequently seen with chronic arterial unsaturation contributing to the development of cyanosis at a higher SaO_2 compared with animals with a normal PCV. An animal with a PCV of 60% may appear cyanotic when their SaO_2 falls below about 87% or a PaO_2 of 55 mm Hg. Cyanosis can also be observed when nonfunctional Hb such as methemoglobin (MetHb) is present within the blood.

Peripheral cyanosis is due to a slowing of blood flow and a relative increased oxygen extraction from normally saturated arterial blood. Vasoconstriction, diminished peripheral blood flow, peripheral vascular disease, or venous obstruction can result in cyanosis. Peripheral vasoconstriction occurs as a compensatory mechanism with decreased cardiac output secondary to congestive heart failure or shock. Blood is diverted from the skin to more vital organs such as the brain, lungs, and heart.

DIFFERENTIAL DIAGNOSIS

Cyanosis is a clinical sign with many possible causes. Box 61-1 lists the common causes and classifications of central and peripheral cyanosis. Peripheral cyanosis results when a regional reduction of blood flow or venous obstruction exists. Causes of reduced capillary arterial blood flow include vasoconstriction (e.g., hypothermia, shock, low cardiac output), arterial thromboembolism (e.g., saddle thrombus, neoplasia, hypercoagulant states, arteritis), and low cardiac output (e.g., cardiac disease, arrhythmias, hypovolemia). Obstruction of venous drainage can be seen secondary to a tourniquet, venous thrombosis, or right-sided heart failure.

Central cyanosis occurs when SaO_2 decreases due to a reduced PaO_2. Reduced PaO_2 is seen with right-to-left shunting congenital cardiac disease, pulmonary disease, and when nonoxygen carrying Hb (e.g., methemoglobinemia) is present. When cyanosis is present in younger animals, congenital cardiac disease should be strongly suspected. Right-to-left shunting cardiac defects result in unoxygenated venous blood bypassing the lungs into the systemic circulation. Systemic vascular resistance normally decreases with exercise augmenting the degree of right-to-left shunting. Right-to-left shunting patent ductus arteriosus (PDA) may occur in the presence of pulmonary hypertension and is associated with *differential* cyanosis. *Differential* cyanosis occurs when unoxygenated blood is delivered to the caudal portion of the body and oxygenated blood is delivered to the cranial portion of the body due to the anatomic location of the ductus. Severely impaired pulmonary function secondary to hypoventilation, airway obstruction, or poorly ventilated portions of the lung results in central cyanosis. This may occur acutely as with pneumonia, pulmonary edema, pleural effusions, and pulmonary thromboembolism, or it may occur with chronic pulmonary disease. Cyanosis resulting from primary pulmonary disease may occur at any age.

Increased amounts of nonoxygen carrying MetHb can result in cyanosis. MetHb is a normal product of Hb oxidation and is maintained at a normal concentration, approximately 1% of the total Hb concentration, by the enzyme MetHb reductase within the erythrocytes. Congenital MetHb reductase deficiency can occur but is rare in dogs and cats. Methemoglobinemia more frequently results from exposure to oxidants. Common oxidants associated with the production of MetHb include acetaminophen, benzocaine, phenazopyridine, and nitrates. If the MetHb content increases to 10% or greater, the patient's blood should have a noticeably brown coloration compared with bright-red blood.

APPROACH TO THE PATIENT WITH CYANOSIS

Initial clinical differentiation of cyanosis into central or peripheral causes is based on history, physical examination, and diagnostic testing (Figure 61-1). Peripheral vasoconstriction can occur with primary pulmonary pathology (e.g., pulmonary edema), and a mixture of both types of cyanosis may be present. Therefore all animals with peripheral cyanosis should be closely evaluated for central cyanosis.

History can sometimes provide useful information leading to the cause of the cyanosis. Recent exposure to oxidants (e.g., acetaminophen) or other toxic agents should be determined. The duration of the cyanosis may be helpful. Chronic cyanosis in a young animal is more likely associated with congenital heart disease. Information related to either chronic cardiac

Box • 61-1

Causes of Central and Peripheral Cyanosis

Central Cyanosis
- Cardiac (right-to-left shunting)
  - Intracardiac
    - Fallot's tetralogy
    - Atrial or ventricular septal defect with pulmonic stenosis or pulmonary hypertension
  - Extracardiac
    - Reversed patent ductus arteriosus (PDA) (differential cyanosis)
    - Pulmonary arteriovenous fistulas
- Pulmonary
  - Hypoventilation
    - Pleural effusion, pneumothorax
    - Respiratory muscle failure (e.g., fatigue, myopathy, or neurologic abnormalities)
    - Toxicity (e.g., sedative or anesthetic overdose)
    - Primary neurologic disease (e.g., neoplasia, inflammatory)
  - Obstruction
    - Laryngeal paralysis
    - Foreign body (e.g., laryngeal, tracheal)
    - Mass lesion of large airways (e.g., neoplasia, parasitic, inflammatory)
    - Inadequate oxygen concentration of inspired gas (e.g., high-altitude, anesthetic complication)
- Ventilation-perfusion mismatch
  - Pulmonary thromboembolism
  - Pulmonary infiltration
    - Edema
    - Inflammation
    - Neoplasia
    - Acute respiratory distress syndrome (ARDS)
    - Chronic obstructive pulmonary disease or pulmonary fibrosis
- Nonoxygen carrying hemoglobin (Hg) (e.g., methemoglobinemia)

Peripheral Cyanosis
- Central cyanosis (e.g., congestive heart failure)
- Decreased arterial supply
- Peripheral vasoconstriction (e.g., hypothermia, shock)
- Arterial thromboembolism
- Low cardiac output
- Obstruction of venous drainage
  - Tourniquet or foreign object (i.e., rubber band)
  - Venous thrombosis
  - Right-sided heart failure

disease or pulmonary disease should be determined (e.g., coughing, labored breathing, fatigue, syncope, medications). Peripheral cyanosis may be associated with a history of acute pain, paresis, or lameness in the affected area.

Peripheral versus central cyanosis is often determined based on physical examination. Typically, peripheral cyanosis involves the extremities and skin, and central cyanosis is most readily apparent in the mucous membranes and tongue. An exception to this rule is differential cyanosis seen with a right-to-left shunting PDA as described earlier in the chapter. Causes for peripheral cyanosis can frequently be determined by careful examination of affected areas. Generalized peripheral hypothermia may be secondary to vasoconstriction. Massaging or gentle warming of a cyanotic extremity will increase blood flow and may abolish the cyanosis. Mechanical venous obstructions or deformities (e.g., rubber band, tumor) may be readily apparent. Typical findings associated with arterial thromboembolism include pain, pulselessness, paresis, pallor, and palpable coolness of the affected area.

Other physical examination findings including respiratory pattern, lung sounds, murmurs, arrhythmias, jugular venous distension, ascites, weakness, and pulse quality may provide information that is useful in differentiating a cardiac or respiratory cause for the cyanosis.

Arterial blood gases (ABGs) or pulse oximetry can be a reliable method to evaluate central cyanosis, suggesting the type of altered physiology present (Table 61-1). Specimens for ABG analysis should be compared on room air and 100% oxygen. Pulse oximetry can be used in clinics where immediate blood gas analysis is not available. If a satisfactory signal is recorded, there can be a good correlation for SaO_2 between pulse oximetry and ABG.

Radiographic analysis provides valuable information in determining the extent of pulmonary disease if present. Radiographs can differentiate the presence of common respiratory abnormalities including pulmonary edema, pleural effusion, pneumonia, pneumothorax, neoplasia, bronchiole disease, and potentially pulmonary thromboembolism. The cardiac silhouette and pulmonary vasculature can also be evaluated. Animals suspected of having congenital cardiac disease should have an echocardiogram and electrocardiogram performed as soon as possible.

THERAPY

Successful therapy of cyanosis relies on understanding the cause. Peripheral cyanosis can be indicative of a very serious condition but is not itself life threatening. Therapy should be directed toward resolution of the underlying disease process and supportive care.

Central cyanosis is often a life-threatening emergency. Immediate determination of airway patency is critical. If airway obstruction is present, either removing the obstruction (e.g., foreign body) or intubation by means of a tracheostomy or endotracheal tube should be performed bypassing the obstruction. Oxygen administration should be instituted as soon as possible via an oxygen mask, nasal cannula, oxygen cage, or tracheal intubation. Significant pleural effusion and pneumothorax require thoracocentesis. If primary pulmonary parenchymal disease is present, direct treatment aimed at relieving the disease process is required (e.g., diuretics should be administered to animals assessed as having cardiogenic pulmonary edema). Chronic obstructive pulmonary disease and pulmonary fibrosis are chronic conditions with limited treatment options. Oxygen supplementation in the home environment is impractical, and chronic management includes weight loss, exercise restriction, and bronchodilators. Future vasodilator therapies (i.e., oral prostacyclins) may provide more hopeful outcomes in these patients.

Right-to-left shunting congenital cardiac disease does not respond well to oxygen administration. In some cases where severe pulmonary hypertension is present, oxygen administration can result in pulmonary artery vasodilation and improve pulmonary blood flow resulting in less ventilation-perfusion

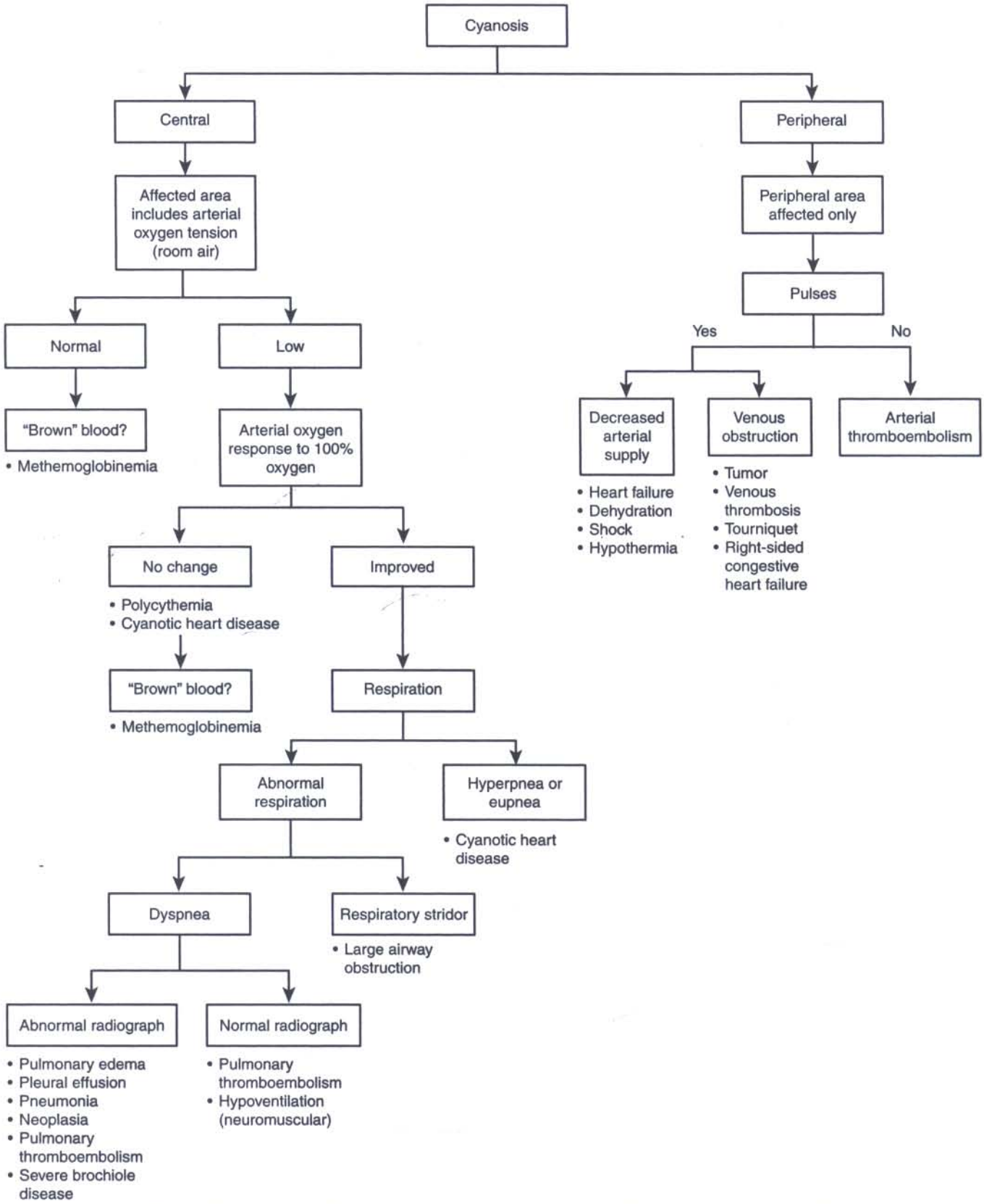

Figure 61-1 Algorithm for the differential diagnosis of cyanosis. All tentative diagnoses should be confirmed with appropriate specific testing.

Table • 61-1

Arterial Blood Gas Patterns with Various Central Cyanotic Causes

PROBLEM	SaO_2 (ROOM AIR)*	PaO_2 (ROOM AIR)*	$PaCO_2$*	PaO_2 RESPONSE TO 100% O_2
Right-to-left shunting cardiac defect	↓↓	↓↓	Normal	–
Pulmonary parenchymal disease	↓↓	↓↓	↑	↑
Hypoventilation	↓	↓	↑↑↑	↑
Systemic hypoperfusion	↓	↓	Normal/↑	↑
Ventilation-perfusion mismatch	↓	↓	Normal/↓	↑
Methemoglobinemia	↓	Normal	Normal	–

*Normal SaO_2 (room air), ~97%; normal PaO_2 (room air), ~100 mm Hg; normal $PaCO_2$ (room air), ~40 mm Hg.

mismatch. Cage rest is recommended. Polycythemia can be treated by phlebotomy or medications (e.g., hydroxyurea). In some cases of cyanotic heart disease, surgical palliation may be an option.

Mild methemoglobinemia does not require specific therapy, but oxidant exposure should be eliminated. After elimination of oxidant exposure, erythrocytes can convert most of the MetHb back to Hb within 24 hours. MetHb cannot bind to oxygen; therefore supplementation with oxygen has limited value. In some cases where the exposure is more severe, the use of N-acetylcysteine or methylene blue may be indicated.

Neurologic or musculoskeletal causes of hypoventilation may require respiratory support including oxygen supplementation with or without mechanical ventilation. Temporary causes (e.g., sedative overdose, respiratory muscle fatigue) may only require short-term treatment. Therapy for pulmonary thromboembolism (PTE) includes oxygen supplementation and fluid therapy. Other more controversial therapies for PTE include anticoagulants and plasma.

In all causes of cyanosis, patients should be monitored for response to therapy by serial assessments of mucous membrane color, oxygen saturation, radiographs, blood gas values, and respiratory rate and effort.

CHAPTER • 62

Jaundice

Susan M. Eddlestone

Jaundice or icterus is a syndrome characterized by hyperbilirubinemia and deposition of bile pigment in the skin, mucous membranes, and sclera with resulting yellow appearance. Visually detectable jaundice may begin to occur when serum bilirubin exceeds 1.5 mg/dl, with most cases being clinically detectable closer to 2 mg/dl. Obvious jaundice is seen at serum bilirubin concentrations of 4 to 5 mg/dl or greater. Inspection of nonpigmented body surfaces including sclera, gingiva, sublingual tissues, soft palate, pinnae, periumbilical area, and mucosal surface of the penis or vagina allows easy recognition. Urine and feces may be a bright orange-gold to dark brown color due to increased excretion of bilirubin. The differential diagnoses of jaundice includes (1) prehepatic conditions such as hemolytic anemia, (2) hepatic diseases causing intrahepatic cholestasis, and (3) posthepatic causes such as biliary obstructive disease.

BILIRUBIN METABOLISM

Bilirubin is a waste product formed during the catabolism of hemoglobin (Hg) from aging or damaged erythrocytes or ineffective erythropoiesis, myoglobin, and a small portion of other hemoproteins in the body. Hg from erythrocytes contains more than 90% of all heme in the body. Aging erythrocytes are phagocytized by macrophages in the liver, spleen, bone marrow, and lymph nodes. Hg is released into the circulation and binds with haptoglobin, an $alpha_2$-globulin and acute-phase reactant that serves as a carrier protein. The Hb-haptoglobin complex is taken up by the reticuloendothelial (RE) system. Both Hg and the carrier proteins are degraded.

After degradation, heme is released from globin and transferred to heme oxygenase in the endoplasmic reticulum of the RE cell and in hepatocytes. Globin is degraded to amino acids and recycled by the body. Ferric (Fe^{3+}) heme is reduced to ferrous (Fe^{2+}) heme and then modified to a ferric iron-biliverdin complex. Released iron binds to iron-carrying proteins, transferritin, and ferritin for storage or recycling. Biliverdin is converted to unconjugated bilirubin via biliverdin reductase available in most mammalian cells, with highest concentration in liver, spleen, and kidney. The lipid soluble unconjugated bilirubin is released into the circulation and must bind with albumin for circulatory transport.

Albumin-bound unconjugated bilirubin binds to receptors on hepatocytes and is taken up and converted to the water-soluble conjugated bilirubin diglucoronide. This occurs by the reaction of bilirubin and two UDPEA molecules catalyzed by glucoronyl transferase to form bilirubin diglucoronide. Approximately 70% of bilirubin in the liver is in the unconjugated form due to the rate-limiting factors of enzymatic activity and availability of glucuronic acid needed for bilirubin conjugation. Conjugated bilirubin is excreted from the hepatocyte into the canaliculi to enter the bile by an active transport process that occurs against a large concentration gradient. This is the rate-limiting step in bilirubin metabolism in the dog and probably the cat.

The liver has a large reserve capacity for bilirubin excretion and can accommodate a thirtyfold to sixtyfold increase above normal. Only a small percent of conjugated bilirubin is refluxed into the circulation, with only a small percentage (<2%) filtered through the glomerulus. Conjugated bilirubin is carried in bile via the common bile duct and emptied into the duodenum. Colonic bacteria deconjugate and hydrogenate the conjugated bilirubin to unconjugated bilirubin. This produces the colorless pigment mesobilirubinogen that is oxidized to a group of colorless tetrapyrolles called *urobilinogens*. Urobilinogens are oxidized to urobilin, which has a yellow-orange color and stercobilin that gives the brown fecal pigment. Small amounts (10% to 20%) of urobilinogen are absorbed from the intestine, with 95% circulating back to the liver for hepatic uptake and 5% excreted through the kidneys. Conjugation of bilirubin inhibits small intestinal absorption, thus impeding the enterohepatic circulation. Increased deconjugation occurs during bacterial overgrowth of the small bowel with colonic anaerobes, leading to increased enterohepatic turnover of bilirubin pigments. Feces lacking brown pigment are referred to as *acholic* and may be caused by decreased bile flow or deficient intestinal bacterial activity. Complete biliary obstruction would be required for development of acholic stools due to the small amount of bile pigments necessary to impart normal color. Absence of fecal pigment develops 7 to 10 days after complete bile duct occlusion by which time clinical jaundice is obvious.

DIFFERENTIAL DIAGNOSIS

Prehepatic jaundice is caused by intravascular or extravascular hemolysis (see Figure 62-1). The greatly increased rate of erythrocyte destruction and subsequent catabolism of Hg causes an increased production of bilirubin. Serum unconjugated bilirubin is increased transiently, with both unconjugated and conjugated bilirubin increased by the time the dog or cat is clinically jaundiced. An increased production of bilirubin accompanied by reduced hepatic clearance has been shown to be present in dogs with severe Coomb's-positive hemolytic anemia. In general, hyperbilirubinemia due to hemolytic anemia without underlying hepatic disease is usually mild with serum bilirubin values below 10 mg/dl.

Hepatic causes of jaundice may occur when disruption takes place in any step of bilirubin hepatocellular transport. Inflammatory conditions of the liver can impede bile flow causing swelling and occlusion of canaliculi, bile ductules, and small bile ducts. Membrane permeability is increased with bilirubin refluxing into the sinusoidal space in conjunction with bilirubin back diffusing into hepatocytes. In addition, canalicular excretion of bilirubin may become compromised.

Chronic inflammation occurring in periportal areas (zone 1) can cause occlusion of smaller bile ducts. Chronic inflammation within bile ducts leading to bile duct hyperplasia or biliary cirrhosis may also cause mechanical obstruction. *Cholestasis* is the term applied to conditions in which bile flow is impaired. Paranchymal lesions occurring away from periportal areas (zone 3) tend not to cause hyperbilirubinemia until later in the disease, when hepatocellular transport of bilirubin fails as opposed to the mechanical occlusion of bile flow. Formation of regenerative nodules due to hepatic injury may cause hyperbilirubinemia in severe cases. Bile flow may be impaired due to compression by fibrotic tissue that results in disruption of normal hepatic architecture. Congenital portosystemic vascular anomalies causing hepatic atrophy do not usually cause hyperbilirubinemia even though other indicators of liver function may become affected (hypoalbuminemia, hypoglycemia, decreased blood urea nitrogen [BUN]).

Primary conditions associated with jaundice in the dog and cat include sepsis. Sepsis causes hyperbilirubinemia due to the production of cytokines that interfere with the transport of bilirubin across the canalicular membrane. Heritable disorders of bilirubin metabolism have not been reported in the dog or cat.

Posthepatic or obstructive jaundice may be caused by intraluminal or extraluminal mechanical occlusion of the larger ducts of the biliary tree. The most common causes are pancreatitis and neoplasia in and around the gallbladder, cystic duct, and common bile duct. Less frequent causes are primary disorders of the walls of the biliary system that obstruct the flow of bile. Inspissated bile and choleliths formed secondary to biliary wall inflammation can obstruct bile flow. Bile duct rupture with bile spillage into the peritoneal cavity can cause extrahepatic jaundice.

CLINICAL SIGNS

The canine or feline patient with prehepatic jaundice due to hemolytic anemia may have anorexia, pale mucous membranes, increased respiratory rate, lethargy, weakness, or collapse. Mucous membranes may be slightly yellow to orange in color due to the combination of pallor and hyperbilirubinemia. Early intravascular hemolysis may cause a port wine-colored urine due to hemoglobinuria if the presence of bilirubin in the urine has not yet occurred. Historical and clinical findings in canine and feline liver disease are nonspecific but may include anorexia, weight loss, vomiting, diarrhea, and abdominal pain. Severely affected animals may be dehydrated, hypovolemic, or have neurologic signs. Posthepatic diseases causing biliary obstruction may have anorexia, depression, weight loss, vomiting, or diarrhea occurring 1 to 3 weeks prior to presentation.

DIAGNOSTIC PLAN

Clinical assessment of the jaundiced dog or cat begins with historical and physical exam findings described previously. Laboratory analysis can distinguish prehepatic jaundice from hepatic and posthepatic jaundice by the presence of severe anemia (packed cell volume [PCV] <20%) and evidence of hemolysis. In the absence of blood loss, hemogram changes consistent with hemolysis and regenerative anemia include low PCV and hematocrit (HCT) (< 20%), low erythrocyte number, increased mean corpuscular volume (MCV), reticulocytosis, poikilocytosis, anisocytosis, regenerative leukocytosis, nucleated erythrocytes, and enlarged platelets. In primary immune-mediated disease causing erythrocyte destruction, spherocytes, and autoagglutination may be seen, as may a delayed regenerative response. Hepatocellular disease occasionally results in hemolysis associated with erythrocyte membrane alterations, but this rarely causes severe anemia or contributes significantly to increased serum bilirubin concentration.

Once hemolysis is ruled out, hepatic and posthepatic diseases need to be considered. Serum biochemical analysis allows evaluation of serum total bilirubin and liver enzymes.

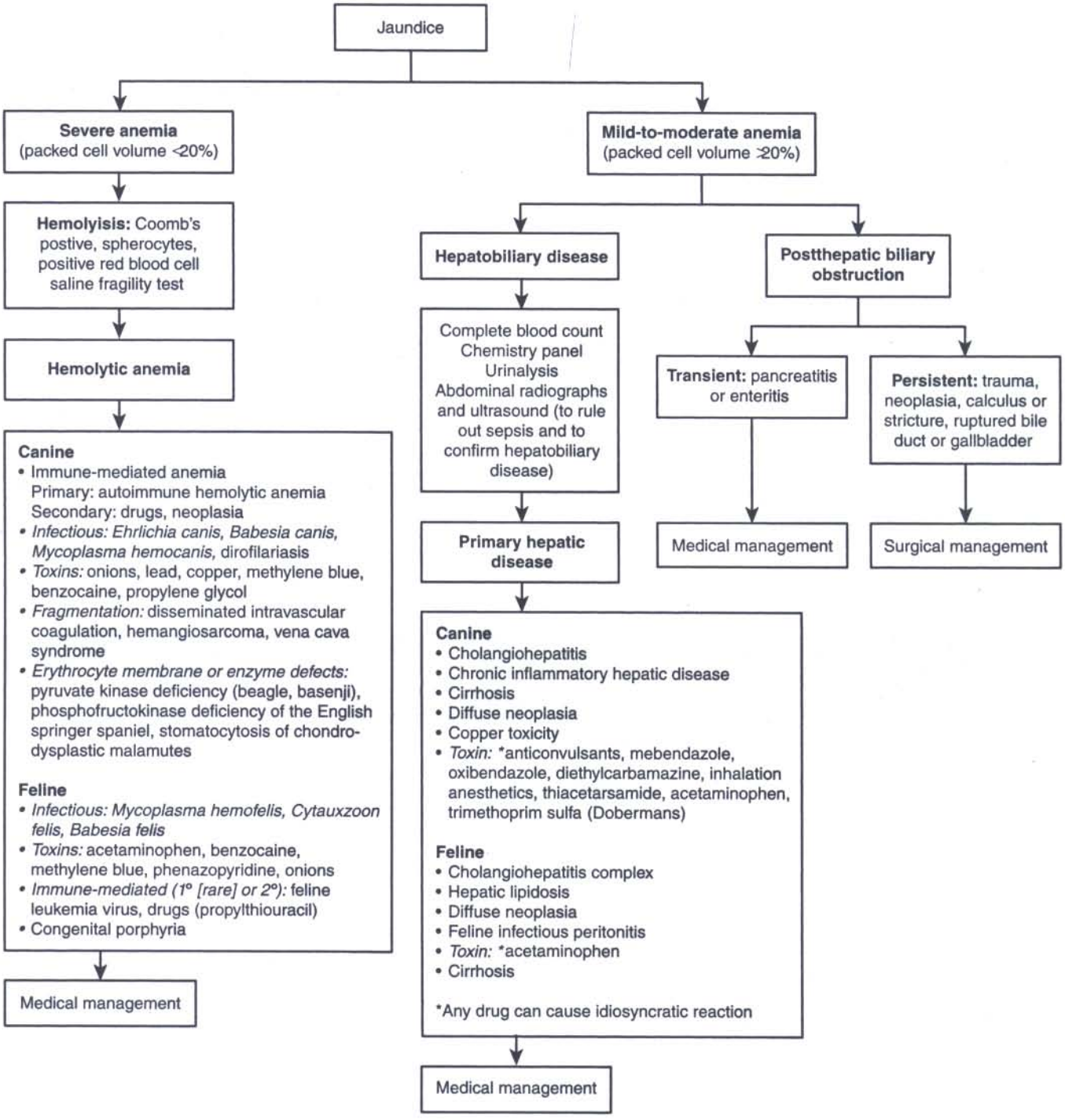

Figure 62-1 Algorithm for differential diagnoses of jaundice.

Increased liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyltransferase [GGT]) are found in primary hepatic disease, in secondary hepatic diseases (sepsis, pancreatitis), and in posthepatic diseases. Therefore these enzymes do not allow differentiation between these categories. Measurement of unconjugated (indirect) and conjugated (direct) bilirubin to distinguish between prehepatic, hepatic, and posthepatic causes of jaundice is not useful in dogs and cats. Serum bile acids will be simultaneously increased with bilirubin in jaundiced animals due to the interruption of the enterohepatic circulation of bile acids noted in hepatic and posthepatic diseases. Urinalysis can confirm the presence of bilirubinuria in discolored urine. Male dogs and occassionally female dogs may normally have small amounts of bilirubin present in urine; however, large amounts in conjunction with hyperbilirubinemia are diagnostic for jaundice. Bilirubinuria in the cat is always significant and indicates hyperbilirubinemia due to a higher renal threshold and an inability of the cat to conjugate bilirubin at the renal tubule, as compared

with the dog. Hemoglobinuria may be seen in patients with intravascular hemolysis.

The initial diagnostic approach to differentiate hepatic from posthepatic disease is the noninvasive use of abdominal radiographs and abdominal ultrasound to identify any obvious structural changes in the biliary tract that may suggest posthepatic biliary obstruction such as an enlarged gallbladder or a tortuous, dilated common bile duct. Duodenal and pancreatic masses and pancreatitis may be suggested on ultrasound. Hepatomegaly, hepatic masses, or changes in hepatic echogenicity on ultrasound examination may indicate liver disease. Ultimately, exploratory celiotomy or laparotomy may be indicated to examine the liver and biliary tract and to biopsy the liver for histologic diagnosis of hepatic disease. Celiotomy may also be indicated when corrective surgery for obstructive masses or biliary reconstruction to preserve bile flow is needed.

TREATMENT AND PROGNOSIS

The specific treatment for jaundice is dependent on the underlying cause. Treatment for hemolytic anemia is directed at the primary initiator of hemolysis. Toxic, infectious, or immune-mediated causes are treated with specific therapies that include specific antidotes, antibiotics, and immunosuppressive therapies, respectively. Supportive care including red blood cell (RBC) or Hg transfusion may be needed in severe cases of anemia. Prognosis is good for toxic and infectious causes of hemolysis if treated appropriately. Prognosis for immune-mediated disease is guarded due to the resistant and relapsing nature of the disease in dogs.

Treatment of specific hepatic diseases requires a liver biopsy for definitive diagnosis. Infectious, toxic, canine copper storage disease; chronic immune-mediated liver disease; feline hepatic lipidosis; and cholangiohepatitis carry fair-to-good prognoses when treated with appropriate therapy. Hepatic neoplasia and cirrhosis carry a much poorer prognosis. Supportive therapy of liver disease may include intravenous fluids to rehydrate the dog or cat and promote forward bile flow, vitamin K1 to replace deficiencies due to cholestasis, vitamin E for antioxidant properties, vitamin B complex , and S-adenosyl for replacement of intrahepatic glutathione levels to restore mechanisms of hepatocyte metabolism.

Treatment of chronic cholestasis associated with chronic hepatic or posthepatic disease may include the use of the cholerectic, ursodeoxycholic acid, a hydrophilic bile acid that displaces the more toxic hydrophobic bile acids from the bile acid pool that can cause hepatocyte membrane damage. Posthepatic obstructive disease is almost always surgically managed except for pancreatitis, which is usually responsive to medical therapy. Prognosis of postobstructive diseases is good if appropriately managed, except for necrotizing pancreatitis and neoplasia that carry a poorer prognosis.

CHAPTER 63

Bleeding Disorders: Epistaxis and Hemoptysis

Tracy Gieger

EPISTAXIS

Epistaxis is defined as hemorrhage originating from the nose. The following areas should be emphasized when evaluating a patient with epistaxis (Figure 63-1).

Signalment

Young animals that roam are susceptible to trauma, infections, and foreign body (FB) inhalation. Intact dogs that roam are susceptible to transmissible venereal tumors. Purebred dogs may be affected with von Willebrand's disease (vWD) or coagulation factor deficiencies. Immune-mediated diseases occur most commonly in middle-aged animals. Nasal tumors are more common in animals over 8 years of age, although nasal lymphoma may occur in younger cats. Nasopharyngeal polyps occur more often in young cats. Brachycephalic cats are more susceptible to chronic viral respiratory infections.

Environment

Outdoor pets are more susceptible to nasal trauma, parasitic and fungal infections, rodenticide toxicity, and FB inhalation. The owner should be questioned about travel to areas endemic for fungal and rickettsial organisms, leishmaniasis, and hepatozoonosis.

Time Course

Nasal trauma results in acute-onset and often severe bleeding that resolves with supportive measures and does not recur. FB inhalation, most commonly wood splinters or grass awns, often causes an acute onset of epistaxis, sneezing, and pawing at the face; however, if foreign objects remain lodged in the nasal cavity, chronic nasal discharge secondary to granuloma formation may result. Chronic or intermittent epistaxis is more common with oronasal fistulas, fungal rhinitis, and nasal tumors; often these diseases begin with mucoid nasal discharge that progresses to epistaxis later in the course of disease. Allergic rhinitis may cause seasonal epistaxis.

Characterization of Epistaxis

Many intranasal diseases such as nasal tumors begin with unilateral epistaxis that becomes bilateral as the disease progresses, disrupting the nasal septum. Bilateral epistaxis often indicates "extranasal" causes such as coagulopathies, hypertension, thrombocytopenia, and thrombocytopathia (a defect in platelet function).

History of Bleeding from Other Sites

Historical bleeding after tooth loss or elective neutering may indicate a congenital coagulation factor defect or platelet

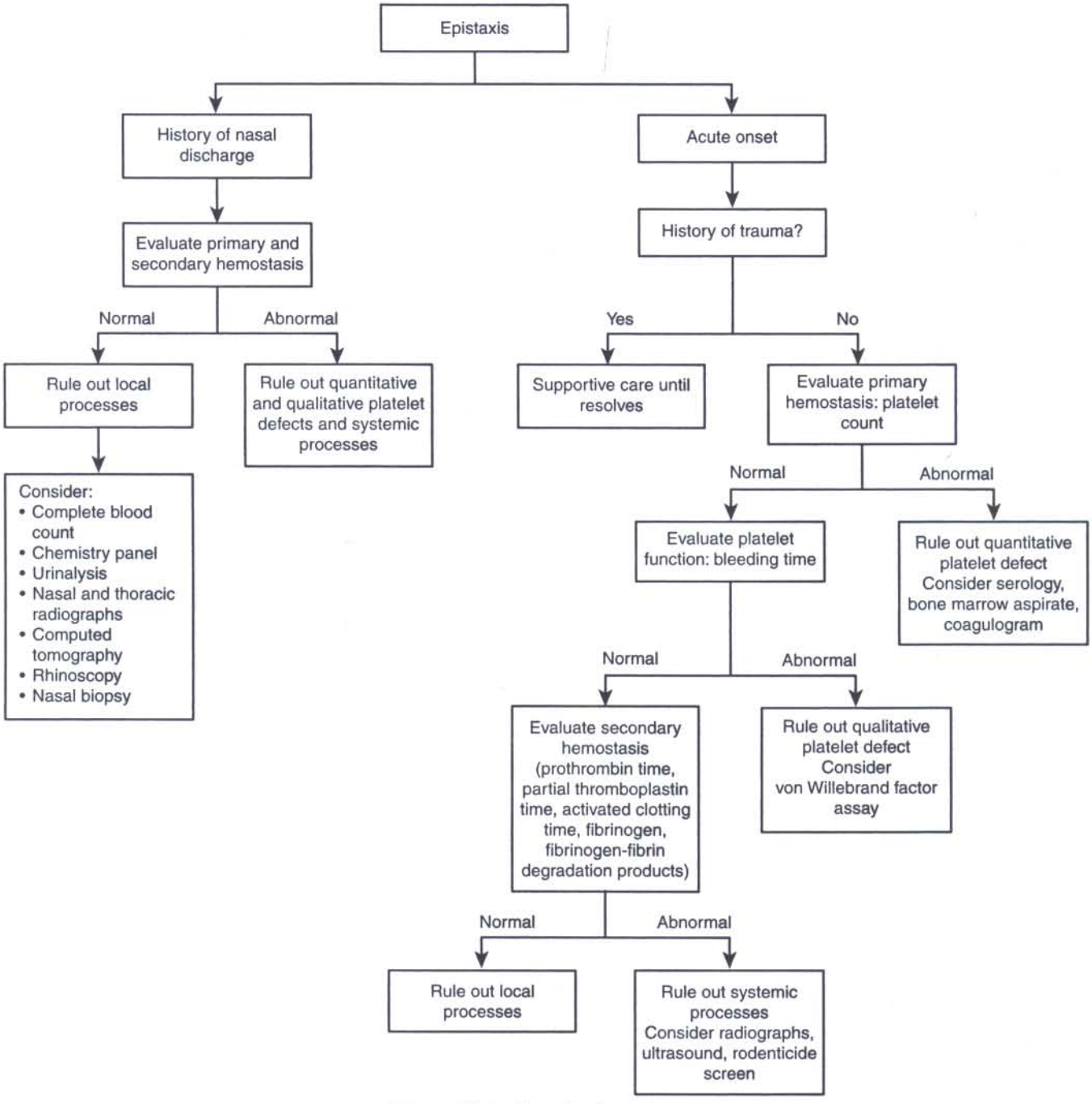

Figure 63-1 Algorithm for epistaxis.

disorder. Animals with petechia, mucosal bleeding, melena or fundic hemorrhages are likely to have a defect of primary hemostasis (platelets), whereas those with hemarthrosis, hematomas, or bleeding into body cavities are likely to have a defect of secondary hemostasis (coagulation factors). Melena and hematemesis may occur when blood from the nasopharynx is swallowed.

Concurrent Problems Not Related to the Nasal Cavity

Central nervous system (CNS) dysfunction may occur with hyperviscosity syndromes or nasal tumors invading the brain. Polyuria and polydipsia are seen with hyperadrenocorticism, chronic renal failure, and hyperthyroidism which uncommonly cause epistaxis secondary to hypertension. A history of dental disease may support oronasal fistula formation as a cause of epistaxis.

History of Drug and Vaccine Administration

Nonsteroidal antiinflammatory drugs (NSAIDs) inhibit platelet function; trimethoprim sulfa and other antibiotics may induce an immune-mediated platelet destruction, whereas chemotherapeutic agents, estrogens, and phenylbutazone may cause myelosuppression and thrombocytopenia. Immune-mediated thrombocytopenia is an uncommon sequela to vaccination.

PHYSICAL EXAMINATION

The clinician should examine the face for visual or palpable asymmetry, which is most commonly secondary to neoplasia. A glass slide may be held up to the nose to document airflow through the nostrils by the presence of condensation on the slide. Ulceration and depigmentation of the nasal planum may be seen with aspergillosis or squamous cell carcinoma. Polypoid masses extending from the nares are seen with rhinosporidiosis and cryptococcosis. Cats with nasal cryptococcosis often have a characteristic convexity of the nose ("Roman nose"). The mouth should be examined for palate deformity, masses, oronasal fistulas, or loose teeth. Nasal tumors often cause facial or hard palate deformity, inability to retropulse the globe, or epiphora. A fundic examination may reveal chorioretinitis, signs of hypertensive retinopathy, or hyperviscosity. Regional lymph nodes should be examined for enlargement secondary to infectious organisms, inflammation, or metastatic neoplasia. Evaluation of the skin, body cavities, and joints will help to eliminate evidence of a coagulopathy.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for epistaxis can be divided into *systemic* and *local* causes (Box 63-1). Local diseases may progress and develop systemic complications that can exacerbate bleeding.

SYSTEMIC PROCESSES

Hemostatic defects or increased capillary fragility are mechanisms of epistaxis. Primary hemostatic defects (platelet plug formation) include thrombocytopenia or thrombocytopathia. Mechanisms of thrombocytopenia include decreased production, increased destruction, sequestration, and increased consumption. Spontaneous bleeding is uncommon unless the platelet count is less than or equal to 50,000/μL. Decreased production of platelets can occur secondary to viral, rickettsial, protozoal, parasitic, or bacterial infections; to neoplastic conditions resulting in myelophthisis; to drug administration; or to immune-mediated phenomena. Increased destruction of platelets may be immune mediated (primary or secondary) or related to microangiopathy (seen with hemangiosarcoma). Sequestration of platelets in the spleen, liver, or large vascular tumors results in thrombocytopenia. Increased platelet consumption is seen with disseminated intravascular coagulopathy (DIC), vasculitis, and hemorrhage. Thrombocytopathia may be primary, such as in vWD, or secondary to uremia, dysproteinemias (associated with ehrlichiosis, multiple myeloma, among others), or drugs such as NSAIDs. Secondary coagulation (coagulation factor) defects such as Hemophilia A and B are uncommon congenital abnormalities that vary in severity. Acquired coagulopathies include anticoagulant rodenticide toxicity and hepatic failure (with decreased coagulation factor production). Increased capillary fragility with subsequent rupture can result from hypertension, neoplasia invading blood vessels, hyperviscosity syndromes, hyperlipidemia, and thromboembolic disease.

LOCAL PROCESSES

Local processes ("intranasal" causes) are the most common cause of epistaxis. Nasal adenocarcinomas are more common in dogs, whereas cats are more often affected with nasal lymphoma and benign polyps. Bacterial rhinitis is almost always secondary to inflammation or damage to the nasal mucosa, although *Bordetella*, *Pasteurella*, and *Mycoplasma* spp. may be primary pathogens. Aspergillosis is more common in dogs, and nasal cryptococcosis is seen more frequently in the cat. Animals with oronasal fistulas may have nasal discharge or epistaxis. Nasal parasites are highly irritating and can cause severe epistaxis and intractable head rubbing and itching. Viral diseases rarely result in epistaxis in dogs, and cats with upper respiratory infections uncommonly develop chronic nasal discharge and sneezing that results in intermittent epistaxis. Allergic (eosinophilic) and lymphoplasmacytic rhinitis are uncommon immune-mediated phenomena that are often steroid responsive. Arteriovenous malformations can rupture, causing sudden-onset epistaxis.

DIAGNOSTIC PLAN

Complete Blood Count Including Platelet Count

Regenerative anemia indicates a bone marrow response to bleeding, but with chronic epistaxis, iron deficiency and a nonregenerative anemia may occur. Schistocytes are observed with microangiopathies that occur with hemangiosarcoma and DIC. Leukocytosis is anticipated with chronic inflammation or infection, and leukopenia suggests chronic ehrlichiosis, cytotoxic drug administration, or sepsis. Thrombocytopenia is the result of increased destruction or consumption, sequestration, or decreased production of platelets. Evaluation of a blood smear may be useful while awaiting laboratory results: normal dogs and cats have 8 to 29 platelets/100X oil immersion field. If the platelet count is 20,000/μL, approximately one platelet per oil immersion field is present. Macroplatelets suggest regeneration associated with peripheral platelet destruction or consumption; these platelets may be more functional than normal, explaining why dogs with platelet counts less than 10,000/μL often do not bleed.

Chemistry Profile

Panhypoproteinemia may develop with chronic blood loss. Hyperglobulinemia is associated with neoplasia or chronic infections, and serum protein electrophoresis helps to distinguish between monoclonal or polyclonal gammopathy. Monoclonal gammopathies occur with multiple myeloma, chronic ehrlichiosis, lymphoma, leukemias, and macroglobulinemia. Evidence of renal, hepatic, or endocrine disease identifies general causes of disease that can cause or exacerbate epistaxis.

Urinalysis

Indirectly, the urine samples provide clues to potential causes of epestosis, such as bladder mucosal bleeding, and hematuria or glomerulonephropathies may be seen with thrombocytopenia and thrombocytopathia.

Hemostatic Studies

Buccal mucosal bleeding time (BMBT) is a useful in-hospital test of platelet function and is reliable if the platelet count is >100,000/μL. If this test is abnormal, searching for a cause of thrombocytopathia is indicated, including a von Willebrand's titer and evaluation for secondary causes of platelet function defects. Coagulation studies such as partial thromboplastin time (PTT), prothrombin time (PT), and activated clotting time (ACT) can be abnormal if the platelet count is <10,000/μL and should be considered in cases of epistaxis in which platelet abnormalities have been ruled out. If these coagulograms are abnormal, tests for specific clotting factors and a PIVKA (proteins inhibited by vitamin K antagonists) should be considered. A coagulogram should also include fibrinogen, fibrin degredation products (FDPs), and an antithrombin III level to examine for evidence of DIC.

Box • 63-1

Causes of Epistaxis

Systemic Processes ("Extranasal" Disease)

Thrombocytopenia (quantitative platelet abnormality)
- Decreased production
  - Infectious: Ehrlichiosis, feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), Rocky Mountain spotted fever, hepatozoonosis, septicemia, endotoxemia, leishmaniasis
  - Drugs: Cytotoxic drugs, modified live virus vaccines, estrogens
  - Neoplasia: Myelophthisis secondary to myeloproliferative or lymphoproliferative diseases
  - Immune-mediated: Antibodies against megakaryocytes
  - Other: Bone marrow aplasia, cyclic thrombocytopenia, myelofibrosis, hyperestrogenism (secondary to Sertoli cell and granulosa cell tumors), myelodysplasia, toxins, osteosclerosis, idiopathic
- Increased destruction
  - Immune mediated: Idiopathic or secondary to drugs, neoplasia, infection
  - Microangiopathy: Shearing of platelets; associated with hemangioma/hemangiosarcoma
- Sequestration
  - Neoplasia: Large vascular tumors
  - Splenomegaly or splenic torsion
  - Hepatomegaly
- Increased consumption
  - Disseminated intravascular coagulopathy (DIC)
  - Vasculitis: Rocky Mountain spotted fever, endotoxemia, neoplasia, heartworm disease, bacteremia
  - Hemorrhage-induced thrombocytopenia

Thrombocytopathia (qualitative platelet defect)
- Congenital: von Willebrand's disease (vWD), platelet procoagulant activity deficiency in German shepherd dogs, Glanzmann's thrombasthenia in Great Pyrenees, Basset hound thrombopathia
- Acquired: vWD (associated with hypothyroidism), uremia, dysproteinemia (associated with multiple myeloma, ehrlichiosis, leishmaniasis), drugs (NSAIDs)

Coagulation factor deficiency
- Congenital: Hemophilia A and B, others
- Acquired: Anticoagulant rodenticide toxicity, liver failure, DIC

Increased capillary fragility
- Hypertension: Primary or secondary to chronic renal failure, glomerulonephropathies, pheochromocytoma, hyperadrenocorticism, hyperthyroidism, heart disease
- Hyperviscosity syndrome: Secondary to multiple myeloma, ehrlichiosis, polycythemia (primary or secondary to hypoxia or neoplasia), leukemias
- Hyperlipidemia
- Thromboembolic disease
- Neoplasia invading blood vessels

Local Processes ("Intranasal" Disease)

Trauma

Neoplasia
- Epithelial: Adenocarcinoma, undifferentiated carcinoma, squamous cell carcinoma, polyps
- Mesenchymal: Chondrosarcoma, fibrosarcoma, hemangiosarcoma, osteosarcoma, melanoma
- Round cell: Lymphoma, transmissible venereal tumor, mast cell tumor

Infection
- Fungal: *Cryptococcus, Aspergillus, Penicillium, Rhinosporidium, Exophiala jeanselmi,* phaeohyphomycosis
- Parasitic: *Pneumonyssus, Eucoleus, Cuterebra, Linguatula, Capillaria*
- Bacterial: Primary *(Bordetella, Pasteurella, Mycoplasma)* or secondary
- Viral: Canine infectious tracheobronchitis, canine distemper, feline viral rhinotracheitis, calicivirus

Inflammation
- Lymphoplasmacytic: Primary or secondary
- Eosinophilic: Allergic rhinitis

Dental disease
- Tooth root abscess
- Oronasal fistula

Foreign body (FB)

Vascular malformation

Serology
Ehrlichiosis and Rocky Mountain spotted fever are diagnosed with serology. *Aspergillus* titers are nonspecific and seldom useful. Latex agglutination tests for *Cryptococcus* capsular antigen are useful for diagnosis and therapeutic monitoring. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) tests are indicated if the viral status is unknown. Thyroxine levels should be part of the minimal data base for cats over 6 years of age.

Imaging
Imaging studies are performed prior to rhinoscopy to avoid difficulties in interpreting iatrogenic lesions (i.e., bleeding induced by biopsy). Images should be examined for asymmetry and bone lysis, which can localize the disease, determine the severity of involvement, and guide biopsy procedures. Nasal radiographs should include lateral, oblique, open-mouth, ventrodorsal, intraoral, and frontal sinus views. Computed tomography (CT) is superior to radiographs for nasal disease because it allows visualization of bony and soft tissue lesions and it images all areas including turbinates, nasal septum, cribriform plate, and sinuses. Uptake of contrast material by tumors can distinguish them from mucus collections.

Rhinoscopy
If a coagulopathy has been ruled out as a cause for epistaxis, rhinoscopy is performed under general anesthesia (with a cuffed endotracheal tube in place) after imaging studies are completed. The least affected side should always be examined first, and the evaluation should begin ventrally and move dorsally in case of iatrogenic hemorrhage. Thorough evaluation of the oropharynx and oral cavity should be performed. Instruments including dental mirrors, spay hooks, and otoscopes provide limited visualization of the nasal cavity but may assist in the diagnosis of foreign bodies and large tumors. Rigid or flexible endoscopes are required for a full examination. The entire nasal cavity including the frontal sinuses (if possible) should be examined for masses, foreign bodies, fungal or inflammatory plaques, and polyps. The distance from the medial canthus to the end of the nostril should be marked on the instrument prior to entry into the nose to avoid penetrating the cribriform plate.

Nasal Swabs, Flushing, and Biopsy
Cryptococcus can be identified on cytology of nasal discharge with use of India ink. Flushing or biopsy of the nasal cavity is performed after the oropharynx has been packed with gauze sponges and the head is positioned ventrally to avoid aspiration of blood or fluid. A flexible endoscope or red rubber catheter retroflexed behind the soft palate may be used to flush saline through the nose. FBs may be retrieved, and parasitic ova may be evident on examination of the fluid. Biopsy should be performed after rhinoscopy, and it may be performed "blindly" if visualization of the nasal cavity is not possible. If lesions are not seen on imaging or rhinoscopy, multiple biopsies throughout the nose should be obtained. Biopsy instruments include alligator or pituitary-cup forceps, and should not be advanced past the medial canthus. Incisional biopsy or aspiration of hard palate defects or areas of facial deformity may be useful. Complications of nasal biopsy that should always be anticipated include life-threatening hemorrhage, aspiration of blood, and neurologic signs if the cribriform plate is violated.

Culture
Primary bacterial rhinitis is rare, but secondary infection is common. Nasal cultures may be obtained through nasal swabs, flush, or tissue culture; the latter is most likely to yield true representation of the nasal cavity flora. A superficial nasal swab is likely to yield growth of normal flora, including *Escherichia coli*, *Streptococcus* spp., *Pasteurella* spp., and others. The growth of only 1 to 2 species is more likely to represent an abnormality, whereas growth of multiple bacteria is usually normal flora; therefore, the laboratory should be advised to report all growth. Treatment with antibiotics may improve clinical signs and can give a false sense of disease resolution to the veterinarian. The growth of *Aspergillus* and *Penicillium* should be interpreted in light of other findings such as fungal plaques and radiographic evidence of bony destruction to make a diagnosis of fungal rhinitis because these organisms may represent normal flora.

Blood Pressure
Blood pressure evaluation is indicated if hypertension is suspected as a contributing cause for epistaxis; it is commonly performed using indirect Doppler or oscillometric methods (see Chapter 28).

Exploratory Rhinotomy
If all other diagnostic procedures have failed to obtain a diagnosis or if an FB cannot be removed via rhinoscopy, exploratory rhinotomy may be indicated. Potential benefits of surgery must outweigh potential complications, including hemorrhage, subcutaneous emphysema, inadvertent entry into the brain, and recurrent nasal cavity infections.

TREATMENT

The goal of treatment is to control epistaxis until a definitive diagnosis and therapeutic plan can be determined. Treatments include cage rest, ice packs, and application of pressure. Sedation may aid in controlling hemorrhage. Sedatives such as diazepam and butorphanol at low doses may help to relieve anxiety, but caution should be used to avoid causing hypotension. In animals that have suffered trauma or are obtunded, suctioning blood from the oropharynx is indicated to prevent aspiration of blood. In severe cases, general anesthesia and packing the nasal cavity and oropharynx with dilute epinephrine-soaked (1:100,000) sponges or tampons, ligation of the external carotid artery on the affected side, or both might help to control bleeding. If a coagulopathy is suspected, transfusions are indicated. In thrombocytopenic animals, transfusions very rarely supply adequate platelet numbers to stop bleeding.

HEMOPTYSIS

Hemoptysis (from Greek *hamia*, "blood" + *ptysis*, "spitting") is defined as expectoration of blood or bloody mucus from the respiratory tract at or below the larynx. Detection and confirmation of hemoptysis may be difficult in dogs and cats because they do not expectorate after coughing. To direct the diagnostic and therapeutic process, it must be determined that the coughed up material is actually blood, the blood was coughed up and not regurgitated or vomited, and the blood originated from the lower respiratory tract. Hemoptysis is generally a serious condition that requires aggressive management. The following areas should be emphasized when evaluating a patient with hemoptysis (Figure 63-2).

History
Information regarding cardiac and pulmonary abnormalities, medications (including heartworm preventative), toxin exposure, and travel history are essential. The owner should be questioned regarding exercise intolerance, dyspnea, syncope, and cough in the patient. Animals that swallow blood from the upper gastrointestinal or respiratory tracts may experience

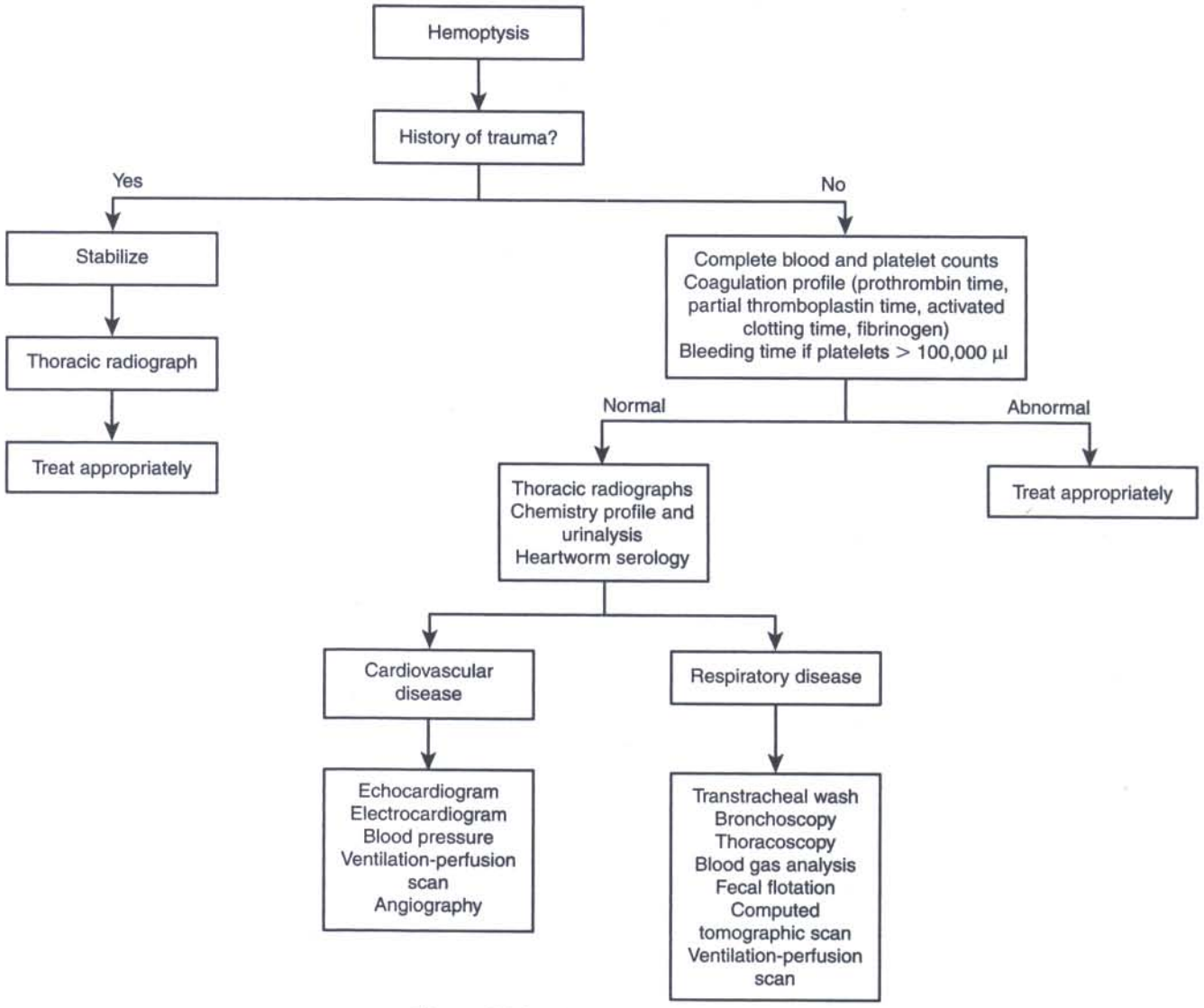

Figure 63-2 Algorithm for hemoptysis.

hematemesis, which can be mistaken for hemoptysis. Prior bleeding episodes suggest a primary or secondary coagulopathy. Animals with a history of cough prior to onset of hemoptysis may have chronic diseases such as bronchitis, neoplasia, heartworm disease, or left-sided heart failure.

Signalment

Older dogs and cats are more likely to suffer from primary lung and metastatic neoplasia.

Environment

Dogs and cats in specific geographic areas are more susceptible to infections with heartworms and lungworms. Outdoor animals are more susceptible to trauma, anticoagulant rodenticide ingestion, and FB inhalation. Specific fungal diseases are endemic in limited regions.

Nature of the Expectorated Material

If the blood is mixed with sputum, suppurative lesions such as bronchopneumonia are likely; pulmonary edema often appears as blood mixed with pink frothy material; and bright-red blood is likely from an artery.

PHYSICAL EXAMINATION

A thorough evaluation of the cardiovascular and respiratory systems is essential to localize the condition. Care should be taken to avoid undue stress, and supportive measures such as oxygen therapy may need to be instituted prior to examination. Examination for coagulopathies should be performed as for epistaxis. Animals with systemic mycosis often have cutaneous or bony lesions.

DIFFERENTIAL DIAGNOSIS

Heartworm disease can cause hemoptysis in dogs and cats (Box 63-2). In dogs, exercise after adulticide therapy may result in worm embolization, inciting inflammatory lesions in the pulmonary vasculature and parenchyma and resulting in hemoptysis. Coagulopathies and platelet defects uncommonly result in airway mucosal bleeding. Cardiogenic pulmonary edema can result in expectoration of blood and pink froth. Pulmonary thromboembolism (PTE) (secondary to cardiac, endocrine, immune-mediated, gastrointestinal, and neoplastic disease) and

Box • 63-2

Causes of Hemoptysis

Pulmonary
Pulmonary thromboembolism: Secondary to neoplastic, endocrine, cardiac, metabolic disease
Pulmonary hypertension: Secondary to heartworm disease, congenital or acquired cardiac defects that result in shunting of blood
Chronic bronchitis/bronchiectasis
Bacterial pneumonia
Nocardiosis
Pulmonary abscess
Kennel cough (rare)
Fungal pneumonia: Blastomycosis, histoplasmosis, coccidiomycosis
Parasites: *Paragonimus kellicotti, Capillaria aerophila, Aelurostrongylus abstrusus*
Pulmonary infiltrate with eosinophils
Neoplasia: lung: Primary adenocarcinoma, undifferentiated carcinoma, squamous cell carcinoma, chondrosarcoma; metastatic; primary tracheal tumors
Lung lobe torsion

Cardiovascular
Heartworm disease
Cardiogenic pulmonary edema
Arteriovenous fistula
Bacterial endocarditis

Systemic
Coagulopathies: Primary (quantitative or qualitative platelet defects) or secondary hemostatic (factor deficiencies, anticoagulant rodenticide toxicity, disseminated intravascular coagulopathy [DIC]) abnormalities
Trauma: Pulmonary contusion, tracheal rupture, foreign body (FB)
Iatrogenic: Endotracheal intubation, complication of lung biopsy/aspirate, transtracheal wash, or bronchoscopy

pulmonary hypertension (secondary to congenital or acquired cardiac malformations that result in abnormal shunting of blood) uncommonly cause hemoptysis. Parasites including *Capillaria, Aelurostrongylus,* and *Paragonimus* species cause cavitated pulmonary lesions that rupture and bleed into airways. Chronic inflammatory conditions of the lung including heartworm disease, chronic bronchitis, bronchiectasis, and pulmonary infiltrate with eosinophils can result in inflamed and edematous mucosa that bleeds easily during coughing. Bacterial and fungal (*Blastomyces, Histoplasma, Coccidioides* spp.) pneumonia and lung abscesses may result in hemoptysis. Hemorrhage is a reported complication of transtracheal wash, lung biopsy, and bronchoscopy, and animals should be appropriately monitored after these procedures. Primary or metastatic neoplasia can result in erosion of pulmonary vessels. Blunt trauma or FB inhalation into the trachea or airways can result in hemoptysis. Rarely, ruptured arteriovenous malformations, bacterial endocarditis, and lung lobe torsions cause hemoptysis.

DIAGNOSTIC PLAN

Measures must be taken to stabilize the animal and avoid undue stress during diagnostics. The minimum data base includes a complete blood count (CBC) with platelet count, chemistry profile, urinalysis, and three-view thoracic radiographs. The blood work should be evaluated for evidence of chronic bleeding, inflammation, infection, and systemic disease. Thoracic radiographs should be carefully evaluated for evidence of cardiac enlargement, pulmonary edema or contusions, pleural effusion, pneumonia, primary or metastatic neoplasia, signs of thoracic trauma such as broken ribs, foreign objects, and evidence of heartworm disease. A heartworm antigen test (and antibody test in cats) should be performed in animals not receiving heartworm preventative. Occasionally, malignant cells or fungal elements may be seen on microscopic evaluation of sputum. Examination of feces, sputum, or both for evidence of parasites may be indicated. Once the patient is as stable as possible, bronchoscopy may be performed if indicated to directly examine the upper airway, trachea, and bronchi, remove foreign objects, and perform bronchoalveolar lavage (BAL) and culture. Additional testing might include pulmonary arterial catheterization, ventilation-perfusion scan, arterial blood gas, coagulation giocardiogram fine needle aspiration or open biopsy of the lung, thoracoscopy, and CT scan of the thorax.

GOALS OF TREATMENT

Establishing a patent airway and intravenous fluid (once cardiogenic causes are ruled out), oxygen, or blood product administration should be instituted as needed until the underlying disease process can be identified. Most commonly, hemoptysis is scant and self-limiting with cage rest and avoidance of stress. Antitussives may be indicated to decrease airway trauma from coughing, but sedation should be avoided because it increases the risk of aspiration of blood. If radiographs can localize bleeding to one lobe, the patient should be positioned with that side dependent. Broad-spectrum antibiotic therapy such as ampicillin and enrofloxacin or amoxicillin and clavulanic acid should be considered if bacterial infection is suspected (while cultures are pending) or as a prophylactic therapy to prevent pneumonia. If hemorrhage is uncontrollable, general anesthesia with suctioning of the airway, ventilatory support, or surgical intervention (or a combination of these treatments) may be indicated.

CHAPTER 64

Petechiae and Ecchymoses

Mary Beth Callan

Superficial bleeding into the skin or mucous membranes is referred to as *purpura*. Purpura can be categorized as petechiae and ecchymoses. Petechiae are small pinpoint hemorrhages (<3 mm) resulting from extravasation of blood from capillaries, whereas ecchymoses are larger areas of hemorrhage resulting from leakage of blood from small arterioles and venules. Petechiae and ecchymoses are observed in primary hemostatic defects (i.e., platelet-vessel abnormalities). They represent a mild form of surface bleeding without external blood loss but may be associated with more serious hemorrhage. Both are commonly seen in dogs but rarely in cats.

PATHOPHYSIOLOGY

The vasculature is lined by a layer of endothelial cells that are linked by continuous and well-organized tight junctions varying in width from 0 to 4 nm. This provides a selectively impermeable membrane that prevents the passive transfer of blood into the extravascular space. The subendothelial matrix and additional layers of the vessels (media and adventitia) also act as barriers against extravasation of blood. Vascular integrity is influenced by many factors, one of which is platelets. Ultrastructural and functional changes develop in the vascular endothelium of thrombocytopenic animals, and these abnormalities are promptly reversed by a rise in the platelet count. However, the molecular basis for the observed changes remains unclear.

Thrombocytopenia (reduced platelet numbers), either as a sole hemostatic defect or as part of a combined hemostatic disorder, is the most common cause of petechiae and ecchymoses in dogs and cats. However, thrombopathias and vascular disorders may also cause capillary bleeding.

Thrombocytopenia

Thrombocytopenia may be a result of decreased platelet production by the bone marrow or increased platelet destruction, consumption, or sequestration. Frequently more than one mechanism is involved. For example, bone marrow suppression, consumption of platelets secondary to vasculitis, splenic sequestration, increased destruction of platelets by both immune-mediated and nonimmune-mediated mechanisms, virus-associated myelodysplasia, and myeloproliferative disorders may contribute to thrombocytopenia in dogs and cats with infectious diseases (e.g., ehrlichiosis, babesiosis, Rocky Mountain spotted fever, leishmaniasis, feline leukemia virus [FeLV], feline immunodeficiency virus [FIV]). In addition to infectious diseases, common underlying causes for thrombocytopenia include neoplasia, drug reactions, and immune-mediated disorders.

The most common cause of petechiae and ecchymoses in the dog is increased platelet destruction associated with immune-mediated thrombocytopenia (IMT), a disorder in which antibodies bound to the surface of the platelet results in premature removal by the reticuloendothelial system. The bone marrow typically has normal to increased numbers of megakaryocytes. However, antibodies may also be directed against the megakaryocytes, resulting in decreased platelet production. Dogs suspected of having IMT should also be evaluated for hemolytic anemia, proteinuria, and polyarthritis. If any of these signs exist, systemic lupus erythematosus (SLE) should be considered. IMT occurs rarely in cats.

Increased sequestration of platelets resulting in thrombocytopenia has been observed in dogs with splenomegaly, hepatomegaly, and endotoxemia, as well as in experimental hypothermia. However, petechiae and ecchymoses are not typically observed as a result of sequestration of platelets.

Thrombopathia

Thrombopathias may be classified as inherited or acquired defects. Inherited disorders of platelet function have been identified in several breeds of dogs (e.g., Glanzmann's thrombasthenia of otter hounds and Great Pyrenees, δ-storage pool disease of American cocker spaniels) and a few cats. Spontaneous formation of petechiae and ecchymoses, mucosal surface bleeding, and excessive bleeding after surgery or trauma are common features of these disorders, and fatal hemorrhage has been observed in some affected dogs. Platelet function, as assessed by the bleeding-time test and various in vitro tests, may be affected by various systemic and hematologic disorders (e.g., uremia, liver disease, dysproteinemias) and by a large number of drugs. Although drugs of nearly every classification have been associated with acquired platelet dysfunction in humans, fewer drugs have been evaluated for adverse effects on platelet function in dogs and cats. Platelet dysfunction induced by aspirin, cephalothin, and acepromazine has been documented in vitro in the dog, but the in vivo effects of these drugs on platelet function are less clear. Nevertheless, it would seem prudent to avoid use of such drugs in dogs with known bleeding disorders.

von Willebrand disease (vWD), the most common inherited bleeding disorder in the dog, results from a reduction in the amount of functional plasma von Willebrand factor (vWF), leading to impaired platelet-vessel adhesion. vWD rarely causes petechiae, although ecchymoses may be observed in some dogs with vWD after trauma and surgical procedures. As with other primary hemostatic defects, typical signs of vWD include bleeding from mucosal surfaces (e.g., epistaxis, melena, hematuria) and excessive bleeding after surgery or trauma.

Vascular Disorders

In the absence of a quantitative or qualitative platelet abnormality, the presence of purpura suggests a vascular disorder. Vasculitis, secondary to infectious, inflammatory, immune-mediated, or neoplastic diseases or drug reactions, is the most common cause of vascular purpura. Some dogs with Cushing's disease are also prone to develop ecchymoses after minor trauma (e.g., cystocentesis), possibly as a result of increased protein catabolism leading to dermal and connective tissue atrophy and thus altered dermal vascular support.

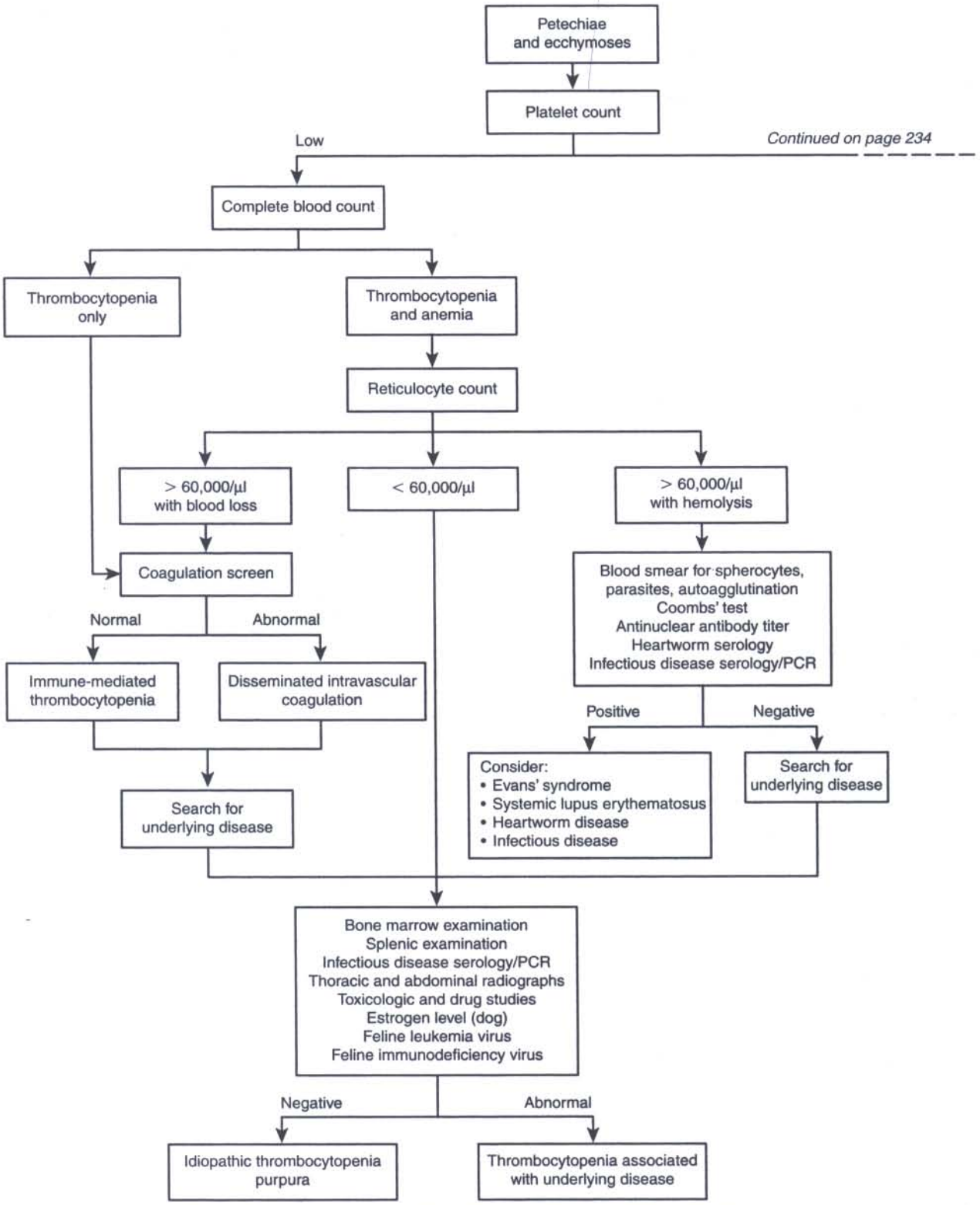

Figure 64-1 Algorithm for diagnostic approach to petechiae and ecchymoses.

PATIENT HISTORY AND PHYSICAL EXAMINATION

In a dog or cat with petechiae, ecchymoses, or both, the history may provide important clues as to the cause of the disorder. Given the many possible effects of various drugs on primary hemostasis (bone marrow suppression, immune-mediated thrombocytopenia, platelet dysfunction, and vasculitis), a complete medication history is imperative. Likewise, recent vaccinations, tick exposure, and previous or concurrent medical problems are relevant. A history of previous episodes of mucosal surface bleeding or purpura in an otherwise healthy

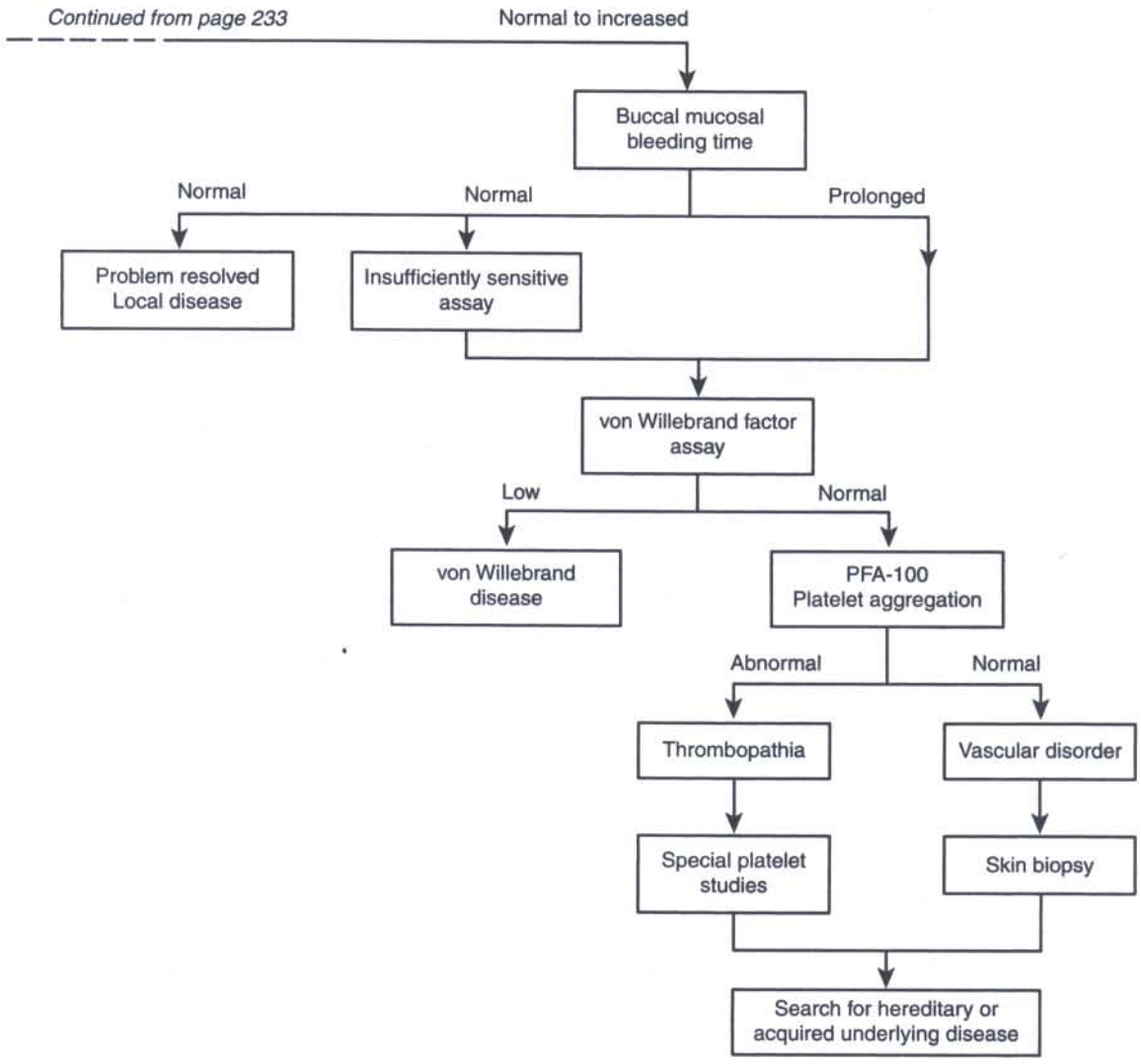

Figure 64-1 *Cont'd.*

animal or a family history of similar bleeding may be suggestive of an inherited thrombopathia.

Given that thrombocytopenia, thrombopathia, and vascular disorders may be associated with an underlying disease, a complete physical examination is essential. Peripheral lymphadenopathy, hepatomegaly, or splenomegaly (or a combination of these abnormalities) may indicate an underlying infectious, inflammatory, or neoplastic disease. Petechiae are most readily found on mucous membranes of the gingiva, prepuce, and vulva, as well as on sparsely haired skin of the ventral abdomen and pinnae. After phlebotomy, ecchymoses are commonly observed around the venipuncture site.

DIAGNOSTIC APPROACH

Because thrombocytopenia is the most common cause of petechiae and ecchymoses, the initial laboratory evaluation should always include a platelet count (Figure 64-1). Although electronic particle counters can quickly and accurately perform platelet counts in dogs, blood smears should also be evaluated. However, cell-counting instruments with a threshold function to separate platelets and red blood cells (RBCs) by volume may not be accurate in the cat (considerable overlap exists between erythrocyte and platelet volumes), resulting in spuriously low platelet counts. In addition, feline platelets tend to clump. A manual platelet count and evaluation of a blood smear are recommended for all cats (although platelet clumping may also lead to inaccurate manual counts) and for dogs in which the automated platelet count is low. In an emergency situation, evaluation of a blood smear to obtain an estimate of platelet number is sufficient; 10 to 20 platelets per oil immersion field are deemed adequate. Platelet counts are often less than 10,000/μL in dogs with IMT. In addition to providing an estimate of platelet number, evaluation of a blood smear may reveal evidence of RBC regeneration (polychromasia, anisocytosis, and macrocytosis), blood parasites, RBC agglutination, spherocytosis, or RBC fragments.

If the dog or cat is thrombocytopenic, evaluation of the complete blood count (CBC) to determine if other cytopenias are present will aid in formulation of a list of differential diagnoses and a focused diagnostic plan. Pancytopenia is most suggestive of bone marrow disease, whereas concurrent anemia and thrombocytopenia may be the result of blood loss anemia due to thrombocytopenia, immune-mediated destruction

of both RBC and platelets, or bone marrow disease. Newly synthesized or reticulated platelets can be identified using the ribonucleic acid (RNA)–binding fluorescent dye thiazole orange and flow cytometry. Reticulated platelets lose RNA within 24 hours after entering the peripheral circulation. The percentage of reticulated platelets is typically increased in dogs with IMT. However, the absolute numbers may be within reference range because of the low total number of platelets. The assay for measurement of reticulated platelets is rapid and less invasive than obtaining bone marrow samples to evaluate thrombopoiesis and may be readily available through commercial diagnostic laboratories in the future.

A bone marrow aspirate or biopsy is indicated in dogs and cats with pancytopenia, nonregenerative anemia and thrombocytopenia, persistent thrombocytopenia despite therapy, or atypical cells noted in the peripheral blood. A bone marrow aspirate is not necessary in all patients with IMT but should be considered when the platelet count has not increased within 5 to 7 days of initiating immunosuppressive therapy. Despite severe thrombocytopenia, excessive bleeding is rarely a complication of bone marrow aspiration or biopsy.

The buccal mucosal bleeding time (BMBT) evaluates only primary hemostasis or the platelet-vessel interaction. A BMBT is indicated in animals with petechiae and ecchymoses that are not thrombocytopenic. The BMBT is performed using a spring-loaded device that is standardized to produce uniform incisions. Simplate devices (Organon Tecknika Corp., Durham, NC) are available with one or two blades and produce incisions approximately 5 mm long and 1 mm deep (clinicians should not use blades with only 0.5 mm depth). Single-blade devices are recommended for cats and small dogs. Normal BMBT in the dog is less than 4 minutes and in the cat is less than 2 minutes. The effect of a low hematocrit (HCT) on bleeding time is often neglected, but ample evidence in the literature indicates an inverse relationship between HCT and bleeding time (the lower the HCT, the more prolonged the bleeding time) in humans with HCTs less than 25%. Altered rheologic properties of the blood and a reduced source of adenosine diphosphate (ADP) (RBCs release ADP) to activate platelets are mechanisms proposed for the prolongation of bleeding time in severely anemic patients. A prolongation of the BMBT in an animal with a normal platelet count and HCT suggests a thrombopathia, vWD, or a vascular disorder. Because vWD is much more common in the dog than intrinsic platelet function defects or vascular disorders, measurement of plasma vWF concentration is recommended before platelet function testing, particularly in dogs being evaluated for development of ecchymoses after surgery rather than for spontaneous formation of petechiae.

A point-of-care platelet function analyzer, the PFA-100 (Dade Behring, Miami, FL), assesses platelet adhesion and aggregation in citrated whole blood (800 µL per test sample) and provides results in less than 10 minutes. As with the BMBT, results of the PFA-100 are dependent on platelet count and HCT. This instrument, now available at a few veterinary teaching hospitals, has been useful in quickly identifying dogs with vWD and some thrombopathias, although measurement of plasma vWF concentration is necessary to differentiate these primary hemostatic disorders.

The cuticle bleeding time assesses both primary and secondary hemostasis and thus cannot differentiate between a thrombopathia and a coagulopathy. In addition, clipping the nail too short is painful. Finally, it is difficult to standardize this bleeding-time test, potentially providing misleading results. Therefore the BMBT is preferred to the cuticle bleeding time in the evaluation of animals with suspected disorders of primary hemostasis.

An activated clotting time (ACT), which assesses the intrinsic and common pathways of the coagulation cascade and thus provides similar information to the activated partial thromboplastin time (aPTT), is useful in ruling out a concurrent coagulopathy. Normal ACT in the dog is 60 to 110 seconds and in the cat is 50 to 75 seconds. In patients with severe thrombocytopenia (< 10,000/µL), the ACT may be slightly prolonged by approximately 10 seconds because of decreased availability of platelet phospholipid to support coagulation.

TREATMENT

Medical management of patients with petechiae and ecchymoses varies widely. Treatment is aimed at the underlying disorder (e.g., rickettsial infections, neoplasia, immune-mediated diseases). Because IMT is the most common cause of severe thrombocytopenia in dogs with resultant formation of petechiae and ecchymoses, most thrombocytopenic dogs should be initially treated with doxycycline and prednisone pending results of diagnostic tests. In some cases, discontinuation of medications (e.g., methimazole, sulfonamides) may be all that is necessary to resolve the primary hemostatic disorder.

Dogs and cats with petechiae and ecchymoses as the sole form of bleeding rarely require blood transfusion support. However, if concurrent mucosal surface bleeding exists, particularly into the gastrointestinal tract, leading to anemia, transfusion of packed RBCs may be indicated to provide additional oxygen-carrying support. Platelet transfusions in the form of fresh whole blood, platelet-rich plasma, or platelet concentrate are indicated in life-threatening or uncontrolled bleeding. A small amount of bleeding into the brain, myocardium, lungs, or oropharynx could have devastating consequences without resulting in anemia. Platelet transfusions are generally not recommended in patients with IMT (unless uncontrolled or life-threatening bleeding occurs) because the transfused platelets have a short life span (typically destroyed within minutes to hours).

CHAPTER 65

Electrolyte Disorders

David Church

Disorders of electrolyte homeostasis are among the most frequently encountered challenges in small animal practice. An understanding of the underlying physiologic interactions is essential for a logical approach to their recognition and management (Figure 65-1).

DISORDERS OF CALCIUM METABOLISM

Only about 1% of total body calcium is freely exchangeable with the extracellular fluid (ECF). Maintenance of normal serum calcium concentration in the ECF is controlled by calcium itself through a specific receptor along with a number of hormones, the most influential of which are parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D_3 (1,25 D_3).

Calcium circulates in the ECF in three fractions. Approximately 50% exists in a biologically active, ionized form and 40% is protein bound, predominantly to albumin, although this proportion can be increased in alkalosis and decreased with acidosis. Additionally, factors that lower albumin can lower total serum calcium concentration without actually lowering the biologically active serum calcium concentration. For these reasons, measurement of serum ionized calcium is recommended in all patients suspected of having a clinically significant perturbation of serum calcium.

Hypercalcemic Disorders

The signs associated with hypercalcemia generally correlate with the magnitude and rate of change in serum calcium and include weakness, lethargy, polydipsia and polyuria, inappetence, and vomiting. Diarrhea, constipation, arrhythmias, seizures, and muscle fasciculations are uncommon.

Mild hypercalcemia can be present in young, large breed dogs and is a reflection of accelerated calcium turnover associated with rapid bone growth. Various degrees of hypercalcemia may occur artifactually (lipemia or sample contamination with detergent). It can be transiently associated with hemoconcentration, hyperproteinemia, hypoadrenocorticism, or severe hypothermia. Hypercalcemia can be a persistent, pathologic abnormality secondary to a number of diseases including malignant neoplasia, primary hyperparathyroidism, and renal failure. Other less frequently encountered associations include vitamin D intoxication, granulomatous inflammatory disease, and marked osteolysis. Over 50% of hypercalcemic cats reportedly have associated renal failure or malignancy; however, no explanation for the hypercalcemia could be found in 12% of these animals. Approximately 70% of hypercalcemic dogs are azotemic, with azotemia uncommon in those with primary hyperparathyroidism.

In cats and dogs with renal failure, hypocalcemia rather than hypercalcemia is generally observed. However, whenever

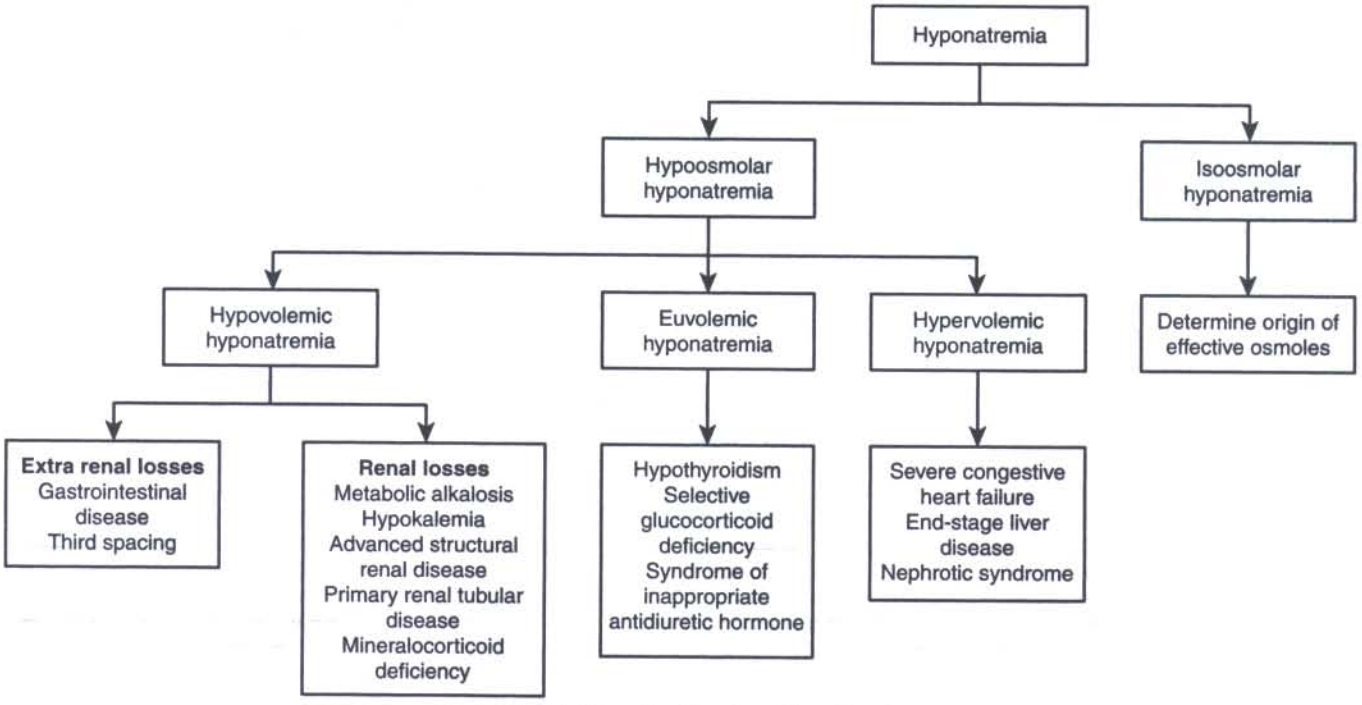

Figure 65-1 Algorithm for electrolyte disorders.

hypercalcemia is present in a renal failure patient, one must determine if the impaired renal function is *due to* the hypercalcemia or the renal failure has *resulted in* the hypercalcemia. Hypercalcemia impairs renal function by reducing renal sensitivity to antidiuretic hormone (ADH). The reduction in ECF volume decreases glomerular filtration rate (GFR), which is exacerbated by calcium's direct vasoconstrictive effect on afferent glomerular arterioles. Furthermore, decreased renal tubular delivery of sodium increases tubular resorption of calcium and aggravates hypercalcemia. Consequently, any hypercalcemic scenario will tend to impair renal function by reversible processes that do not affect renal structure nor necessarily cause irreversible nephron loss.

Hypercalcemia does, however, result in nephron destruction through tubular calcium phosphate deposition (so called nephrocalcinosis). Once sufficient nephrons are destroyed, this loss of functional renal mass will further impair renal function. Consequently, persistent hypercalcemia will eventually lead to significant structural renal disease.

Malignancy may cause hypercalcemia through secretion of calcemic factors by malignant cells. Many tumors produce either PTH or parathyroid hormone–related peptide (PTH-rP), which binds to PTH receptors and has similar bioactivity to PTH. Primary hyperparathyroidism is another recognized cause of hypercalcemia and is generally diagnosed by finding a mild-to-moderate hypercalcemia in dogs and cats with normal renal function and an inappropriately increased (midreference range to increased) intact serum PTH concentration. Granulomatous diseases may produce hypercalcemia due to granulomatous tissue conversion of 25 D_3 to 1,25 D_3.

Vitamin D toxicosis and hypercalcemia may be observed in animals oversupplemented with vitamin D analogues. Vitamin D intoxication can also occur with ingestion of cholecalciferol rodenticides, calcipotriol-containing psoriasis preparations, or plants containing calcitriol glycosides.

Hypercalcemia may also result from exposure to aluminum salts, vitamin A intoxication, various nonmalignant skeletal lesions, hyperthyroidism, and the administration of thiazide diuretics.

Hypocalcemic Disorders

Hypocalcemia occurs when calcium is lost from the ECF, often through renal mechanisms, in greater quantities than can be replaced by accelerated absorption from the intestine or bone depots. As with hypercalcemic disorders, falsely low levels of serum calcium due to hypoalbuminemia should be excluded by measuring serum ionized calcium concentration.

The clinical signs of hypocalcemia generally correlate with the magnitude and rapidity of the fall in serum calcium concentration. Manifestations of neuromuscular irritability predominate and include generalized muscle weakness with or without muscle fasciculation, which in severe cases may progress to tetanic spasms and even seizures. Cardiac manifestations include a prolongation of the QT interval that may progress to ventricular tachydysrythmias or various degrees of heart block.

Causes for hypocalcemia are extensive. Because calcium phosphate has a low solubility quotient, any condition that increases serum phosphate concentration such as release of large amounts of cellular phosphorous or acute impairment of renal function may result in a reduction in serum calcium concentration. In idiopathic disease after removal of a PTH-secreting tumor, a deficiency of PTH leads to increased renal calcium excretion and decreased intestinal calcium absorption, the latter secondary to reduced 1,25 D_3 production.

Hypocalcemia and hypomagnesemia frequently coexist and are often due to decreased absorption of dietary divalent cations. Hypomagnesemia impairs both PTH secretion and activity. A loss of extracellular calcium leading to hypocalcemia can occur with pancreatitis through the release of pancreatic lipase, degradation of retroperitoneal and omental fat, and binding of calcium in the peritoneum. Hypomagnesemia and hypoalbuminemia may also contribute to the hypocalcemia associated with acute pancreatitis. Other infrequent causes of hypocalcemia include endotoxic shock and dietary deficiency of vitamin D.

Disorders of Phosphate Metabolism

Plasma phosphate concentrations are relatively increased in young animals, decreasing to adult values by approximately 1 year of age. Phosphorous is predominantly absorbed from the gut by passive transport processes, although active transporters are stimulated by 1,25 D_3. Phosphorous is freely filtered by the glomerulus and more than 80% of the filtered load is reabsorbed in the proximal tubule. Proximal reabsorption occurs by passive transport coupled to sodium and is regulated mainly by phosphorous intake and serum PTH. Acute adaptation to a low- or high-phosphorous diet involves the insertion or retrieval of Na-P transporters from the brush border membranes of the renal proximal tubules, whereas chronic adaptation involves the synthesis of new transport proteins. PTH induces phosphaturia by inhibition of the Na-P cotransporters, thus its phosphaturic effect is diminished in phosphate deficiency. In addition, the renal tubules respond to dietary phosphate intake, although this effect is independent of plasma phosphate and PTH levels. The precise nature of the dietary phosphate signal is uncertain. In parallel with the antiphosphaturic effect of reduced dietary phosphate, an increase in bone resorption takes place leading to mobilization of phosphate and calcium from the skeleton. This renal tubular response to dietary phosphate means dietary restriction of phosphorous rarely leads to hypophosphatemia. However, hypophosphatemia can occur through internal redistribution, increased urinary excretion, decreased intestinal absorption, or combinations of all three.

Alterations in Sodium Metabolism

Although characterized by an abnormal sodium concentration, hypo- and hypernatremia generally reflect abnormalities in water balance that may or may not be accompanied by changes in sodium balance. Despite marked fluctuations in water intake and excretion, stable plasma sodium concentration is maintained by a complex interplay between osmoreceptors and baroreceptors, both of which control secretion of ADH, the primary physiologic determinant of the rate of free water excretion. The major stimuli to ADH secretion are hyperosmolality and depletion of the effective circulating volume. ADH-induced water retention lowers plasma osmolality and raises effective circulating volume. It is important to remember the physiologic response to hyperosmolality includes a second mechanism for modifying free water—the sensation of thirst mediated through the satiety centre. Although thirst is regulated centrally, it is sensed peripherally through sensory oropharyngeal receptors. The cessation of thirst is also mediated initially in the periphery by oropharyngeal mechanoreceptors that are stimulated by swallowing relatively large volumes of fluid.

Modification Due to Altered Osmolality

The osmoreceptors that govern ADH release are located in the hypothalamus and are activated by changes in intracellular water content and consequent alterations in intracellular osmolality. These changes in intracellular water content are determined by the levels of so called effective osmoles in both the intracellular and extracellular compartment. Effective osmoles are those determinants of serum osmolality that do

not readily cross cell membranes. Because sodium has poor cell membrane permeability and is by far the most abundant cation in the ECF, the serum sodium concentration with its accompanying anions generally accounts for nearly all of the effective osmotic activity of the plasma and is the primary osmotic determinant of ADH release. An increase in serum sodium invariably predicts a hyperosmolar state. However, a subnormal serum sodium concentration does not always reflect hypo-osmolar conditions because the presence of significant amounts of other osmotically active substances can modify osmolality with resultant variable effects on serum sodium concentration. In these situations the hyponatremia is a reflection of translocation of intracellular water rather than an indication of hypo-osmolality.

Modification Due to Altered Effective Circulating Volume

The carotid sinus baroreceptors are pressure receptors that induce secretion of ADH from cells in the paraventricular nuclei of the hypothalamus. The relationship between mean arterial blood pressure and plasma volume means they also function indirectly as volume receptors. They are much less sensitive than osmoreceptors, although once activated they produce marked increases in ADH secretion that exceed those induced by hyperosmolality. Potential exists for interaction between the osmoreceptors and volume receptors. Volume depletion will potentiate the ADH response to hyperosmolality but can also prevent inhibition of ADH release normally induced by a fall in the plasma osmolality. Volume depletion is also a potent stimulus to the thirst center, with hypovolemic patients having persistent activation of the thirst center even in the presence of hyponatremia. In other words, volume and tissue perfusion are maintained at the expense of plasma osmolality.

Hypo-Osmolar Hyponatremia

Underlying all hypo-osmolar hyponatremic states is a limitation of urinary water excretion due either to secretion of ADH through nonosmolar mechanisms despite serum hypo-osmolality or impaired renal diluting ability. Consequently in animals with hyponatremia, once hypo-osmolality has been established, assessment of the extracellular fluid volume allows each pet to be classified as hypovolemic, hypervolemic, or euvolemic. This classification can provide possible explanation or explanations for the hyponatremia.

Hypovolemic hyponatremia occurs with concurrent deficits of both total body sodium and total body water, with the former exceeding the latter. This occurs as a result of persistent ADH secretion in response to marked volume depletion with continued oral or parenteral hypotonic fluid intake. The reasons for the sodium depletion can be broadly divided into *extrarenal* or *renal* sodium losses. Extrarenal sodium losses are invariably due to gastrointestinal (GI) or third-space losses and are characterized by concentrated urine with minimal natriuresis.

The causes for renal sodium losses are more extensive. Some individuals with GI disease resulting in vomiting and metabolic alkalosis may have both extrarenal and renal sodium loss. Renal sodium losses may occur in these animals for a number of reasons. In a proportion of cases there may be an appreciable bicarbonaturia that, despite severe volume depletion, leads to natriuresis through attempts to maintain tubular electroneutrality. Furthermore, these dogs and cats may have concurrent hypokalemia that will interfere with renal sodium resorption and reduce osmoreceptor and thirst receptor sensitivity. The mineralocorticoid deficiency of hypoadrenocorticism will result in hypovolemic hyponatremia with marked natriuresis along with moderate to marked hyperkalemia and azotemia. In primary hypoadrenocorticism both the hypovolemia and the markedly increased secretion of ACTH provide a dual stimulus for ADH release regardless of the serum sodium concentration. Animals with advanced renal disease, primary renal tubular disorders, and osmotic diuresis all may have hypovolemic hyponatremia.

In hypervolemic hyponatremia, although total body sodium is increased, total body water is increased even more. This is an unusual occurrence in veterinary medicine, although it may be associated with severe cardiac or hepatic failure, nephrotic syndrome, and oliguric and anuric renal failure.

Euvolemic hyponatremia is an uncommon finding in small animal medicine, although theoretically it may occur in dogs and cats with glucocorticoid deficiency through nonspecific cosecretion of ADH with ACTH, as well as ADH-independent, glucocorticoid-mediated disturbances in renal hemodynamics. In man, euvolemic hyponatremia has been associated with hypothyroidism, postsurgical stress with overzealous hypotonic fluid administration, and the syndrome of inappropriate ADH secretion (SIADH) in which defective osmoregulation of ADH secretion through heightened osmoreceptor sensitivity takes place. In the most common form of SIADH in man, ADH release varies appropriately with serum sodium concentration; however, the threshold for ADH secretion occurs at an abnormally low osmolality.

The clinical signs induced by hyponatremia depend upon its severity and the rate of development. Although sodium remains above 130 nmol/L clinical signs are rare. When the serum sodium concentration decreases to <130 m/q/L, animals may have inappetence, vomiting, muscular weakness, and ataxia, whereas severe or acute hyponatremia may result in seizures and irreversible central nervous system (CNS) damage. Animals with an acute hyponatremia are at risk of developing permanent CNS damage through marked cerebral edema, whereas those animals with chronic hyponatremia are at risk of osmotic demyelination if the hyponatremia is corrected too rapidly.

Hypernatremia

The presence of hypernatremia represents a hyperosmolar state and may develop when water loss exceeds loss of sodium and potassium. Free water can only be lost from one of three places: (1) through the skin and respiratory tract (so called insensible water loss), (2) through the urine, or (3) through the gut. Urinary water loss requires impairment of either ADH secretion or end-organ sensitivity. Water loss through diarrhea is more variable. With diseases resulting in secretory diarrhea the fluid that is lost is iso-osmotic with plasma and is almost entirely composed of sodium and potassium salts. Although the animal may become profoundly volume depleted, the plasma sodium concentration will remain relatively unaffected. In conditions resulting in osmotic diarrhea the fluid lost is again iso-osmotic; however, the nonreabsorbed solute accounts for most of the osmolality. Consequently, water loss markedly exceeds sodium and potassium loss, and hypernatremia and volume depletion occurs. Similar considerations may apply to urinary water loss induced by osmotic diuretics such as glucose or mannitol, although the tendency for hypernatremia to develop will be offset by the translocational effect of these effective ECF osmoles.

As the thirst center will normally be concurrently activated by the increasing osmolality, any hypernatremic tendency should be offset by increased water consumption. Consequently, hypernatremia usually requires not only increased loss of free water but also reduced water consumption. The latter is generally due to either reduced availability of water to an appropriately thirsty animal or impaired activation of the thirst center through neurologic pathology or dysfunction in the hypothalamic region that may be either a primary problem or secondary to intercurrent illness.

DISORDERS OF POTASSIUM METABOLISM

Although sodium is primarily located extracellularly, roughly 98% of total body potassium is located within cells. Localization of sodium and potassium to the different fluid compartments is maintained by the Na-K ATPase cell membrane pump that actively pumps sodium from the cell and potassium into it in a ratio of two potassium ions for every three sodium ions.

Potassium Homeostasis

The plasma potassium concentration is predominantly determined by various homeostatic mechanisms controlling both internal and external balance, although total body potassium levels may have a modifying influence.

Internal potassium balance determines the ratio of intracellular to extracellular potassium and is influenced by many factors including extracellular pH, bicarbonate, insulin, glucagon, catecholamines, and osmolality. Acidosis and alkalosis are potentially potent influences on the internal balance of potassium. As H^+ ions move relatively freely across cell membranes, potassium tends to move in the opposite direction to maintain electrical neutrality. Consequently, ECF acidosis results in intracellular movement of H^+ ions and extracellular movement of K^+. The opposite occurs with alkalosis. Acidosis also inhibits Na-K ATPase activity, although this hyperkalemic effect is countered to some degree by an associated acidosis-induced reduction in the cell membrane's permeability to potassium.

Equally alkalemia, either metabolic or respiratory, promotes intracellular potassium entry although the effect tends to be relatively mild. A more potent hypokalemic effect may be seen with bicarbonate administration because plasma bicarbonate directly promotes intracellular potassium movement.

Various hormones including insulin, the catecholamines, and thyroxine may modify normal transcellular potassium balance. Insulin promotes potassium influx and sodium efflux from the cell through insulin's activation of the electroneutral Na^+/H^+ exchanger. Na-K ATPase then removes the resultant increase in intracellular sodium, with a consequent intracellular shift of potassium. In contrast, catecholamines lower plasma potassium by β_2 activation of membrane-bound adenylate cyclase and subsequent stimulation of Na-K ATPase. Synthesis of Na-K ATPase is stimulated by thyroid hormone, and this effect can contribute to the hypokalemia of hyperthyroidism.

External potassium balance is predominantly determined by renal modification of kaliuresis based on a complex array of factors. Although the majority of filtered potassium is resorbed actively in the proximal tubule, regulation of potassium excretion predominantly occurs in the cortical collecting duct (CCD). The cells lining the CCD contain high numbers of Na-K ATPase pumps on their basolateral membranes and abundant numbers of potassium channels on their luminal surface. Altering the activity of the basolateral Na-K ATPase pumps or changing factors that encourage diffusion of intracellular potassium into the CCD through the luminal potassium channels can modify renal potassium excretion.

The most potent modifiers of renal potassium excretion include potassium intake, aldosterone, ADH, and the animal's acid-base status. In man, a chronic high potassium intake increases the number of basolateral Na-K ATPase pumps in the CCD (and in the colon), thereby facilitating increased renal and colonic potassium excretion. Aldosterone, ADH, and alkalosis increase kaliuresis by activation of both basolateral Na-K ATPase pumps and luminal potassium channels. Additionally the mechanism by which potassium and hydrogen may exchange for one another in the CCD favors renal potassium wasting in alkalosis and retention in acidosis. Luminal fluid flow rate and sodium content in the CCD will also influence renal potassium excretion. Sodium ions in the CCD tubular fluid are resorbed through luminal sodium channels down their concentration gradient, making the tubular fluid more electronegative and consequently increasing the tendency for intracellular potassium, through its luminal potassium channels, to move down both its concentration and electrical gradients into the CCD tubular fluid. This effect will be enhanced with increased tubular fluid delivery to the CCD.

Hypokalemia

Hypokalemia may develop as a postcollection artifact in some animals with a marked leukocytosis due to excess potassium uptake by the nucleated cells. Generally, however, hypokalemia reflects a breakdown in normal homeostatic mechanisms resulting in marked intracellular shifts or excessive losses of potassium.

A syndrome of fluctuating muscle weakness with concurrent hypokalemia has been reported in Burmese cats. The underlying cause for this condition is poorly understood, although it may be a result of dramatic intracellular shifts in potassium similar to the syndrome of familial hypokalemic periodic paralysis in man.

Insulin, catecholamines, and thyroxine all increase intracellular uptake of potassium, whereas accidental ingestion of barium compounds may cause hypokalemia by blocking potassium membrane channels and hence extracellular potassium movement. However, most commonly, hypokalemia is the result of either abnormal kaliuresis or GI losses associated with vomiting or diarrhea. As discussed previously, renal potassium loss will occur in any metabolic alkalosis, particularly if induced by selective chloride depletion due to vomiting, hypersecretory disorders of the upper GI tract, or both. The association is further enhanced because hypokalemia itself may play a role in the development and maintenance of metabolic alkalosis.

Additionally, primary hyperaldosteronism and various genetic abnormalities that influence the activity of renal ion transporters or activation and deactivation of cortisol in renal tubules may be rare causes of metabolic alkalosis and hypokalemia.

Increased urinary loss of potassium will also occur in several forms of metabolic acidosis in which concurrent increased distal tubular sodium delivery and flow takes place, as is seen with the osmotic diuresis associated with diabetes mellitus. The acidosis will tend to increase plasma potassium concentration and mask the tendency for depletion of total body potassium through kaliuresis. By increasing distal tubular sodium delivery, the thiazide and loop diuretics, as well as larger doses of the intravenous penicillins, may cause hypokalemia. Aminoglycoside antibiotics, cisplatin, and amphotericin B all cause renal potassium loss through magnesium depletion. Hypomagnesemia can lead to potassium depletion and hypokalemia because it not only reduces intracellular potassium movement through impairment of Na-K ATPase activity but also leads to decreased potassium resorption in the loop of Henle and the CCD.

Hypokalemia can result in varying degrees of muscle weakness and enhanced myocardial excitability through activation of the normally inactive cell membrane sodium channels. Potassium depletion also may interfere with renal function. Diminished urinary concentrating capacity is a reversible consequence of hypokalemia and is due in part to impaired renal responsiveness to ADH through reduced expression of aquaporin-2 and decreased renal countercurrent function caused by impaired NaCl transport in the loop of Henle. In addition, these changes will result in an increased delivery of tubular fluid to the CCD and a consequent reduction in GFR.

Hyperkalemia

Hyperkalemia may occur as a postcollection artifact. This is a particular problem in the Japanese Akita breed, although rare changes in plasma potassium concentration occur in other dogs or cats. Although the presence of hyperkalemia is a common finding in many diseases, it invariably reflects impaired renal function together with varying degrees of nonspecific tissue damage, cell destruction, and intracellular potassium release into the ECF. Conditions characterized by hyperkalemia include hypoadrenocorticism, primary hypoaldosteronism, malignant hyperthermia, thromboembolic disorders resulting in marked myonecrosis, and idiosyncratic reactions to angiotensin converting enzyme inhibitors and nonsteroidal antiinflammatory agents. Hyperkalemia can be associated with any form of renal failure although it tends to be more profound in conditions resulting in either acutely impaired renal function, or urethral obstruction.

The clinical signs that are directly referable to hyperkalemia include varying degrees of muscular weakness and disturbances in cardiac conduction. These signs are due to changes in neuromuscular conduction caused by reduced membrane excitability, a result of further inactivation of cell membrane sodium channels.

The clinical consequences of hyperkalemia are uncommon unless plasma potassium exceeds 7.5 mmol/L. However, substantial interpatient variation occurs because factors such as the plasma calcium concentration and acid base status can modify the toxicity of hyperkalemia.

DISORDERS OF MAGNESIUM METABOLISM

Magnesium is predominantly an intracellular cation, with only 1% of total body magnesium found extracellularly. Although the majority of filtered magnesium is resorbed in the proximal tubule and loop of Henle, magnesium regulation occurs through variable resorption in the distal tubule. Many hormones can influence renal handling of magnesium; however, the major regulator of reabsorption is the plasma magnesium concentration itself.

Depletion of total body magnesium can occur through GI losses associated with acute or chronic diarrhea, malabsorption, and/or steatorrhea. Some evidence suggests that Yorkshire terriers, collies, and German shepherds are more prone to developing hypomagnesemia with these types of enteropathies, and a recent report suggested hypomagnesemia was a common finding in Cavalier King Charles spaniels. Many other factors may contribute to hypomagnesemia, including increased intracellular movement of magnesium induced by alkalosis or insulin, impaired renal resorption, and the pharmacologic actions of various drugs.

Urinary magnesium loss is often the basis for magnesium depletion. Tubular resorption is related to urine flow, so long-term parenteral fluid therapy and volume expansion may result in magnesium deficiency. Hypercalcemia and calciuria reduce tubular resorption of magnesium, as does glucosuria or any cause for osmotic diuresis.

A close link exists between magnesium and potassium concentrations. Potassium depletion is associated with reduced distal tubule resorption of magnesium, magnesuria, and hypomagnesemia. Furthermore, hypomagnesemia produces secondary cellular potassium depletion, kaliuresis, and hypokalemia as a result of increased potassium secretion in the loop of Henle and the CCD. Finally, reversible hypocalcemia due to impaired PTH secretion and target tissue PTH insensitivity is a consistent finding with hypomagnesemia. Consequently, otherwise unexplained hypocalcemia and hypokalemia is highly suggestive of underlying magnesium depletion.

SECTION II

Toxicology

CHAPTER 66

Intoxication versus Acute, Nontoxicologic Illness: Differentiating the Two

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Any acutely ill animal can present a diagnostic challenge if toxicosis is suspected but a clear recent history is not available. Common examples of such a situation include the pet that disappears and returns home with clinical signs or the found stray dog or cat that is ill. To address this challenge, this chapter presents common clinical problems that often are due to either intoxication or naturally occurring disease, and it highlights features of each to help elucidate the problem's cause in the absence of a medical history.

The categorization of toxicants and illnesses presented in this chapter is based solely on the patient's predominant clinical sign or abnormality. For management of suspected intoxications prior to the onset of overt signs or for details of specific diseases or intoxications, the reader is referred to the chapters indicated in each section and the references listed at the end of the chapter.

In general, intoxications probably are more likely in individuals known to be susceptible to ingestion (dogs or cats that are known to chew or swallow foreign material). Whether this behavior exists should be established as an initial part of the history whenever possible.

CENTRAL NERVOUS SYSTEM ALTERATIONS AND SEIZURES

Many intoxications are systemic and thus produce diffuse effects, such as central nervous system (CNS) alterations and seizures (see Chapter 48). Therefore in general, an interictal neurologic exam that reveals asymmetrical CNS deficits is inconsistent with ongoing toxicity.

With *lead* toxicity, such as from ingestion of paint chips, lead ornaments, or fishing weights, the onset of CNS signs and seizures may begin within a few days after the ingestion. Other signs of lead toxicity can include anorexia, vomiting, diarrhea, or constipation. Due to poor bioavailability, lead that is not ingested (e.g., gun pellets embedded in the tissues) almost never causes toxicity. In lead toxicity, basophilic stippling (25%) and nucleated red blood cells (RBCs) (54%) occur more often than anemia (8% of cases) and radiographic signs of metal in the gut (20%). Seizures that occur with *metaldehyde* (snail and slug bait) toxicity are distinctive in their speed of onset (30 minutes to 6 hours after ingestion) and in the prominent muscle tremors they generally produce, often resulting in marked hyperthermia (>106° F) that should be treated with cooling measures, not antipyretic drugs. A sweet, acetone-like smell of the vomitus or the whole animal may be apparent to some clinicians. Metaldehyde-induced seizures tend to respond well to antiseizure medications (high doses may be necessary). Clinical signs generally last 1 to 2 days, but acute hepatic damage can occur 24 to 48 hours later. Seizures induced by such *tremorgenic mycotoxins* as penitrem A or roquefortine occur within a few hours of consumption of moldy refrigerated foods or organic debris. Hypersalivation and vomiting commonly precede the seizures, and severe muscle tremors causing hyperthermia are also common. Uncomplicated cases resolve in 2 to 3 days. A similar syndrome occurs with ingestion of certain *blue-green algae* (see following discussion of acute hepatic damage). *Organophosphate-* and *carbamate*-induced of seizures very often occur with concurrent cholinergic signs, including vomiting, profuse diarrhea, hypersalivation, and increases or decreases in muscle tone, heart rate, or pupil size (though pupils remain symmetrical). Onset of signs is usually within minutes to a few hours of ingestion. Low blood cholinesterase levels (human or veterinary laboratory) are diagnostic. In dogs, *chocolate* toxicity that leads to seizures usually does so within 12 hours of ingestion. Signs that precede the seizures commonly include polydipsia (PD), vomiting (brown color), tachycardia, and restlessness. *Marijuana* toxicity typically first produces CNS depression; vomiting, hypersalivation, and vocalization also occur. Rapid confirmation of toxicity is possible with over-the-counter (OTC) illicit drug test kits or by submitting a urine sample to a human hospital. The presence of anuria, azotemia, or a high osmole gap raises the possibility that seizures could be due to *ethylene glycol* toxicity (see discussion of acute renal failure that follows). Large ingestions of *ethanol* or *methanol* (distilled alcohol; fermented foods or grains) may terminally cause seizures, often preceded by vomiting, CNS depression, ataxia, disorientation, and coma.

Naturally-occurring illnesses that cause CNS alterations and seizures include *head trauma* (signs of blunt or penetrating injury should be present if trauma alone is causing seizures), *meningitis* (asymmetrical deficits during interictal period, neck pain, or papilledema on fundic exam would increase likelihood; cerebrospinal fluid [CSF] tap for diagnosis), *hydrocephalus* (persistent fontanelle may or may not be an indicator but allows transcranial ultrasound for diagnosis), *intracranial neoplasia* (more likely than intoxication if asymmetrical neurologic deficits are present during interictal period), *congenital portosystemic shunts* (PSS); (majority of symptomatic patients <6 months of age; concurrent cryptorchidism suggestive of PSS; liver commonly small on radiographs; pre- and post-prandial bile acid levels with or without skilled ultrasonography are most valuable for diagnosis, but if icterus, ascites, or very high liver enzyme elevations are present, PSS alone is unlikely), *rabies* (unvaccinated status, endemic area, and possible exposure to wildlife increase likelihood; fresh bite wounds are not usually relevant to seizures because rabies virus incubation period is at least 2 weeks), and *canine distemper* (fundic lesions, "hard pad disease" increase likelihood; if present, signs of conjunctivitis, rhinitis, or gastroenteritis are *not* usually from distemper once seizures are occurring; indirect fluorescent antibody [IFA] test for diagnosis). *Hypocalcemia*

(measure blood calcium) and *hypoglycemia* (measure blood glucose) should be ruled out immediately in all seizuring patients because they are common, rapidly controllable causes of seizures. Sustained, profound *bradycardia* (e.g., <40 beats/minute for large dogs, <80 beats/minute for cats or small dogs) may cause syncope, progressing to cerebral hypoperfusion and seizures; heart rate should be measured during examination and on an electrocardiogram (ECG) if necessary. *Idiopathic epilepsy* remains the diagnosis of exclusion for recurrent seizures of unidentifiable cause.

MUSCLE WEAKNESS, PARESIS, AND FLACCID PARALYSIS

Weakness, paresis, and paralysis caused by intoxications tend to be symmetrical and diffuse, whereas a regional distribution may be observed with nontoxic causes. When it occurs, progression from weakness to paresis and paralysis is often quite rapid (hours) and uninterrupted with intoxications; it may be much slower or even chronic or malingering (e.g., wax-wane) with nontoxic causes. (For more on muscle weakness, paresis, and flaccid paralysis, the reader is referred to Chapter 46.)

Coral snakes (Southwestern, Southern United States and southward) can inflict a bite that produces paresis and paralysis within hours. Concurrent dysphagia and dyspnea are common, causing overlap in signs with botulism. However, coral snake bites usually cause swelling at the site of envenomation and may cause such additional signs as muscle fasciculations, vomiting, hypersalivation, and anemia with hemoglobinuria due to hemolysis. Bites of *black widow spiders* (*Latrodectus* spp.) throughout the United States typically cause an onset of signs within 8 hours of the bite. Muscle fasciculations, salivation, and generalized weakness, followed by flaccid paralysis can be observed. Such *phenoxy herbicides* as 2,4 D can cause muscle weakness and paresis within 24 hours of exposure. These common household herbicides can be absorbed by animals walking through wet, recently-treated lawns and usually cause other signs including vomiting, diarrhea, occasionally hepatic damage, and possibly may induce muscle rigidity. Dogs that ingest *macadamia nuts* (>1 to 2 g/kg body weight) may show diffuse muscle weakness and ataxia within 12 hours of ingestion and for 1 to 2 days' duration. Vomiting commonly occurs first, and depression, muscle fasciculations, and hyperthermia may occur concurrently.

Medical differential diagnoses for diffuse muscle weakness, paresis, and flaccid paralysis include *acute polyradiculoneuritis/coonhound paralysis* (diffuse muscle pain fairly common), *tick paralysis* (ticks may or may not be present [e.g., *Dermacentor* spp. in North America, *Ixodes* spp. in Australia]), *botulism*, and *myasthenia gravis* (acetylcholine receptor antibody test required for diagnosis; edrophonium test less commonly rewarding; weakness may classically be exercise induced and rest responsive, or it may be profound and continuous). Disorders not affecting the neuromuscular system directly, such as *joint pain* (suggested by joint swelling, resentment to manipulation of joints, and radiographic and cytologic abnormalities) or *aortic thromboembolism* (more likely if cyanosis of nail beds, absent pulse, cool extremity of affected limb, heart murmur, gallop sound, or cardiac arrhythmia are present) may also produce clinical signs appearing to suggest weakness. Such systemic disorders as *hyperviscosity* (evaluate hematocrit, serum globulins), marked *hyponatremia* (measure serum sodium), and *hypokalemia* (measure serum potassium) may also cause these signs. Diffuse muscle weakness can be caused by *profound anemia* (measure hematocrit) or such systemic disorders as *severe hypovolemia* (more likely if poor pulse quality, cool extremities, and tachycardia are present), or *marked hypo-* or *hyperthermia* (body temperature should be checked), all of which can alter mental alertness along with the weakness. Finally, degenerative spinal cord diseases such as *degenerative myelopathy* may cause ataxia and weakness; however, in most cases the hindlimbs are predominantly (or solely) affected and patients tend to be older, larger dogs, often with evidence of chronicity (e.g., worn dorsal toenails) if signs are severe.

ACUTE BLINDNESS

With massive ingestion of *salt*, severe mentation changes (profound mental depression, seizures) are expected simultaneously if blindness is present, as well as extreme hypernatremia (serum Na >180 mEq/L). Accidental ingestion of *horse dewormers* containing ivermectin or similar compounds (moxidectin) by dogs can cause acute blindness that is usually reversible, may last for a few days, and is accompanied by ataxia, tremors, shaking, CNS depression, or seizures. Differentiation from nontoxic causes is difficult and relies on the possibility of exposure (e.g., rural setting, horses in region); resolution is possible with supportive care. (For more on acute blindness, the reader is referred to Chapter 26.)

Medical differential diagnoses for acute blindness include *trauma* (more likely if signs of blunt or penetrating injury to the head or face, or obvious corneal, conjunctival, or scleral lesions are present); *retinal hemorrhage* or *detachment* (fundic exam; blood pressure measurement; assessment of coagulation if signs of coagulopathy); *glaucoma* (tortuous conjunctival vessels and corneal haze are common; intraocular pressure >30 mm Hg is diagnostic); acute onset of *cataracts* (presence of diabetes mellitus increases likelihood; ocular exam); *optic neuritis* (fundic examination; possibly CSF tap); *other disorders of the optic nerves, optic chiasm, optic radiation, or occipital cortex* (increased likelihood with other intracranial signs; CSF tap, imaging for diagnosis, or both); and *sudden acquired retinal degeneration* (electroretinogram for diagnosis).

ORAL MUCOSAL LESIONS

Ingestion of such substances as *corrosive acids* (e.g., some toilet cleaners, drain openers, antirust compounds), *alkalis* (e.g., alkaline batteries, bleaches, homemade soaps), *cationic detergents* (e.g., disinfectants, fabric softener sheets), *liquid potpourri* (more commonly in cats), or *formaldehyde* can cause mucosal injury and oral ulcers when ingested. Induction of vomiting is usually contraindicated, to avoid chemical esophagitis. (For more on oral mucosal lesions, the reader is referred to Chapter 219.)

Medical differential diagnoses for oral mucosal lesions include *uremic stomatitis* (more likely with abnormal kidneys on palpation, especially if azotemia and inadequately concentrated urine also are present), *periodontal disease* (usually concurrent with severe dental calculus; distribution of lesions more along gingivae and cheeks than tongue), *trauma* (e.g., persistence of foreign body such as porcupine quills), chewing on *electrical cord* (often including other signs of electrocution, such as mentation changes, dyspnea from noncardiogenic pulmonary edema; oral lesions commonly linear or regional, rather than multifocal), *systemic lupus erythematosus* or other autoimmune diseases (ulcerations most commonly at mucocutaneous junction; other cutaneous and systemic signs common), *feline calicivirus* infection (unvaccinated cats more susceptible; often, concurrent nasal congestion or purulent nasal with or without ocular discharge), *candidiasis* (cytology), or *feline leukemia virus* (FeLV) or *feline immunodeficiency* virus (FIV) infection (other signs possible; serologic tests).

ACUTE RENAL FAILURE

Ethylene glycol intoxication may first manifest with signs mimicking drunkenness, followed by weakness, ataxia, vomiting, recumbency, and seizures. Metabolic acidosis may be detectable within 1 to 2 hours of ingestion, hyperglycemia by 3 to 9 hours, and hyperkalemia and hypocalcemia by 6 to 9 hours. Serum urea and creatinine (CR) elevations are usually first apparent only 12 hours postingestion. Ethylene glycol intoxication can be suspected with an osmole gap greater than 15 mOsm/μL (osmole gap = measured serum osmolality – [2X (Na+K) + blood urea nitrogen (BUN)/2.8 + glucose/18]; for Système International Units [outside United States], osmole gap = measured serum osmolality – [2X (Na+K) + BUN + glucose]); an elevated osmole gap typically is detectable within 1 to 2 hours of ingestion of ethylene glycol. Confirmation is with a veterinary test kit or by submitting a urine or blood sample to a veterinary or human hospital laboratory for ethylene glycol analysis. In dogs, acute renal failure caused by ingestion of *grapes* or *raisins* typically manifests with vomiting within a few hours of ingestion, followed by polyuria (PU) and PD, depression, anorexia, and signs of abdominal pain. The vomitus can be informative (visible traces of grapes or raisins). Signs of renal failure occur in the subsequent 24 hours, and some have responded to supportive treatment (a few days to 3 weeks). Pancreatitis can occur concurrently. In cats, ingestion of *lilies* (Easter lily *[Lilium longiflorum]*, tiger lily *[L. tigrinum]*, *L. rubrum*, Japanese showy lilies *[L. speciosum, L. lancifolium]*, or day lily [*Hemerocallis* spp.]) can cause acute renal failure. Vomiting, anorexia, and depression occur 2 to 4 hours postingestion, and azotemia and isosthenuria occur 24 to 72 hours later.

Medical differential diagnoses for acute renal failure include *renal infiltration* as with lymphoma (kidneys often enlarged on palpation; ultrasound and cytology [and/or biopsy] for diagnosis), *renal thromboembolism* (more likely with procoagulant states; Doppler ultrasound of renal vessels to assess), *pyelonephritis* (urinalysis may reveal evidence of urinary tract infection; ultrasound, urine culture indicated), and *end-stage chronic renal failure* (azotemia, nonregenerative anemia, isosthenuria, and negative urine culture are needed to make this diagnosis). (For more on acute renal failure, the reader is referred to Chapter 258.)

ACUTE HEPATIC DAMAGE

Mushroom poisoning (e.g., *Amanita phalloides*) may cause acute hepatic damage in dogs 1 to 2 days postingestion; these signs usually follow acute vomiting, diarrhea, signs of abdominal pain, and anorexia that begin a few hours after ingestion. Similarly, ingestion of *blue-green algae*, usually from drinking pond water, produces acute vomiting, diarrhea, and signs of abdominal pain within 6 hours, progressing to intrahepatic hemorrhage, hypovolemic shock, and acute liver failure in hours to days depending on dose and type of algae. The patient's muzzle should be inspected because in some cases the exposure and diagnosis are strongly aided by the finding of algae around the lips or nose. *Iron* toxicity, most commonly from the ingestion of an overdose of multivitamins, may first produce signs of gastrointestinal (GI) disturbance, followed by apparent recovery for a few hours, and then progressive weakness and possibly shock. Signs of liver failure occur 1 to 2 days later. The iron in vitamins is not radiographically detectable as metal. Iron toxicity produces elevated serum iron levels, usually more than the total serum iron–binding capacity. Ingestion of any part of the *sago palm* or *cycad palm* (*Cycas* spp.), native to the Southwestern United States, can cause acute GI disturbances, followed by signs of acute liver failure 1 to 3 days after ingestion. Some dogs also show such neurologic signs as weakness, ataxia, depression, or seizures. All parts of the plant are considered toxic, especially the seeds (1 to 2 of which can be lethal to an average-sized dog), and mortality in dogs in general is high (33%). (See also Chapters 227, 228, and 230.)

Medical differential diagnoses for liver failure include acute systemic processes such as *sepsis* (suggested by the presence of a focus of infection, elevated white blood cell [WBC] count, left shift and toxic changes on complete blood count [CBC]); *heat stroke* (elevated body temperature); *leptospirosis* (renal failure often concurrent; serology); *heartworm caval syndrome* of dogs (likelihood dependent in part on geographic location; heartworm antigen test positive; heartworms may be seen in right heart or cavae on echocardiogram); *trauma* (more likely with signs of trauma elsewhere on patient; hemoabdomen, fractures possible); and advanced cases of primary hepatobiliary disorders including *hepatic lipidosis* of cats (more common in obese cats; abdominal ultrasound shows diffusely hyperechoic liver; biopsy should be done to confirm); *cholangitis, cholangiohepatitis,* and *lymphocytic portal hepatitis* of cats; *chronic hepatitis* of dogs (in advanced stages, microhepatica possible on radiographs or ultrasound; ascites possible [pure transudate]; see previous discussion of CNS alterations.) In general, ultrasound evidence of marked microhepatica, a markedly nodular liver, or ascites that is a pure transudate (or a combination of these factors), are suggestive of chronic liver disorders or infiltrative liver disease rather than acute toxicity. Similarly, normal liver enzyme values (alanine aminotransferase [ALT], aspartate transaminase [AST], alkaline phosphatase [ALP]) may occur with liver failure originating from longstanding, naturally occurring liver disorders (e.g., PSS, chronic hepatitis) but are inconsistent with acute, toxic causes of liver failure. Ultimately, in the absence of a medical history, persistent signs of hepatopathy for more than several days despite supportive care warrant a liver biopsy to further pursue the diagnosis.

SEVERE ANEMIA

Ingestion by dogs of *onions* or *garlic* (as little as 3.5 oz of minced onions in a 25 lb [11 kg] dog), *zinc* (ingestion of U.S. pennies minted in 1983 or thereafter or galvanized nuts or cage wires), or *naphthalene mothballs* (one mothball for a medium-sized dog can cause signs; breath may smell like mothballs can all acutely produce GI signs), followed by Heinz body hemolytic anemia and hemoglobinuria within 1 to 2 days of ingestion. In cats, *acetaminophen* causes methemoglobinemia, Heinz body anemia, and hemolysis. Severe anemia of toxic origin may also come from blood loss caused by *anticoagulant rodenticide* ingestion, in which case overt signs of hemorrhage (e.g., melena, epistaxis, hematuria) may be present, or dyspnea (pulmonary hemorrhage, airway hematoma) or lethargy (hypovolemia, anemia) may be dominant features. Suspicion of the latter diagnosis comes from these signs together with failure of blood to clot in vitro or bruising after venipuncture or handling. Hematocrit may or may not be decreased depending on acuity and severity of blood loss. A markedly increased prothrombin time (PT) is highly suggestive of anticoagulant rodenticide toxicity. (For more on severe anemia, the reader is referred to Chapters 59, 270, and 271.)

Medical differential diagnoses for severe anemia include traumatic overt blood loss (physical exam); GI blood loss (more likely in presence of feces with melena; hematochezia; or vomitus with black flecks of digested blood or strong positive reaction on blood square of urine dipstick); bleeding abdominal mass (more common in larger breed, older dogs; palpable abdominal mass or abdominal fluid wave [or both]; ultrasound

and abdominocentesis for confirmation); immune-mediated hemolytic anemia (IHA) (spherocytosis, positive Coombs' test, in-saline autoagglutination are all more suggestive of IHA); immune-mediated thrombocytopenia (thrombocytopenia often marked [<30 k]); ehrlichiosis (anemia classically with neutropenia, thrombocytopenia, and hyperglobulinemia, but variable; titers or polymerase chain reaction [PCR] to pursue the diagnosis); *Mycoplasma hemofelis* infection in cats (formerly *Hemobartonella felis;* seen on blood smear; may be incidental finding only); feline leukemia (FeLV test); hookworms (fecal flotations; evidence of regeneration, iron loss; empiric deworming); chronic renal failure (often small kidneys; azotemia with isosthenuria); and other neoplasia (thoracic radiographs may reveal mass, effusion, or metastases; abdominal palpation or ultrasound may reveal intestinal thickening or mass; if present, biopsy should be considered to confirm). With the exception of intoxications causing aplastic anemia, anemias of toxic origin tend to be regenerative, whereas anemias of several days' duration or more that show no evidence of regeneration are unlikely to be caused solely by ingestion of the toxins listed previously.

CARDIAC ABNORMALITIES

Substances with toxic effects on the heart include the plants *foxglove* (*Digitalis* spp.), *lily of the valley* (*Convallaria* spp.), *oleander (Nerium oleander), azalea* and other *Rhododendron* spp., *mistletoe (Phoradendron),* and yew (*Taxus* spp.); as well as bufo toads (*Bufo* spp.). These toxins produce cardiac effects that manifest mainly as cardiac arrhythmias such as premature atrial or ventricular complex, as opposed to causing structural heart disease like valvular regurgitation. Therefore physical abnormalities from the previously listed intoxications commonly include lethargy or weakness associated with an irregular pulse and heart rhythm, perhaps a weak pulse, or syncope and collapse; monitoring of these patients begins with continuous ECG. Signs of structural heart disease such as valvular regurgitation (e.g., heart murmur) are almost never due to intoxication alone. (For more on cardiac abnormalities, the reader is referred to Chapter 202.)

Medical differential diagnosis for cardiac arrhythmia would include *automobile trauma* (physical exam or radiographic evidence of recent trauma); *gastric dilatation* and *volvulus* (physical examination; abdominal radiographs); such metabolic disturbances as *anemia, hypokalemia, acidosis,* or *hypoxia; abdominal mass* (palpation, radiographs, ultrasound), and *primary heart disease* including cardiomyopathy, advanced valvular heart disease, congenital heart disease, or heartworm (heart murmur, cardiomegaly on radiographs, or congestive heart failure would increase likelihood of primary heart disease as cause of arrhythmia).

GASTROINTESTINAL (GI) SIGNS

Many intoxications provoke vomiting as an initial manifestation before producing additional clinical signs. (The reader is referred to the previous sections of this chapter for information on GI signs occurring jointly with chief complaints or problems already discussed). In addition, ingestion of *arsenic* (in some ant baits and some herbicides; urinary arsenic concentration > 1 ppm is diagnostic [human hospital laboratory]); *castor beans* (*Ricinus communis*: colorful, 6 mm seeds often incorporated into jewelry as beads; vomiting usually begins within 6 hours of ingestion); nitrogen-phosphorus potassium [NPK] *fertilizers; calcium oxalate-containing plants* (e.g., elephant's ear [*Caladium* spp.], dumb cane [*Dieffenbachia* spp.], and peace lily [*Spathiphyllum* spp.]; oral mucosal swelling a common occurrence with ingestion); *zinc oxide* (skin ointment either licked off the skin or eaten from a chewed tube); or *zinc phosphide* (gopher bait; concurrent pulmonary edema common; onset of signs within 15 minutes to 4 hours of ingestion; odor of rotting fish [phosphine gas] suggests hazard to veterinary personnel) may all initially produce GI abnormalities. (For more on GI signals, the reader is referred to Chapters 33, 35, 38, and 39.)

Medical differential diagnoses include *gastroenteritis* of unknown cause (self-resolving in 24 to 72 hours with minimal supportive care); *parvoviral enteritis* (fecal parvovirus test positive; leukopenia common; dog often unvaccinated); *small intestinal infiltration* (more likely if intestine is palpably thickened or with weight loss; abdominal lymph nodes may be enlarged; ultrasound may show bowel thickening; biopsy should be done for diagnosis); *GI obstruction* such as with a foreign body, mass, or intussusception (palpable mass with or without discomfort; abdominal radiographs may suggest obstruction; *pancreatitis* (ultrasound can show abnormal pancreatic echogenicity with or without apparent abnormal size); *intestinal parasites* (serial fecal flotations; empiric deworming); *hypoadrenocorticism* (most dogs are young to middle-aged adults; usually hyperkalemia and hyponatremia are seen when GI signs are present; adrenocorticotropic hormone [ACTH] stimulation test for confirmation); *peritonitis* (ascites almost always present [may be small amount, only on radiographic or ultrasound]; cytology of fluid is diagnostic; penetrating injury around abdomen highly suggestive); *renal failure* (small kidneys on physical exam, uremic halitosis are suggestive; azotemia with isosthenuria highly consistent); *liver failure* (icterus with normal hematocrit very suggestive; liver enzymes, bile acids, hepatobiliary ultrasound abnormalities suggestive); *hypovolemic shock* (physical exam shows depression, recumbency, poor pulse, often tachycardia [or bradycardia in cats]); or *right-heart failure* (ascites, pleural effusion possible with normal serum albumin; echocardiogram shows right-heart disease or pericardial disease causing tamponade).

CHAPTER • 67

Venomous Bites and Stings

Patrick M. Burns

Venomous bites by snakes, spiders, and other species account for 1% to 1.3% of calls to poison information centers and approximately the same proportion of deaths in pets. The practitioner must know which venomous creatures inhabit the local area and the various treatments for envenomation.

A number of misconceptions exist about the treatment of envenomation, and new therapies are being developed for several of the conditions discussed here. In general, two important requirements are to keep the animal calm and quiet and to transport it quickly to the nearest veterinary facility. Administration of antivenin and supportive care are the mainstays of treatment for most envenomations, and this requires accurate identification of the toxin.

CROTALIDS (PIT VIPERS)

Nearly all snake bite envenomations in the United States are caused by snakes of the Crotalidae family. The three genera of crotalids in the United States are *Crotalus* (rattlesnakes) (Figures 67-1, 67-3, 67-8), *Sistrurus* (pygmy rattlesnakes and massasauga) (Figure 67-7), and *Agkistrodon* (copperheads, cottonmouth water moccasins) (Figure 67-2). *Crotalus catalinensis* is the only rattlesnake that does not have a keratinized rattle on the end of the tail.

A single bite may produce as many as six puncture marks. The maxillary teeth are rotated forward at the time of the bite. Pit vipers have characteristic retractable rostral maxillary fangs (Figure 67-4). They can control the amount of venom delivered with each bite, and the first, defensive bite often is "dry." Bites to the torso tend to develop more severe clinical signs, and bites are more serious during the spring and summer months.

Cats are more resistant than dogs to crotalid venom, but they often present with more severe clinical signs because of their small size relative to the amount of venom. Also, the interval between the occurrence of the bite and administration of medical therapy frequently is longer because of the hiding behavior of sick cats.

Crotalid venom is a mixture of enzymatic and nonenzymatic proteins. The enzymatic proteins (hyaluronidases and collagenases) cause local tissue injury and help the venom enter the systemic circulation. Different toxins found among the various species affect the clotting cascade through different mechanisms and result in impaired platelet function, thrombocytopenia, activation of clotting factors, fibrinolysis, and vasculitis. The venom of some crotalid species can cause neurologic signs, such as convulsions and alterations in mentation. The severity of the local reaction does not correlate with the severity of the systemic signs.

Clinical signs include localized pain, salivation, weakness, fasciculations, hypotension, alteration in respiratory pattern, regional lymphadenopathy, mucosal bleeding, prolonged bleeding times, echinocytosis of erythrocytes, obtundation, and convulsions.

Hematologic changes suggestive of envenomation include hemoconcentration followed by anemia, stress leukogram findings, and echinocytosis. The coagulation panel may show prolongation of the prothrombin time and partial thromboplastin time, with a reduction in fibrinogen and an increase in fibrin degradation products. Rhabdomyolysis may also be seen, especially with envenomation by Mojave, canebrake and tiger rattlesnakes. Urinalysis can reveal proteinuria, hemoglobinuria, and myoglobinuria. Electrocardiographic abnormalities occur in more severely affected victims.

Antivenin is indicated in moderate-to-severe cases of envenomation. Some first aid procedures are not efficacious, including application of ice or hot packs; incision and suction on the wound; the use of tourniquets; and electric shock therapy at the bite site. Most patients require one to two vials of the polyvalent antivenin given intravenously over 30 minutes. The antivenin reverses the coagulopathy, electrocardiographic findings, and neurologic changes. Tissue necrosis cannot be reversed by antivenin; however, the extent of the damage is limited. The practitioner should monitor the hemolysis and coagulation profile in order to judge the amount of venom required. Administration of blood products to reverse the coagulopathy without neutralization of the antivenin may result in further fibrinolysis.

Hypotension, hemolysis, and rhabdomyolysis are reasons for aggressive fluid therapy. Administration of antihistamines and corticosteroids usually is not necessary and tends to increase morbidity. Slow infusion of the antivenin reduces the chance of anaphylactoid reactions. Prior administration of an antivenin does not appear to increase the chance of a reaction. Broad-spectrum antibiotics and analgesics are indicated in patients with severe envenomation.

ELAPIDS (CORAL SNAKES)

Most elapids are found in the southern and southeastern United States (i.e., *Micrurus fulvius tenere* [Texas coral snake]; *M. fulvius fulvius* [Eastern coral snake]; *M. fulvius barbouri* [South Florida coral snake]; and *Micruroides euryxanthus euryxanthus* [Sonoran coral snake]). The incidence of elapid envenomation is extremely low compared with that from crotalids, and the percentage of dry bites is high because these snakes must "chew" on their victims to inject venom. Another difference between the elapids and crotalids is the lack of proteolytic enzymes in elapid venom (and therefore the lack of a local reaction). The neurotoxic venom of elapids affects the nervous system mainly by means of a nondepolarizing postsynaptic neuromuscular blocking activity, similar to the effect of curare. Some reports have mentioned an intravascular hemolysis, which is speculated to be mediated by phospholipase A.

The clinical onset of symptoms commonly is delayed 10 to 18 hours. In the dog, emesis, salivation, agitation, and central depression, followed by quadriplegia, hyporeflexia, intravascular hemolysis and, finally, respiratory paralysis, are seen. Cats show a loss of cutaneous nociception and hypothermia but not

hemolytic anemia. Hematologic studies in dogs reveal erythrocyte membrane damage, such as burr cells and spherocytes.

Application of a compression bandage, where possible, has been shown to be helpful. The definitive treatment is with *Micrurus fulvius* antivenin (Wyeth Laboratories, Marietta, Pennsylvania). However, this antivenin is not effective against the Sonoran coral snake. Early administration of the antivenin produces the maximum effect. It should be administered slowly intravenously to help reduce the chances of anaphylactic and anaphylactoid reactions. (A new ovine Fab antivenin with fewer side effects may become available in the near future.) Subcutaneous injections at the bite site are ineffective. Initially, one to two vials of antivenin may be given, and the clinical signs are closely monitored to gauge the requirement for more antivenin. In severe cases of envenomation, respiratory support by means of artificial ventilation may be required for several days. Broad-spectrum antibiotics are recommended for local wound infections. Treatment of Sonoran coral snake envenomation is supportive at this stage. Tick paralysis, botulism, polyradiculoneuritis, myasthenia gravis, and certain drugs can have clinical signs similar to those of elapid envenomation.

LATRODECTUS spp. (WIDOW SPIDERS)

The widow spiders belong to the genus *Latrodectus*. *Latrodectus mactans* (black widow), *L. variolus, L. bishopi* (red widow), *L. hesperus* (western black widow), and *L. geometricus* (brown widow) are the five species found in all the U.S. states except Alaska. The cat seems more susceptible to *latrodectism*, or envenomation by a widow spider, than does the dog. Alpha latrotoxin is the major active component of the venom. The lethal dose (LD_{50}) of the venom varies, depending on the species of widow spider. The brown widow is the most potent, with an LD_{50} of 0.43 mg/kg body weight. The LD_{50} of the black widow is 1.39 mg/kg body weight. Alpha latrotoxin causes an initial release of neurotransmitters from nerve endings throughout the nervous system and ultimately causes depletion of these transmitters, resulting in a blockade. It affects both motor and sensory fibers.

Clinical signs are commonly detected within 8 hours of envenomation, with most occurring in the first hour. The toxin does not cause a significant local reaction at the bite site. Small, young, and geriatric patients are most susceptible to the venom. Hyperesthesia, muscle fasciculations, and cramping occur, and somatic abdominal pain is a characteristic clinical sign. The motor signs may give way to a flaccid paralysis within 24 hours of the bite. An acute abdomen, rabies, or intervertebral disk disease are differential diagnoses. Respiratory compromise, hypertension, tachycardia, and seizures may also occur. Cats also show vocalization, salivation, agitation, muscle cramping, and ataxia leading to paralysis. Severe bites tend to occur in the autumn.

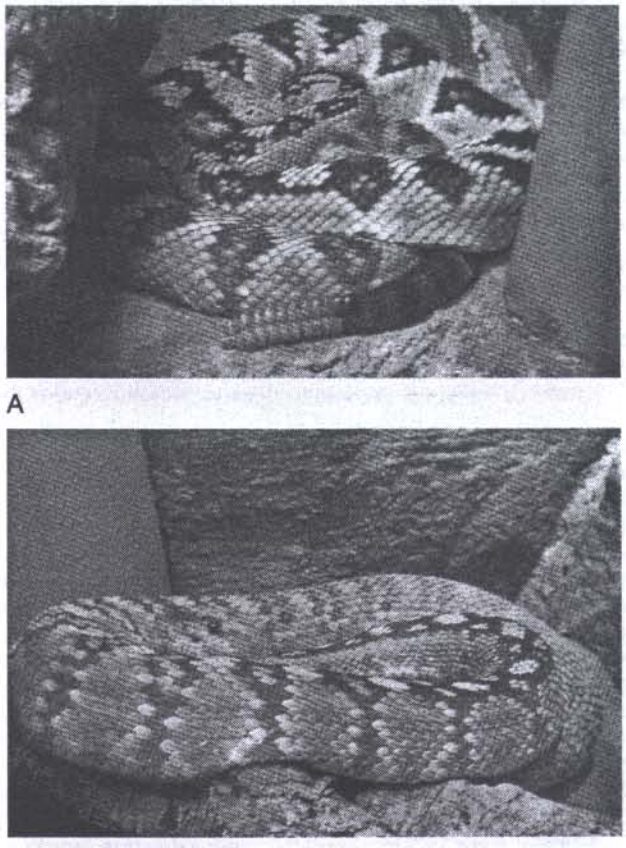
The diagnosis is based on the clinical signs and historical exposure to the spider habitat. Occasionally cats may vomit up a spider. A stress leukogram with hyperglycemia is often seen. The muscle cramping may lead to a rise in creatinine phosphokinase. Urinalysis may reveal concentrated urine, casts, and an elevated albumin level. The reduction in urine output occurs secondary to dehydration and urinary retention.

The main treatment modality consists of administration of the antivenin (Lyovac antivenin, Merck, Sharpe & Dohme). This may be give intramuscularly or intravenously. One vial is usually enough, but at times a second is required. Relief of clinical signs is usually seen within 30 minutes. Slow administration reduces the risk of anaphylactoid reactions. Blood pressure monitoring is advantageous because of the hypertension that occurs. Intravenous fluids to correct dehydration and oliguria should be administered only after the hypertension has been corrected. Pulmonary edema has also been seen with latrodectism. In the early stages of the clinical signs, calcium gluconate 10% theoretically may help reduce muscle cramping and pain; however, the effect is short-lived, and this therapy is not a substitute for the antivenin. Muscle relaxants such as methocarbamol and diazepam may be of some help, but results from clinical trials have not been supportive of their efficacy.

LOXOSCELIDAE (RECLUSE OR BROWN SPIDERS)

Recluse spiders are members of the family Loxoscelidae, genus *Loxosceles*. Five species (*L. reclusa, L. refuscens, L. arizonica, L. unicolor,* and *L. laeta*) found in the south-central United States are capable of causing necrotic arachnidism. Two forms of *loxoscelism* (envenomation by recluse or brown spiders), cutaneous and viscerocutaneous, have been described. The cutaneous form, which is more common, starts with a bull's-eye lesion at the bite site. A pale center, caused by localized thrombosis, is surrounded by an area of erythema. Within 24 to 72 hours, a hemorrhagic bulla with an underlying eschar develops in the center. The eschar eventually sloughs, leaving an ulcer that may take months to heal. The severity of these lesions depends on the response of the immune system to the toxin.

The viscerocutaneous form involves the development of a Coombs'-negative hemolytic anemia that may last for 7 days, thrombocytopenia, and disseminated intravascular coagulopathy. The extent of the cutaneous lesion and the severity of the systemic signs do not appear to be correlated. A single bite can



A

B

Figure 67-1 A, *Crotalus molossus*, blacktail rattlesnake; B, Color variant.

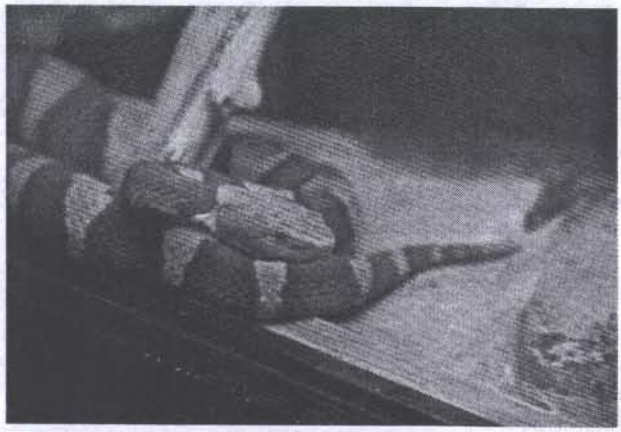


Figure 67-2 *Agkistrodon contortrix*, broad banded copper snake.

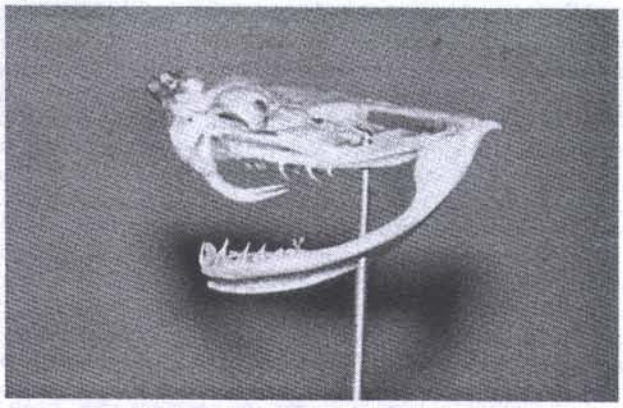


Figure 67-4 *Crotalus* spp. skull.

be lethal but in most cases results in dermonecrosis and prolonged wound healing (2 to 3 months). The bite itself is painless. Renal failure from the hemolytic anemia is the major cause of death from *Loxosceles* envenomation.

The exact mechanism of loxoscelism is unknown; however it is likely the result both of the toxin and the immune response to the toxin. An immune-mediated vasculitis, hemolysis, and platelet abnormalities all play a part in the mechanism. Sphingomyelinase D is the major toxin. The venom causes rapid coagulation and thrombosis of the capillaries. Depletion of clotting factors VIII, IX, XI, and XII also occurs, with resultant prolongation of the activated partial thromboplastin time.

No definitive test for *Loxosceles* envenomation exists. The diagnosis is based on the history and clinical signs and on laboratory findings of a Coombs'-negative hemolytic anemia, hemoglobinemia, hemoglobinuria, and a prolonged activated partial thromboplastin time. Hemolysis usually is seen only in the early stages and is followed by the cutaneous lesions. Systemic signs may be used to monitor the response to therapy. Other diagnostic possibilities include necrotizing fasciitis, mycobacterial infection, a burn wound, or a decubital ulcer.

Antivenin has had disappointing results when given after the lesions became obvious. Dapsone (1 mg/kg given orally for 14 days) has shown some efficacy in reducing the size of the cutaneous lesions. Dapsone inhibits chemotaxis, thereby minimizing the vasculitis caused by polymorphonuclear cells. Some evidence suggests that the use of hyperbaric oxygen (2 atmospheres twice daily) may be beneficial. Corticosteroids and surgery have not been shown to be efficacious in these cases. Viscerocutaneous symptoms may require intravenous fluids or blood products, and systemic antibiotics and analgesics may be necessary. Any analgesic that interferes with renal function should be avoided.

Figure 67-3 Crotalus horridus, timber rattlesnake.

TICK PARALYSIS

Dermacentor andersoni, *D. variabilis*, and *Haemaphysalis cinnabarina* are found in the western United States and British Columbia, and *D. variabilis* is found in the central and eastern United States and in southern portions of Canada. However, tick paralysis does not occur at all locations, which suggests a variation in the potency of the toxin. This is also true for the transmission of tick-borne diseases. Tick paralysis is more likely to occur in the spring and summer months.

Holocyclotoxin, a presynaptic neurotoxin at the neuromuscular junction, is secreted in the saliva of *Ixodes holocyclus*. It is similar to the toxin isolated from *D. andersoni*. The toxin inhibits the release of acetylcholine. The *Dermacentor* toxin can cause mortality, if left untreated, by means of a progressive, ascending paralysis that results in respiratory failure. Local effects of paralysis may be noted before the generalized form is seen. This is most evident when the tick bite occurs close to the eye, resulting in ptosis or lack of a palpebral reflex. In such cases exposure keratitis may develop, requiring a temporary tarsorrhaphy. Recent studies on *I. holocyclus* have shown that toxin to have a direct effect on the heart, causing a reduction in the fractional shortening and a prolongation of the QT interval. Aspiration pneumonia secondary to megaesophagus is not uncommon in severely affected animals.

Clinical signs usually first appear 5 to 9 days after tick attachment. The diagnosis is based on the clinical signs and a history of exposure to ticks. Most ticks are found around the head, neck, and forelegs, and clipping of the patient sometimes is necessary to find them. Recovery from the paralysis usually occurs spontaneously 3 days or more after removal of the tick. Treatment is supportive during this time, which in severe cases may mean artificial ventilation for respiratory failure. Fiprinol sprays are a good alternative to organophosphates for eliminating other ticks. The main differential diagnoses for tick paralysis are polyradiculoneuritis and botulism.

Figure 67-5 *Heloderma horridum*, beaded lizard.

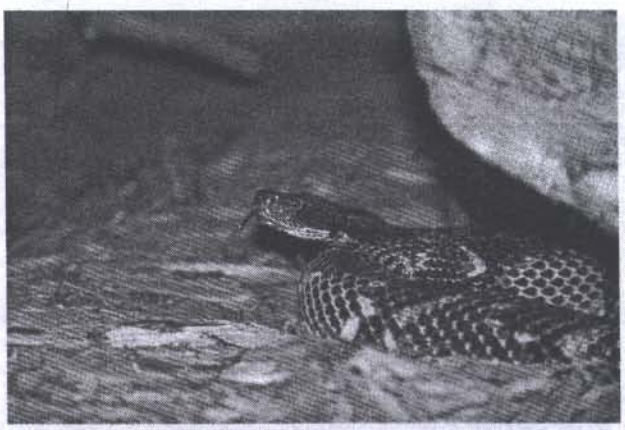


Figure 67-7 *Sistrurus catenatus*, Eastern massauga.

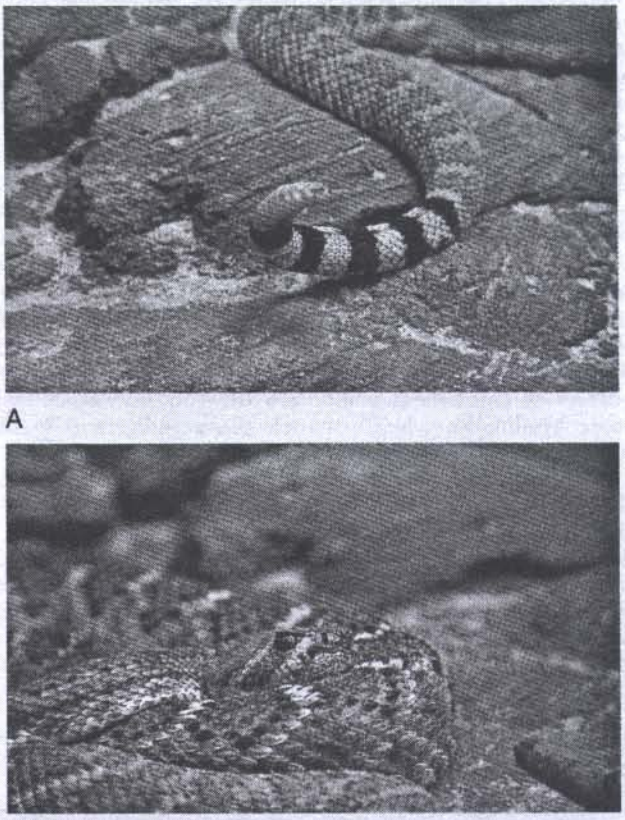
HYMENOPTERAN STINGS (INSECT BITES)

The bites and stings of some winged insects and fire ants (*Solenopsis* sp.) have the potential to cause serious toxic or allergic effects. Toxic reactions are dose dependent unless hypersensitivity to the toxin is a factor. The venoms of this group have three broad components: low molecular weight toxins, peptides, and high molecular weight toxins. Low molecular weight toxins consist of histamine, dopamine, noradrenaline, amino acids, epinephrine, and acetylcholine and are involved only in the local reaction. Peptides (melittin, apamin, kinins, hemolysin, mast cell degranulating factors, and chemotactic factors) cause cytolysis and can act as neurotoxins, inducing hyperexcitability. High molecular weight toxins consist of phospholipase A and B, hyaluronidase, and proteases and cause allergic reactions. Dialkydpiperidine is the main cytotoxic alkaloid found in fire ants.

Allergies are mediated by immunoglobulin E (IgE) and usually occur after a period of sensitization. The common bee *(Apis mellifera)* has the greatest propensity to cause an allergic reaction. Reactions to hymenopteran stings can include localized angioedema, urticaria, emesis, diarrhea, hematochezia, respiratory distress, and death. The most significant stings occur around the head and neck.

The diagnosis of hymenopteran stings is based on historical evidence of contact with stinging insects and clinical signs. Certain breeds of dogs (boxers, Staffordshire terriers, and bull terriers less than 18 months of age) have a higher chance of a severe reaction to the stings. Other diagnostic possibilities include skin testing, specific IgE or IgG antibodies, histamine release assay, and sting challenge. Treatment consists of administration of corticosteroids and antihistamines and supportive care. In severe cases, prednisolone sodium succinate may be administered intravenously; however, most cases respond to dexamethasone sodium phosphate given intravenously or intramuscularly. Severe cases may require supportive care with oxygen therapy, intravenous fluids, gut protectants, positive inotropes, and vasopressors. Patients with airway obstruction or bronchial constriction may require a tracheostomy or the use of bronchodilators.

Figure 67-6 *Heloderma suspectum*, Gila monster.



A

B

Figure 67-8 *Crotalus atrox*. **A**, Western diamondback rattlesnake tail; **B**, Western diamondback rattlesnake.

Table 67-1

Toxins of the Gila Monster

TOXIN	ACTION
Gilatoxin	Acts as a neurotoxic protein
Helothermine	Reduces body temperature
Hyaluronidase	Damages local tissue, allowing toxins to spread
Phospholipase A_2	Causes release of histamine, serotonin, acetylcholine, kinins, and other slow-release substances
Helodermatine	Causes vasodilatation, increased permeability and edema
Arginine hydrolase	Causes release of bradykinin
Helospectin and helodermin	Have activity similar to that of vasoactive intestinal peptides

HELODERMATIDAE LIZARD (GILA MONSTER)

The genus *Heloderma* includes two species of lizard that are venomous to humans (*H. suspectum* and *H. horridum*) (see Figures 67-6 and 67-5, respectively). The venom of the helodermatids is a mixture of proteins and peptides. The intravenous LD_{50} of the crude toxin is 0.4 to 2.7 mg/kg in mice; the toxic dose in dogs and cats is unknown.

Bite wounds typically are obvious and commonly are found around the face or forelegs. Clinical signs include salivation, lacrimation, emesis, tachypnea, respiratory distress, tachycardia, hypotension, and shock. Coagulopathies have not been reported, although a coagulation profile and minimum data base are indicated to help rule out snake envenomation. Treatment is symptomatic and may include intravenous fluids, respiratory support, debriding of the wound, and administration of broad-spectrum antibiotics and analgesics. An antivenin has been produced by the Poisonous Animal Research Laboratory at Arizona State University, but it is not yet commercially available.

CHAPTER 68

Plant Toxicities

Lynn R. Hovda

Plant toxicity continues to account for about 10% of all companion animal exposures reported to poison control centers. Pets less than 1 year of age make up about 50% of the cases, with dogs having significantly higher exposure rates than cats.[1] Ingestion usually occurs secondary to playfulness, boredom, or confinement; although the number of pets poisoned by well-meaning owners is increasing.

Veterinarians and pet owners are often faced with determining whether or not a plant ingestion is responsible for poisoning. This is rarely an easy task because most ingestions are not witnessed and many pet owners do not know the names of plants in their house, garden, or yard. Several reliable sources of plant identification aid the veterinarian, as does some baseline knowledge of toxic plants indigenous to the local area.

Very few antidotes are available for plant poisoning. Treatment generally consists of symptomatic and supportive care. Unless contraindicated, emesis or gastric lavage followed by activated charcoal with a cathartic should be performed. Identification of the specific plant, the quantity and parts ingested, the time of ingestion, and the age and breed of animal all are necessary for formulating a treatment plan. Examination of stomach contents (seeds, bulbs, flowers) may confirm ingestion, assist in plant identification, guide therapy, and offer a prognosis.[1]

NEWER PLANT TOXICITIES

Grapes and Raisins

Ingestion of grapes and raisins has just recently been associated with the onset of acute renal failure in dogs. Literature is sparse, and signs and treatment are based on case reports with no firm scientific research as a backup.[2] No specific breed predilection or geographic location has been noted. Neither the toxin nor the mechanism of action has been identified. Toxicity varies and has been reported with ingestion of just a few raisins or grapes up to several pounds. Homegrown grapes or raisins appear to be just as toxic as those purchased in stores. Vomiting partially digested grapes or raisins occurs 1 to 3 hours after ingestion and is followed by anorexia, severe abdominal pain, and diarrhea with partially digested grapes or raisins in feces. Later signs include central nervous system (CNS) depression and decreased urine output. Results of serum chemical analysis taken 24 to 36 hours after ingestion are consistent with acute renal failure. Treatment is symptomatic and includes early and aggressive intravenous (IV) fluid diuresis or peritoneal diuresis in anuric dogs. Signs may last from a few days to many weeks. Prognosis is good if treated early, although sporadic deaths have occurred in well-treated cases.

Macadamia Nuts

Reports of dogs poisoned by ingesting macadamia nuts have increased over the past 3 to 4 years.[3] Macadamia nuts, produced by *Macadamia integrifolia* and *Macadamia tetraphylla* trees in Hawaii, can be found in most grocery stores throughout the United States. Both the toxin and mechanism of action remain unknown. Generally, signs occur within the first 2 to 12 hours after ingestion, with the most frequently reported signs associated with locomotor disturbances. Almost all dogs have difficulty walking, with the gait best described as drunken or staggering. Tremors, ataxia, and weakness (hind end > front end) have also been reported.[3] Other reported

signs include depression, vomiting, abdominal pain, and hyperthermia.[3] Laboratory analysis shows a mild increase in serum alkaline phosphatase and lipase, as well as a delayed increase in serum triglycerides. No antidote exists, and treatment is mainly supportive. Prognosis is excellent, with signs generally resolving over 24 to 48 hours with appropriate care.

COMMON PLANT TOXICITIES

Plants Affecting the Blood

Ingestion of raw or cooked onion (*Allium* spp.) is well associated with toxicity in dogs and cats.[1] A hereditary abnormality makes Akitas and Shibas more susceptible to toxicity than other dogs.[4] Most recently, reports have surfaced of cats poisoned by eating baby food with onion powder as an ingredient.[5] The primary toxin is *n*-propyl disulfide, an alkaloid found in onions, wild onions, leeks, garlic, and chives. The toxin oxidizes free sulfhydryl groups on hemoglobin, and the oxidized hemoglobin precipitates Heinz bodies in red blood cells (RBCs).[1] Anemia occurs when the spleen removes affected RBCs. Onset of action varies from a few hours to several days. Signs are consistent with anemia and include increased heart and respiratory rates, pale mucous membranes, fatigue, weakness, exercise intolerance, and collapse.[4] Laboratory findings include hemoglobinuria, decreased hematocrit, decreased hemoglobin, Heinz bodies in RBCs, and mild methemoglobinemia. Treatment depends on the hematocrit; some animals need a transfusion.

Plants Primarily Affecting the Cardiovascular System

Plants with cardiac glycoside activity include the common oleander *(Nerium oleander)*, yellow oleander *(Thevetia peruviana)*, foxglove *(Digitalis purpurea)*, lily of the valley *(Convalleria majalis)*, and kalanchoe *(Bryophyllum* spp.*)*.[1] Five different types of cardiac glycosides have been identified in common oleander. The seeds, stems, and roots are toxic. Yellow oleander contains the cardiac glycosides thevetin A, thevetin B, and peruvoside. All parts of the plant are toxic, with seeds having the highest concentration. Digoxin, digitoxin, and digitonin are the most common toxins in foxglove, with seeds again having the highest concentration. Lily of the valley contains at least 15 toxins, with convallatoxin, convallarin, and convallamarin the most common. Seeds contain the highest concentration, whereas the fruit flesh is minimally toxic. Kalanchoe contains bufadienolides, with most poisonings occurring during the plant's flowering season. The mechanism of action for all cardiac glycosides occurs at the cellular membrane level. Inhibition of the sodium-potassium ATPase pump causes slowed electrical conductivity with decreased active transport of sodium and an efflux of potassium.

Signs associated with cardiac glycoside-containing plants are generally related to either the cardiovascular system or gastrointestinal (GI) tract.[1] Vomiting and abdominal pain begin several hours before deterioration in myocardial function. Marked bradycardia with first-, second-, or third-degree atrioventricular (AV) block, ventricular arrhythmias, asystole, and sudden death can occur. Hyperkalemia is usually prominent, although scattered reports of hypokalemia exist. Sap from oleander plants has caused contact dermatitis and blistering of the nose and footpads. Diagnosis depends on physical identification of the plant. Digoxin assays could aid in identification of oleander and foxglove.[1] Serum digoxin levels might be a screening tool, but the correlation between the level and degree of toxicity is very poor.

Treatment varies from case to case but may include correction of potassium abnormalities, appropriate antiarrhythmic drugs, implantation of a temporary pacemaker, and antidigitalis antibody fragments (Fab). Prognosis is generally poor unless intervention is early and aggressive. An extremely bitter taste and spontaneous vomiting help limit the number of deaths from oleander.

Azaleas (*Rhododendron* spp.) are associated with severe toxicity and death.[1] The precise mechanism of action is unknown, but it appears that grayanotoxins act by binding to closed sodium channels. Slower opening and increased sodium permeabilities cause a decreased resting membrane potential in Purkinje's fibers. Clinical signs include severe weakness, hypotension, dyspnea, and respiratory failure. GI signs unrelated to grayanotoxins include salivation, vocalization, vomiting, and diarrhea. Sodium channel–blocking drugs like quinidine and procainamide have been used successfully.

The yew (*Taxus* spp.) is a common ornamental shrub found in the United States and Canada.[1] Common species include the Japanese yew *(T. cuspidata)*, English yew *(T. baccata)*, Florida yew *(T. floridana)*, and ground hemlock *(T. canadensis)*. Bark, leaves, and seeds are toxic but not the fleshy part of the bright-red fruit. Taxine, a cardiotoxic alkaloid, causes conduction disturbances by direct effect on cardiac muscle ion channels. In dogs, bradycardia, vomiting, diarrhea, weakness, and seizures have been reported. Sudden death may occur. Caged birds may be poisoned by bark or other shrub pieces placed in their cages. Clinical signs in birds include crop regurgitation, ruffled feathers, dyspnea, weakness, ataxia, and sudden death. Treatment is supportive and symptomatic. Prognosis is poor, and once clinical signs have occurred, further treatment is of limited value.

Plants Primarily Affecting the Gastrointestinal System

Oxalate-containing plants (family Araceae) are the most frequently reported household exposures.[1] Common household plants containing insoluble crystals include dumbcane *(Dieffenbachia* spp.), philodendron (*Philodendron* spp.), peace lily (*Spathiphyllum* spp.), and devil's ivy (*Epiprennum aureum*). Crystals are usually concentrated within a raphite structure in the stalk. Chewing on the stalk releases oxalate crystals and other as yet unidentified enzymes. Clinically, stomatitis and glossitis, ocular, or systemic scenarios can occur.

Stomatitis and Glossitis

Irritation to the mucous membranes of the mouth and throat causes immediate and intense pain, local swelling, and profuse salivation. These may be accompanied by head shaking, loss of vocalization, and rarely airway compromise. Treatment is symptomatic. The mouth should be thoroughly examined and any remaining plant pieces removed. Cool fluids, ice chips, and analgesics increase comfort until signs resolve. Most typically, it takes 30 to 90 minutes for this to occur, but signs can be prolonged for hours in animals with airway compromise.

Ocular

Eye exposures, although rare in animals, cause severe burning pain and swelling. Left untreated, conjunctivitis, abrasions, and corneal ulcers develop. Treatment includes a 10- to 15-minute eye irrigation followed by a thorough eye examination with fluorescein dye staining or slit lamp examination. Ophthalmic protectant medications are used as indicated.

Systemic

Systemic effects occur primarily in cats exposed to *Philodendron* spp. Signs are referable to the renal system and CNS and include hyperexcitability, tetany, and seizures. Treatment is symptomatic and supportive.

Rhubarb (*Rheum* spp.) contains soluble oxalate crystals concentrated in the leaf. The stalk is edible and generally causes no systemic effects. When leaves are ingested, soluble

oxalates can be absorbed and bind to circulating calcium ions. Symptoms include diffuse GI tract irritation and infrequently systemic hypocalcemia. Oral calcium hydroxide is used to bind oxalates in the GI tract. If systemic signs are noted, IV calcium gluconate or chloride should be administered.

The chinaberry tree *(Melia azedarach)* can be found throughout temperate regions of North America. All parts of the tree are toxic, although dogs are generally poisoned by eating fruit fallen from trees.[6] Toxicity has been reported in rabbits, guinea pigs, rats, and other species. Many potential toxins have been isolated, with meliatoxins found in highest concentration in the fruit. Clinical signs usually occur within 1 to 2 hours after ingestion. Vomiting and diarrhea (with or without blood) are the most common signs along with anorexia, severe abdominal pain, hypersalivation, and straining to defecate.[6] Neurologic effects are similar to nicotine, and signs include depression, ataxia, seizures, and coma. Other reported signs include hyper- or hypothermia, tachycardia or bradycardia, mydriasis or miosis, and muscle rigidity.[6] Death generally occurs from respiratory depression and arrest. Treatment is symptomatic and supportive. Prognosis for recovery decreases significantly with the onset of neurologic signs.

Cycad palms or sago palms (*Cycas and Macrozamia* spp.) are subtropical to tropical houseplants known to cause toxicity in dogs.[7] All plant parts are toxic, with the seeds containing the greatest concentration. The plants contain three toxins: (1) cycasin, which causes GI effects and liver necrosis; (2) β-methylamino-L-alanine, which causes neurologic effects; and (3) an unknown toxin associated with neurologic effects. The onset of action is variable, with signs occurring from a few hours to a day or so. The most commonly reported signs are vomiting and diarrhea (with or without blood) followed by lethargy, depression, liver failure, and death.[7] Laboratory work shows an increase in liver enzymes (alanine transferase and alkaline phosphatase) and bilirubin. Treatment includes multiple-dose activated charcoal and supportive care with special emphasis on the liver.

English ivy *(Hedera helix)*, a common houseplant and ground cover, contains hederagenin, a saponin associated with GI irritation.[1] Other *Hedera* spp. of ivy with suspected toxicity include Persian ivy, Irish ivy, Atlantic ivy, and Nepal ivy. Ingestion of leaves and berries causes profuse salivation, abdominal pain, vomiting, and diarrhea. Treatment is symptomatic and supportive.

Abrus precatorius, the jequirity bean, has been used for centuries in Latin American necklaces and jewelry. It has long been illegal to import this jewelry into the United States, yet it frequently shows up at flea markets and garage sales. Abrin, the toxin, is a toxalbumin similar to botulinum, cholera, and diphtheria.[1] The castor bean plant *(Ricinus communis)* has similar toxic principals. Castor bean plants are widely used as an ornamental shrub throughout North America. Ricin, the toxin, is present in all parts of the plant but is most concentrated in seeds. Abrin and ricin are among the most deadly poisons in the world but must be released from their shell to be absorbed. Dogs are most often poisoned by chewing on the hard outer shell and ingesting the contents. Once absorbed, abrin and ricin enter cells and inhibit protein synthesis resulting in cell death. Signs of toxicity occur within 6 hours of ingestion and include severe abdominal pain, vomiting, diarrhea, seizures, and cerebral edema.[1] Treatment is supportive. Prognosis for recovery is poor once clinical signs develop.

Ornamental holiday plants include holly (*Ilex* spp.), poinsettia *(Euphorbia pulcherrima)*, and mistletoe *(Phoradendron flavescens)*. Well over 300 species of holly are found in the United States alone, making actual plant identification difficult. The toxin remains unidentified but may be ilicin (ilexanthin and ilex acids), a saponin causing GI effects. Poinsettias produce only mild toxicity. The unidentified toxin in the latex sap, thought to be a diterpenoid ester, rarely causes more than mucous membrane irritation or contact dermatitis. Clinical signs include salivation, mild GI irritation, and occasional diarrhea. Mistletoe has the potential for more serious effects, although few animal case reports exist.[8] The toxin is a phytotoxin or toxalbumin that can cause severe gastroenteritis with prolonged emesis. Signs occur up to 18 to 24 hours after ingestion of leaves, berries, or tea made from berries. Treatment associated with any of these plants is symptomatic and supportive. Demulcents and antacids are often of great benefit.

Several varieties of poisonous plants grow from bulbs, tubers, or corms. Included are amaryllis, jonquil, and daffodil (family *Amaryllidaceae*); tulip (family *Liliaceae*); and iris (family *Iridaceae*).[1] The toxic principal is unknown, but ingestion of the bulb has been associated with only mild-to-moderate gastroenteritis. Treatment is symptomatic and supportive.

Autumn crocus *(Colchicum autumnale)* and glory lily (*Gloriosa* spp.) contain colchicine, a toxic alkaloid that concentrates in the tuber and seeds. Colchicine causes cell death by inhibiting normal cell division.[9] Clinical signs include vomiting and diarrhea (with or without blood), hypersalivation, abdominal pain progressing to depression, weakness, ataxia, and collapse. Signs progress further to include several organ systems and finally, multiple organ system collapse. Treatment is supportive. Prognosis is poor if multiple organ systems are affected.

Solanine-containing plants are members of the Solanaceae family. Included are the tomato *(Solanum lycopersicon)*, potato *(S. tuberosum)*, eggplant *(S. melongena)*, bittersweet *(S. dulcamara)*, deadly or black nightshade *(S. nigrum)*, and Jerusalem cherry *(S. pseudocapsicum)*.[1] The primary toxin is solanin. Some plants also produce tropane belladonna (deadly nightshade) or solanocapsine (Jerusalem cherry). Solanine is poorly absorbed orally, and most members of this family act only as GI irritants. Systemic absorption only occurs when substantial GI mucosa damage exists. Systemically, solanine causes CNS depression and cardiac arrhythmias. Deadly nightshade may cause a mixed picture, depending on which toxin is prevalent. Solanine usually predominates, but anticholinergic signs occasionally occur and physostigmine may be indicated. Solancapsine affects cardiac muscle, causing decreased heart rate and conductive changes. Treatment is symptomatic and supportive.

Life-threatening mushroom ingestions include amanitin poisoning *(Amanita virosa, Amanita phalloides, Conocybe filaris)*, orellanine poisoning *(Cortinarius orellanus, Cortinarius rainierensis)*, and monomethylhydrazine *(Gyromitra esculenta)*. Of these, amanitin toxicity is the most widely reported in dogs. *A. phalloides* are found in wooded areas throughout the United States and Canada. Signs usually do not develop for 6 to 24 hours after ingestion. Typically, signs include a 24- to 36-hour GI phase, followed by 24 hours of remission, then a late hepatic phase characterized by jaundice, coma, and death. Survivors of the hepatic phase may ultimately die from renal tubular necrosis. Diagnosis is difficult. Liver enzymes are marked early in the process and blood urea nitrogen (BUN) and creatinine increase later. Occasionally, spores are found in GI contents or feces. A few commercial laboratories are able to perform amatoxin tests on urine. If a sample mushroom is available, the Meixner blue test is a useful qualitative test for amatoxins. Early treatment includes gastric lavage and activated charcoal with a cathartic. Charcoal hemoperfusion is perhaps the most helpful therapeutic agent but rarely performed on animals. Further treatment is supportive and symptomatic. Experimentally, high-dose penicillin, silymarin, *S* Adenosylmethionine, thioctic acid, N-acetylcysteine, cimetidine, and cytochrome-*c* have all been

used with mixed success. Liver transplant remains the proven therapy.

Plants Primarily Affecting the Neurologic System

Animals ingest tobacco *(Nicotiana tobacum)* from cigarettes, chewing tobacco, cigars, or pipe tobacco.[1] Nicotine is a rapidly acting toxin that stimulates and then depresses the autonomic ganglia. Centrally mediated emesis often occurs before significant absorption, and no further signs develop. Animals with severe poisoning show signs of CNS involvement and cardiac abnormalities. Death is from paralysis of the muscles of respiration. Treatment is first aimed toward assisting respiration and then removing residual tobacco from the GI tract.

Many plants are associated with hallucinogenic effects. Poisoning may be accidental or intentional. Diagnosis is often difficult because many owners are reluctant to cooperate. Sporadically reported in dogs are poisonings from psilocybins or "magic mushrooms."[1] Muscle weakness, ataxia, abnormal mutation, vocalization, and temperature changes occur 20 to 30 minutes after ingestion. Marijuana *(Cannabis sativa)* poisoning is infrequently reported in dogs. Dogs become glassy eyed, ataxic and hyperactive, or comatose. Other less common hallucinogenic plants are jimsonweed *(Datura stramonium)*, thorn apple *(Datura metaloidyl)*, blue morning glory *(Ipomoea violacea)*, nutmeg *(Myristica fragrans)*, and peyote (family Cactaceae). Signs vary from plant to plant; however, in general all of these plants cause changes in the CNS. Treatment is supportive and signs generally resolve in 24 to 48 hours.

Nettle toxicity (family Urticaceae) is seen primarily in hunting or field dogs.[1] Some species of nettles contain hairs that break off when an animal rubs against them, allowing injection of the contents into the animal. The toxic agents are histamine, acetylcholine, serotonin, and formic acid. Clinical signs are variable and depend on which toxin predominates. Muscle weakness is the most common sign but may be accompanied by salivation, vomiting, pawing at the mouth, tremors, dyspnea, and a slow, irregular heartbeat. Atropine in large doses, antihistamines, and sedation are useful. Generally, animals respond to treatment in less than 24 hours.

Plants Primarily Affecting the Renal System

All parts of the Easter lily *(Lilium longiflorum)* and day lily (*Hemerocallis* spp.) are toxic to cats.[10] Tiger lilies *(L. tigrinum)*, Japanese showy lily *(L. speciosum)*, and Asiatic lilies have also been implicated.[10] The toxic agent and mechanism of action are unknown. Clinical signs generally occur within 2 hours and include vomiting, depression, and anorexia, followed in 1 to 3 days by acute renal failure.[1,10] Laboratory work shows an increase in BUN, creatinine, potassium, and phosphorous. Epithelial casts have been found in the urine as early as 18 hours after ingestion. Early intervention is necessary for survival. Treatment includes aggressive GI decontamination with multiple doses of activated charcoal and fluid diuresis until BUN and creatinine have returned to normal. Peritoneal dialysis may be helpful in anuric cats. Prognosis is poor if treatment is delayed past 18 to 24 hours or anuria is present. Renal tubular epithelial cell necrosis precedes death.

Plants Primarily Resulting in Respiratory Signs

All above-ground parts of the avocado tree *(Persea americana)* are toxic to caged birds, rabbits, and mice.[11,12] The toxin is unknown but is suspected to be persin.[12] The mechanism of action is unknown. Onset and duration of signs vary from species to species. In caged birds, signs occur 12 to 29 hours after ingestion and consist of acute respiratory distress, ruffled feathers, abnormal wing posture, and sitting in the bottom of the cage. Death is from respiratory arrest. Rabbits develop acute cardiac arrhythmias, mammary gland enlargement, and sudden death.[12] Treatment is symptomatic and supportive. Prognosis is poor once respiratory or cardiac signs occur.

Plants Resulting in Sudden Death

Seeds and leaves from many fruit trees (apple, apricot, cherry, peach, plum) contain cyanogenic glycosides.[13] The glycosides concentrate in the seed and, depending on the tree, as few as 5 to 25 fruit seeds can cause toxicosis. Cyanide binds to cytochrome oxidase and inhibits cellular respiration. Onset of signs occurs within 30 to 90 minutes after ingestion; once signs occur, death follows in just a few minutes.[13,14] The most common clinical sign is sudden death although this may be preceded by ataxia, dyspnea, and tremors. Many treatment modalities have been tried, but the use of IV sodium nitrite followed by IV sodium thiosulfate is still the most successful and widely used.[14] Repeated doses of IV sodium thiosulfate and administration of 100% humidified oxygen[14] may be helpful.

CHAPTER 69

Topical Toxins

Patrick M. Burns

According to poison information centers throughout the United States, topical toxins are a major cause of death in companion animals. Synthetic pyrethrins, organophosphates, and carbamates are discussed in chemical toxicities. This chapter focuses on some of the more commonly encountered topical toxins.

When dealing with these types of intoxications, practitioners must protect themselves from exposure by wearing gloves. Washing the patient with a mild soap is adequate for most poisons, although a degreaser may sometimes be necessary. Long-haired patients may require clipping of the coat. Care must be taken in handling any skin that has been burnt. Analgesia and or a general anesthesia may be required to handle these animals humanely. A thorough endoscopic examination may also be required in some cases.

TOAD POISONING

The two main species of toads found in the United States are *Bufo marinus* (the marine or cane toad) and *Bufo alvarius* (the Colorado River toad). These Hawaiian natives are introduced species that are found mainly in Arizona, Colorado, Florida, and Texas. Intoxications tend to occur more often in spring and summer, especially after a period of rain. The peak time of exposure ranges from late afternoon to around midnight. In a common scenario, the pet is allowed out at night briefly and then is found acutely drooling and having seizures.

The most common signalment is a young male terrier weighing approximately 5 kg. The smaller the pet, the more toxin that is absorbed on a body weight basis. In the toad, the toxin is secreted by two large parotid glands just caudal to the eyes and then is spread over the rest of the body. The toxins are absorbed via mucosal membranes. Swallowing of toads is very rare because the toxins have a bitter taste. However, they are still active even if the toad has died and the body has dried up.

Toad toxins contain a variety of catecholamines, along with digitalis-like substances (bufagenins and bufotoxins) and a hallucinogen (bufotenin) that is similar to the hallucinogen lysergic acid diethylamine (LSD). A synergism exists between these groups of toxins. The bufagenins and bufotoxins also have potent local anesthetic properties.

Major clinical signs of intoxication are disorientation, ataxia, stupor, seizures, nystagmus, profuse drooling, brick-red mucous membranes, mydriasis, cardiac arrhythmias, and death. The onset of clinical signs occurs within minutes of exposure. Laboratory changes may consist of the following: a stress leukogram, mild fluid loss, mild elevation in serum alkaline phosphatase activity and mild increase in serum potassium concentration, whereas serum sodium, phosphorous, and total protein concentration tend to decrease. It is also possible to confirm exposure with a digoxin serum immunoassay, although practically not required. Geographic differences exist in the severity of clinical signs; the worst are seen in Florida.

Clients should be advised to flush the animal's mouth with water for at least 10 to 15 minutes prior to transportation to the veterinarian's office. Charcoal is thought to be of some benefit because some of the toxins enter the enterohepatic circulation. Seizures may be controlled with diazepam given nasally, rectally or intravenously. Propofol and pentobarbital also can be used to treat the seizures. Control of the seizures allows further flushing of the mouth and eyes. In severe cases, cerebral edema may occur secondary to the seizure activity and may need to be treated with short-acting corticosteroids, mannitol, and furosemide.

As soon as possible, an electrocardiogram should be analyzed to determine the type of electrical disturbance present. Bufagenins and bufotoxins can cause any type of digoxin-like arrhythmia. Also, any type of bradydysrhythmia or tachydysrhythmia may be seen, and these should be treated with the appropriate drug (Table 69-1). Most of the arrhythmias improve with flushing of the mouth and control of the seizures.

A novel therapy that may prove very useful in counteracting the deleterious effects of the digoxin-like toxins is administration of digoxin immune Fab. These anti-digoxin antibodies have been shown to cross-react with bufagenins and bufotoxins. This therapy would be useful for plant-derived cardiac glycoside intoxications.

Administration of intravenous fluids may be indicated in severe cases. Most animals respond favorably to this therapy within 1 to 2 hours. Of patients that reach veterinary care, the vast majority survive. The differential diagnoses for toad poisoning include heat stroke; metaldehyde, organophosphate, carbamate, oleander, or theobromine poisoning; and contact irritants. A good history helps in the differentiation of the diagnosis.

Table • 69-1

Toad Poisoning: Treatment of Electrical Disturbances

TYPE OF ARRHYTHMIA	TREATMENT OPTIONS
Bradycardia and heart blocks	Atropine, 0.02 mg/kg intravenously (IV)
Sinus tachycardia	Esmolol, 0.5 mg/kg IV, then a constant-rate infusion (CRI) of 50 to 200 µg/kg/min. Propranolol, 0.5 to 2.0 mg/kg IV +/– CRI 60 µg/kg/min.
Ventricular tachycardia	Lidocaine, 1 to 2 mg/kg IV bolus, followed by CRI 40 to 80 µg/kg/min. Procainamide, 6 to 8 mg/kg IV, then CRI 25 to 40 µg/kg/min. Correction of hypomagnesemia if present.

NEW GENERATION INSECTICIDES

Topical agents such as fipronil, imidacloprid, lufenuron, and selamectin all have wide margins of safety; the only reported side effect has been one unverified case of localized dermatitis. However, all these drugs have the potential to cause hypersensitivity reactions. The clinical signs seen with overdoses are caused by the carrier vehicle rather than the active ingredient. Mild gastrointestinal upset is usually seen, and symptomatic therapy may be required. Ocular exposure is best treated with saline lavage and fluorescein staining to assess the extent of any damage. Hypersensitivity reactions require shampooing with a mild soap and the use of glucocorticoids if indicated. Lufenuron appears to reduce fertility in the dog in high doses (Table 69-2).

ANTIBIOTICS

The antibiotics found in dermatologic preparations are well tolerated orally; extremely high dose rates over a prolonged period (on the order of months) are required to produce any serious effects. In general, antibiotics cause signs of gastrointestinal upset, such as nausea, anorexia, vomiting, and diarrhea. Neomycin, polymyxin B, bacitracin, and ampicillin, to name a few, are antibiotics used in topical preparations that have low bioavailability, hence the high oral tolerance. It should also be remembered that with any antibiotic preparation, an anaphylactic reaction is possible. Anaphylaxis to bacitracin-neomycin-polymyxin ointments in cats has been reported when the ointments were used prophylactically with routine surgeries.

TOPICAL GLUCOCORTICOSTEROIDS

Ophthalmic and dermatologic preparations of glucocorticoids usually contain hydrocortisone, betamethasone, or triamcinolone. Oral intoxication from ingestion of these preparations may result in mild gastrointestinal signs caused by the carrier vehicle. Overdoses usually are self-limiting and require only supportive care. Clinical signs are caused by the local and systemic effects of glucocorticoids. Long-term use of these preparations may result in a cushingoid patient.

Table • 69-2

Topical Pesticides and Their Mode of Action

DRUG	VETERINARY PRODUCT LD_{50}	MODE OF ACTION
Fipronil (Frontline; Merial Laboratories)	>2000 mg/kg (rabbit dermal)	Noncompetitive blocker of gamma aminobutyric acid-gated chloride channels +/– glutamate-gated channels
Imidacloprid (Advantage; Bayer Animal Health)	2000 mg/kg (rat dermal)	Competitive inhibitor of nicotinic receptors in postsynaptic nerves
Lufenuron (Program; Novartis Animal Health)	Tested in dogs using 20 times the recommended dose and in cats using 10 times the recommended dose; no ill effects seen	Inhibitor of chitin synthetase
Selamectin (Revolution; Pfizer Animal Health)	Safe in doses up to 10 times the recommended dose	Inhibitor of glutamate-gated channels

ANTIFUNGALS - ZINC UNDECYLENATE

Sunscreens, diaper rash ointments, and antifungals can all contain zinc. Acute ingestion of zinc oxides usually results in a self-limiting emesis that rarely requires treatment. These episodes do not usually result in zinc toxicosis. Prolonged use of sunscreens and antifungals may cause zinc toxicosis, manifesting as gastrointestinal disturbances, hypotension, hemolytic anemia, jaundice, and pulmonary edema. Milk or water given orally helps reduce intestinal absorption of zinc, and calcium ethylenediamine tetra-acetic acid (EDTA) chelates the zinc that has been absorbed systemically. In severe cases of zinc toxicosis, the use of blood products may be indicated.

CLEANING PRODUCTS

In the United States, the number of animals that die of poisoning from cleaning products is more than three times the number that die of bites and stings from poisonous insects. This discussion focuses on chemicals that are directly irritating to the skin or that are absorbed through the skin and cause systemic signs of intoxication. Acids and alkalis are commonly found throughout the household (Box 69-1).

Acids induce intense pain, which limits the duration of contact with these chemicals. Acids cause rapid protein coagulation, resulting in a localized necrotic lesion. Full-thickness mucosal lesions are rare. Alkaline substances tend to be more damaging to the skin and alimentary tract. Chemicals with a high pH have a greater propensity to cause full mucosal thickness injuries, with a resultant liquefactive necrosis.

The formulation of the preparation also affects the extent and location of the lesions. Solids tend to cause more buccal cavity and upper esophageal injuries, whereas liquids cause more lower esophageal and stomach lesions. However, this is a generalization, and it should be remembered that up to 30% of esophageal burns show no oral lesions. A full inspection of the entire upper alimentary tract is always indicated for complete evaluation of the extent of injury. A thoracic radiograph may reveal signs of esophageal perforation, as indicated by a pneumomediastinum.

Neutralization of any acid or alkali is contraindicated, because the resultant exothermic reaction may cause a thermal burn. Charcoal is ineffective, and gastric lavage is contraindicated with corrosive substances. Washing the affected area with copious amounts of water or administering milk helps dilute the effects of these corrosive substances on the alimentary tract. Ocular lavage may also be necessary. These measures must be taken as quickly as possible to have any effect. If any evidence suggests esophageal perforation (e.g., signs of bleeding), a full endoscopic examination may be prudent; however, it must be done with caution. Stricture formation may not be evident until some time after the injury. Glucocorticoids may help reduce the amount of fibroblastic activity early in the healing process; however, their efficacy is unproven. Caution should be used if gastric ulceration has occurred. Prophylactic antibiotics may be necessary with severe mucosal damage or extensive dermal burns, but their use is controversial, especially if no signs of infection are present at the time this therapy is instituted. In severe cases of buccal cavity or esophageal injury, an esophagostomy or a gastrostomy tube feeding regimen may be indicated.

Box • 69-1

Examples of Household Acids and Alkalis

Acids
Antirust compounds
Toilet bowl cleaner
Gun barrel cleaning fluid
Automobile batteries
Swimming pool cleaning agents

Alkalis
Drain and toilet bowl cleaners
Liquid cleansers
Washing detergents and powders

Phenols

Phenols can be found in disinfectants, soaps, shampoos and detergents. These compounds are rapidly absorbed via the oral, respiratory and dermal routes. The phenol LD_{50} in the dog is approximately 0.5 g/kg body weight. Limitations in glucuronide transferase activity in the cat make this species more susceptible to intoxication. Dermal burns have resulted from concentrations greater than 1%; however, the severity of dermal absorption depends more on the area of contact than on the concentration. Phenols cause intense pain followed by local anesthesia to the affected skin. The coagulative necrosis discolors the skin white, and a dry eschar eventually forms over

several days. Corrosive burns to the mouth and esophagus occur with oral ingestion. Severe burns are seen with ocular exposure.

Initially, with phenol intoxication, vomiting, hypersalivation, apprehension, panting, and ataxia may be seen, with progression to muscle fasciculations, shock, cardiac arrhythmias, and death. Phenols cause methemoglobinemia. Histopathologically, both hepatic fatty degeneration and necrosis and renal tubular degeneration and necrosis are seen.

Demulcents such as milk or eggs, rather than water, should be given as soon as possible, because some evidence suggests that water may enhance phenol absorption. For dermal exposure, the area should be washed first with polyethylene glycol or glycerol and then with a mild, soapy solution, followed by a final rinse with water. Gloves must be worn during this procedure. Any wounds should be bandaged with dressings soaked with sodium bicarbonate 0.5%. Oily dressings enhance dermal absorption. Ocular lesions must be flushed with saline for 20 to 30 minutes and treated appropriately. Aggressive fluid therapy is needed to correct any acid-base disturbance, to support hepatic and renal function and to reverse any signs of shock. Hepatic and renal function may also be supported by use of N-acetylcysteine for the first 3 days after intoxication. Methylene blue and ascorbic acid may be indicated for methemoglobinemia. Tube feeding is necessary for severe injuries to the oral cavity and upper alimentary tract.

Essential Oils

Essential oil extracts, which are incorporated into products such as insecticide sprays, collars, shampoos, soaps, fragrances, and cleaning solutions, are generally thought by the general public to be nontoxic. Two commonly used essential oils are citrus oil (*Citrus* spp.) and tea tree oil *(Melaleuca alternifolia)*. The main active ingredients are *d*-limonene and linalool oils (citrus oil) and terpenes (tea tree oil). Cats appear to be more susceptible to essential oils than dogs, partly because they metabolize these oils poorly and because their grooming habits increase oral exposure. The lipid nature of essential oils allows them to be absorbed rapidly via the dermal and oral routes, especially when mixed with organic solvents or surfactants. Urinary excretion is the main route of excretion.

The exact mechanism of intoxication by essential oils is unknown, and the LD_{50} varies. Clinical signs can develop within 6 to 8 hours of exposure. Central and peripheral vasodilatation tends to occur with exposure. Transient hypersalivation is seen in the cat. Muscle tremors may occur in response to the mild-to-severe hypothermia that can develop. Mydriasis, weakness, collapse, and paralysis are seen in advanced cases. In the dog, lesions similar to toxic epidermal necrolysis have been documented and were followed by disseminated intravascular coagulopathy and death. Tea tree oil has caused transient paresis in small dogs when applied as a flea treatment to the backline. With severe exposure, hepatic failure may result, especially in the cat because of the need for glucuronide conjugation. Induction of the cytochrome P-450 system may also occur.

Decontamination of the skin with a mild soap and symptomatic treatment of other clinical signs are necessary. Gut decontamination, through the use of emesis, gastric lavage, charcoal, or enemas, may be performed, especially in cases of recent exposure. Emesis should not be performed if the level of consciousness is altered or if aspiration pneumonia is a concern. No specific antidote exists for essential oil intoxication. In humans, N-acetylcysteine has been used for pennyroyal toxicosis. The prognosis is guarded, depending on the severity of clinical signs, which may last several days; however, with supportive care most animals recover.

CHAPTER 70

Chemical Toxicities

David C. Dorman
Janice A. Dye

Hazardous chemicals are found throughout the home, and a significant potential exists for poisoning after exposure to these agents. Most veterinary toxicology cases are the result of accidental dermal or oral exposure arising from improper storage or handling of these chemicals within the home. Timely decontamination through bathing, gastric lavage, or use of emetics, activated charcoal, and cathartics serve to reduce systemic absorption acutely after exposure. However, risks associated with these procedures (e.g., handling, aspiration, sedation) must be weighed against potential therapeutic benefits. This chapter provides brief synopses of commonly involved chemicals, both active and vehicle ingredients. Its purpose is to provide a framework for appropriate case management of the poisoned small animal patient. For success, management must always be tailored to the animal's initial, and ever changing, clinical signs.

PETROLEUM DISTILLATES AND OTHER ALIPHATIC HYDROCARBONS

Sources

Kerosene, gasoline, and mineral seal oil are prototypical hydrocarbons.[1] Turpentine, a similar hydrocarbon product, is derived from pine oil. Hydrocarbons are found in lubricants, degreasers, waxes, varnishes, cleaning fluids, lamp oil, and starting fluids.

Signs

Most commonly the pulmonary system, central nervous system (CNS), and gastrointestinal (GI) system are involved.[1] Some animals emit a characteristic hydrocarbon odor, and many develop vomiting or diarrhea. Hepatotoxicity, renal toxicity, and cardiac arrhythmias may also occur. Of note, aspiration and chemical-induced pneumonitis are especially

common after exposure to low-viscosity or highly volatile hydrocarbons. Aspiration is less common with higher viscosity hydrocarbons such as tar, oil, and grease. Nevertheless, owing to the risk of aspiration during drug-induced emesis or gastric lavage, these procedures are generally not recommended. Because volatile hydrocarbons may displace oxygen when aspirated, transient hypoxia and respiratory dysfunction may occur within minutes of exposure. Other signs related to aspiration pneumonitis include cough, hyperthermia, dyspnea, and cyanosis.

Management

Thoracic radiographs may reveal changes consistent with aspiration pneumonia. Oxygen and positive end-expiratory pressure therapy may prove necessary in cases where alveolar collapse and cyanosis are evident. Animals that remain asymptomatic for 6 to 12 hours after exposure are unlikely to develop pneumonitis. For dermal contamination with thick tarry or asphalt materials, mild detergents and fur clipping is most useful. Vegetable oil may be used to soften the material prior to removal. Of note, solvents or other hydrocarbons should never be used in an attempt to "dissolve" these compounds. Prophylactic antibiotics and steroids are generally not recommended.

NAPHTHALENE

Source

The primary source of naphthalene is moth balls.

Signs

Ingestion of large quantities of naphthalene may be associated with vomiting, lethargy, seizures, acute hemolytic anemia (reportedly at "doses of" 411 mg/kg), Heinz body formation, methemoglobinemia, hemoglobinuria, and renal failure.

Management

Treatment is largely based on GI decontamination and supportive care (i.e., fluid therapy, warming, control of methemoglobinemia with ascorbic acid or methylene blue) until recovery.

ETHANOL

Sources

Sources of ethanol[2] are ethanol-containing beverages, consumer products, and fermenting materials (e.g., raw sourdough, uncooked pizza dough, rotting apples[3]). The oral lethal dose is 5 to 8 g/kg.

Pathogenesis

Ethanol is metabolized by alcohol dehydrogenase to acetaldehyde, which is subsequently metabolized to acetate by aldehyde dehydrogenases. Metabolic acidosis resulting from acetate accumulation has been reported.

Signs

Intoxication generally develops within 1 hour of ingestion and may result in CNS depression, behavioral changes (e.g., vocalization, excitability), ataxia, hypothermia, and respiratory or cardiac arrest.

Management

Blood alcohol levels can confirm a diagnosis. Treatment is largely based on GI decontamination and supportive care (i.e., fluid therapy, warming, assisted ventilation) until recovery.

METHANOL (WOOD ALCOHOL)

Sources

Sources of methanol (wood alcohol[2]) are methanol-based automotive windshield fluid, antifreezes, and related consumer products. The oral lethal dose of methanol in the dog is 4 to 8 g/kg.

Pathogenesis

Methanol is metabolized to formaldehyde and formate. Unlike people, formate accumulation and subsequent blindness does not occur in dogs or cats exposed to methanol.

Signs

Clinically, methanol toxicosis resembles that of ethanol poisoning; it is therefore treated similarly.

ETHYLENE GLYCOL

Sources

Sources of ethylene glycol are automobile radiator antifreeze, heat exchange fluids, and some photographic solutions. A lethal dose of 95% ethylene glycol is 1.4 mL/kg in cats and 4.4 mL/kg in dogs. It remains one of the most common causes of poisoning in small animals.[4]

Pathogenesis

The initial metabolism of ethylene glycol to glycoaldehyde by alcohol dehydrogenase is rate limiting. Other major metabolites include glycolic acid, glyoxylic acid, and oxalic acid. An anion gap metabolic acidosis typically develops due to formation of these organic acids, in particular glyoxylic acid. Most of the oxalic acid is excreted in the urine; however, some may be retained as calcium oxalate. Calcium oxalate and hippuric acid crystals often precipitate in the renal tubules and in other organ vasculature systems.

Signs

Ethylene glycol toxicosis is best described as a triphasic syndrome.[4] Initially (within 1 hour of exposure), the animal appears ataxic or "drunk," followed by a relatively asymptomatic period. Secondly (12 to 24 hours after ingestion), cardiopulmonary involvement inconsistently develops (e.g., cardiac failure). Thirdly (1 to 3 days later), animals commonly develop oliguric renal failure with renomegaly. These animals are depressed, anorexic, and often develop vomiting, renal pain, hypothermia, coma, and ultimately death. Unfortunately, many companion animals are not presented until this third phase.

Management

Urinalysis with polarized light microscopy may reveal the presence of calcium oxalate crystalluria. In addition, blood and tissue ethylene glycol levels can confirm a diagnosis. For recent exposure (≤2 hours), treatment consists of administering an emetic followed by activated charcoal and a cathartic. If the animal is presented within 8 to 12 hours after ingestion, treatment with ethanol or fomepizole (4-methylpyrazole [4-MP]) is indicated to inhibit further ethylene glycol metabolism.[5] Ethanol is given intravenously (IV) as a 20% solution in saline at a dose of 5 to 5.5 mL/kg every 6 hours for 5 to 6 treatments. The dose should be titrated to produce CNS depression but not semicoma. Alternatively, in dogs, 4-MP may be administered as a 5% solution, given as a slow IV bolus using a decreasing dose regimen. Initially, 4-MP is given at 20 mg/kg; followed by 15 mg/kg at 12 hours and again at 24 hours; and then 5 mg/kg at 36 hours.

Additional 4-MP doses of 3 mg/kg every 12 hours may be required if the animal has yet to fully recover or if ethylene

glycol blood levels are still detectable. The advantage to using 4-MP is that it has minimal depressive side effects; however, it is not effective in cats.[5,6] Sodium bicarbonate may be given intraperitoneally to dogs and cats to control acidosis. In addition, diuresis with furosemide, mannitol, or dopamine may be necessary to correct unresponsive anuria or pulmonary edema. Peritoneal dialysis may also be used to manage acute oliguric renal failure. In general, with aggressive and appropriate therapy, exposed animals that have been examined before developing overt renal insufficiency would be expected to recover. Symptomatic animals have a poorer prognosis as a result of associated renal damage; however, renal tubular regeneration is still possible because the tubular basement membrane remains relatively unaffected.

PROPYLENE GLYCOL

Source
The source of propylene glycol is automotive radiator antifreeze. The acute oral lethal dose is approximately 9 mL/kg (dogs).

Signs
This toxic syndrome is similar to that observed during the acute phase of ethylene glycol toxicosis (i.e., ataxia, CNS depression).

Management
Treatment largely consists of supportive care and early GI decontamination. Alcohol dehydrogenase inhibitors are not required because propylene glycol is metabolized to lactic and pyruvic acid, both of which have low renal toxicity.

PHENOL PRODUCTS

Sources
The sources of phenol products[7,8] are household cleaners, disinfectants, and some antiseptic and germicidal agents. They are also used, in lesser concentrations, as preservatives. The oral LD_{50} of phenol in dogs is estimated to be only 0.5 g/kg. Cats are even more sensitive because of their limited glucuronyl transferase activity. Toxicosis induced by phenolic compounds is considered a medical emergency.

Pathogenesis and Signs
Phenols are very cytotoxic. Dermal exposure may result in coagulative dermal necrosis accompanied by intense pain. Ocular exposure may lead to significant corneal damage. Ingestion is associated with severe corrosion of the upper GI tract. Systemic effects include ataxia, weakness, tremors, coma, seizures, methemoglobinemia, and respiratory alkalosis. Liver and kidney damage may develop within 12 to 24 hours after exposure.

Management
N-acetylcysteine administration (140 mg/kg orally [PO] or IV initially; then 50 mg/kg every 4 hours for 3 days) may be partially effective to reduce hepatic and renal injury. Resultant methemoglobinemia should be treated with ascorbic acid or methylene blue.

ANTICOAGULANT RODENTICIDES

Sources
Anticoagulant rodenticides[9] include short-acting (e.g., warfarin) and long-acting (e.g., bromadiolone, brodifacoum, chlorophacinone, diphacenone, valone, pindone) agents.

Pathogenesis
These compounds principally interfere with vitamin K_1 hydroquinone recycling and thus inhibit clotting factor synthesis. A coagulopathy affecting the intrinsic, extrinsic, and common pathways ensues. Lethal doses vary considerably depending primarily on the anticoagulant involved but also on patient predisposing factors such as age, concurrent disease, and exposure history (single dose versus repeated ingestions). The acute oral toxic dose of warfarin in the dog or cat is 5 to 50 mg/kg; whereas repeated daily ingestion of as little as 1 mg/kg may result in severe toxicosis. The toxic dose of brodifacoum in dogs and cats is 0.2 to 4 and 25 mg/kg, respectively. Secondary or relay toxicity arising from the ingestion of poisoned rodents is uncommon.

Signs
Typically, signs develop within 2 to 5 days after exposure and may vary considerably depending upon the site and volume of blood loss. Signs may include petechiae and ecchymosis of the skin and mucous membranes, hematomas, weakness, pallor, respiratory distress, and CNS depression. Hematemesis, epistaxis, melena, ataxia, paresis, seizures, and sudden death have also been reported.

Diagnosis
Significant prolongation of the activated clotting time (ACT), prothrombin time (PT), and activated partial thromboplastin time (aPTT) occurs. Elevated levels of the carboxylated forms of the vitamin K dependent coagulation factors also occur in exposed animals, and the proteins inhibited by vitamin K antagonists (PIVKA) test can help identify a vitamin K_1–responsive coagulopathy. Poisoned animals exhibiting respiratory distress should be radiographed to establish the presence of pleural, mediastinal, or pericardial fluid. Necropsy findings often include hemoperitoneum, hemothorax, and pulmonary hemorrhage. Postmortem samples for chemical analysis should include unclotted blood, liver, and GI contents.

Treatment
Vitamin K_1 is antidotal, with a recommended oral dose of 2.5 to 5.0 mg/kg given every 8 to 12 hours for either 2 or 4 weeks depending upon whether the ingested anticoagulant was a short- or long-acting agent. Synthesis of new clotting factors takes at least 12 hours. In the interim, clinically ill patients may need life-support measures (e.g., whole blood, fresh-frozen plasma transfusions) to prevent further blood loss. Coagulation screening tests should be reassessed 48 to 72 hours after cessation of vitamin K_1 therapy to determine whether additional K_1 supplementation is warranted. Restricting movement and exercise and providing a warm, safe environment is essential in preventing trauma-induced hemorrhage.

ZINC PHOSPHIDE

Source
Zinc phosphide[9,10] is a rodenticide. The lethal dose in dogs and cats is 20 to 50 mg/kg. Secondary toxicity is rare.

Pathogenesis
Within the acidic environment of the stomach, ingested zinc phosphide is converted to phosphine gas that in turn damages capillary endothelium and erythrocyte membranes within the lung, liver, and kidney.

Signs
Anorexia, lethargy, weakness, abdominal pain, and vomiting commonly occur within 1 to 4 hours of ingestion. Signs may

progress to recumbency, whole-body tremors, seizures, cardiopulmonary collapse, and death. Gross and microscopic findings may include pulmonary edema and hemorrhage, as well as mild hepatic and renal necrosis.

Management
No specific antidote exists; however, supportive therapy including antacids (containing magnesium or aluminum hydroxide) is considered beneficial.

CHOLECALCIFEROL (VITAMIN D)

Sources
The sources of cholecalciferol (vitamin D[9,11]) are certain rodenticides and vitamin D–based creams and medications. The toxic dose of cholecalciferol in dogs is 1.5 to 8 mg/kg. Cats are likely equally sensitive.

Pathogenesis
Cholecalciferol and other vitamin D metabolites abnormally increase intestinal absorption of calcium, stimulate bone resorption, and increase the renal tubular reabsorption of calcium, thereby resulting in persistent hypercalcemia (serum calcium >12 mg/dl). Soft tissue mineralization may occur and when severe can be apparent radiographically. Death is usually due to cardiac failure, renal failure, or both. Serum phosphorus, ionized calcium, parathyroid hormone, and 25-hydroxycholecalciferol levels may serve to rule out other causes of hypercalcemia.

Signs
Signs of cholecalciferol toxicity typically appear within 3 to 5 days after ingestion and include anorexia, CNS depression, vomiting occasionally with hematemesis, muscle weakness, constipation, bloody diarrhea, polyuria, and polydipsia.

Treatment
Prompt GI decontamination is indicated as soon after ingestion as possible. Ancillary therapy is directed at increasing renal calcium excretion via furosemide administration (5.0 mg/kg IV followed by 2.5 mg/kg PO three times a day (tid) or four times a day (qid) in combination with aggressive fluid therapy (physiologic saline at rates up to two times maintenance). In addition, prednisone (2 to 3 mg/kg PO once a day [qd] to twice a day [bid]) aids in decreasing both osteoclastic activity and GI calcium absorption. Calcitonin (4 to 6 IU/kg subcutaneously [SQ] every 2 to 3 hours) may serve to further reduce serum calcium concentrations; however, some animals become refractory. Vomiting and anorexia are common adverse side effects. Pamidronate disodium IV (1.3 to 2.0 mg/kg in 0.9% saline) has been shown to reverse cholecalciferol-induced hypercalcemia.[6] Prolonged treatment (up to 4 weeks in some cases) may be required. Periodic reassessment of serum calcium, phosphorus, potassium, blood urea nitrogen (BUN), and creatinine levels is prudent. Once serum calcium and phosphorus levels have been normalized and the patient appears stable, most animals can be treated on an outpatient basis.

BROMETHALIN RODENTICIDES

Cats are especially sensitive to bromethalin rodenticides,[8,12,13] with toxic doses of 0.3 and 2.5 mg/kg in cats and dogs, respectively.

Pathogenesis
Bromethalin uncouples oxidative phosphorylation, resulting in myelin edema in the brain and spinal cord.

Signs
Relatively high-dose acute exposure results in severe muscle tremors, hyperexcitability, vocalization, running fits, seizures, hyperesthesia, vomiting, and dyspnea. More commonly, however, this toxic syndrome has a delayed and insidious onset (>12 to 24 hours); with clinical signs characterized by progressive ataxia, paresis, hind limb paralysis, and progressive CNS depression that may culminate in semicoma or coma.

Management
Treatment consists of (1) GI decontamination using repeated administration of oral activated charcoal; (2) control of cerebral edema with mannitol, dexamethasone, and furosemide; and (3) supportive care including effective control of seizures. Animals ingesting mild-to-moderate doses may improve over a 2- to 3-week period with aggressive supportive care. Prognosis is poor for severely affected animals.

PYRETHRINS AND PYRETHROID INSECTICIDES

Pyrethrins and pyrethroid insecticides[14,15] are lipophilic insecticides used for the control of ectoparasites. They are rapidly metabolized and excreted and rarely cause adverse effects in dogs and cats when used according to label instruction. Excessive or inappropriate administration, however, may result in clinical toxicity.

Signs
Most commonly, affected animals develop an acute onset of CNS depression, hypersalivation, muscle tremors, vomiting, ataxia, dyspnea, and anorexia. Less commonly, hyperthermia, hypothermia, weakness, and seizures may occur. Death is rarely observed. Of note, neither pyrethrins nor pyrethroid insecticides are inhibitors of acetylcholinesterase. Gross and microscopic changes are nonspecific.

Management
Treatment is aimed at reducing dermal or GI absorption and providing supportive care. Diazepam may be used to control muscle tremors and seizure activity. Atropine, although not a true antidote, can be used at low doses to control hypersalivation. The overall prognosis is very favorable, and the majority of animals recover within 1 to 3 days.

ORGANOPHOSPHOROUS AND CARBAMATE INSECTICIDES

Organophosphorous (OP) and carbamate insecticides[15] are lipophilic insecticides that are well absorbed from the skin and GI tract. Toxicity due to these agents is highly variable (Box 70-1).

Box • 70-1

National Pesticide Telecommunications Network

The National Pesticide Telecommunications Network is a useful source of toxicity data for pesticides (phone: 800-858-7378; website: http://ace.orst.edu/info/nptn). ASPCA-Animal Poison Control Center is another valuable resource that is provided on a fee-for-service basis. (phone: 888-426-4435).

Pathogenesis
Carbamate insecticides are reversible acetylcholinesterase inhibitors. Most OP insecticides irreversibly inhibit this enzyme. In fact, most OP insecticides covalently bind this enzyme (i.e., aging) within 24 hours of exposure.

Signs
Toxicity results in a "cholinergic crisis" that is marked by muscarinic (i.e., salivation, lacrimation, bronchial secretion, vomiting, diarrhea), nicotinic (i.e., muscle tremors, respiratory paralysis), and mixed (i.e., CNS depression, seizures, miosis, hyperactivity) signs.

Diagnosis
Determination of reduced cholinesterase activity (<50% normal activity) in blood, brain, and retinal tissues is highly supportive of a diagnosis.[16] The prognostic value of this test is difficult to assess, especially in cats, where the very sensitive pseudocholinesterase enzyme comprises a large percentage of total blood esterase activity.

Treatment
Life-saving symptomatic therapy should be instituted immediately. Atropine sulfate (0.1 to 0.2 mg/kg, repeated as needed) is useful to alleviate severe bradycardia and excessive bronchiolar constriction and mucus hypersecretion. The reader should note, however, atropine will not abolish muscle tremors and other signs related to excessive nicotinic stimulation. Atropine doses should be adjusted to provide the minimum amount that alleviates dyspnea, bradycardia, and other signs of cholinergic stress. However, if tachycardia, GI stasis, hyperthermia, or severe behavioral changes (e.g., aggressiveness, delirium) occur, atropine should be decreased or discontinued. Enzyme reactivators may be used for treatment of OP insecticide toxicosis. Reactivators act on the OP insecticide-acetylcholinesterase complex to free the enzyme and restore normal function. Reactivators are most effective if "aging" has not yet occurred. Of the enzyme reactivators, pralidoxime chloride has received the widest clinical use. Pralidoxime chloride is given (20 mg/kg intramuscularly, repeated every 12 hours) to relieve tremors and other nicotinic signs and should be continued until these signs are alleviated or until additional benefit is no longer observed. Pralidoxime chloride generally has low toxicity; however, overdoses can cause tachycardia and cardiac arrhythmias. It is critical that further exposures to OP and carbamate insecticides be avoided until the animal is fully recovered. Complete recovery is ultimately dependent on the resynthesis of sufficient quantities of acetylcholinesterase enzyme—which may require up to 4 to 6 weeks.

2,4-DICHLOROPHENOXYACETIC ACID

Source
Animals are occasionally poisoned with the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D).[17,18] The approximate lethal dose of 2,4-D in dogs is 100 mg/kg. Poisoning is not expected to occur after exposure of pets to treated lawns.

Pathogenesis
The mechanism of action of 2,4-D is poorly understood.

Signs
Moderate exposure can result in an acute onset of anorexia, vomiting, and diarrhea with signs of toxicity typically abating within 48 hours. Greater exposures may result in CNS depression, ataxia, and hind limb myotonia.

Management
The diagnosis often relies on a known history of exposure, development of compatible clinical signs, typical electromyogram changes (e.g., fibrillation potentials), and residue analysis of urine samples. Treatment is nonspecific and includes the general principles of decontamination and maintaining normal fluid and electrolyte status. Fortunately, affected animals typically recover within a 24- to 72-hour period.

LEAD

Lead poisoning continues to be a significant toxicologic problem in companion animals.

Sources
A common cause of lead poisoning is ingestion of paints found in the interior of older buildings.[19] Veterinarians should warn owners of lead-poisoned animals that exposure of children may occur in the same environment. Other lead sources include batteries, linoleum, solder, plumbing supplies, and fishing line weights.

Signs
Chronic low-level lead poisoning is most commonly associated with GI signs, as evidenced by vomiting, abdominal pain, anorexia, diarrhea, and megaesophagus.[20] Constipation occurs less frequently. Acute, high-level lead exposure results most commonly in CNS signs, including behavioral changes, hysteria, ataxia, tremors, opisthotonos, blindness, and seizures.[21,22] In cats, GI signs appear to be more common than CNS signs.

Diagnosis
Nucleated erythrocytes may be found in peripheral blood smears of affected dogs without evidence of severe anemia.[22] Basophilic stippling is sometimes observed in red blood cells (RBCs). In cats, nucleated erythrocytes and basophilic stippling is found only occasionally. Toxicosis may be confirmed definitively by chemical analysis with blood lead concentrations ≥0.20 ppm being considered diagnostic.

Treatment
The cornerstone of treatment is the use of chelators to enhance metal elimination.[23] In general, chelator therapy should be initiated as soon after metal exposure as possible. However, prior to chelator use one should attempt to eliminate the source of lead within the GI tract. Surgery is indicated for removal of large lead-containing objects. For dispersed lead-laden material (e.g., paint dust, paint chips), oral administration of magnesium sulfate or sodium sulfate may serve to precipitate lead within the intestinal tract, thereby limiting further absorption. Of note, chelator administration may initially aggravate the clinical signs, and one should be prepared to control aggressiveness or seizures. Furthermore, to safely mobilize lead in patients with relatively high-dose exposures, several "courses" of chelator therapy may be warranted (i.e., 5 days of chelator therapy followed by 5 days of no therapy and so forth). Of the available agents, succimer (meso-2, 3-dimercaptosuccinic acid) is an orally active agent that appears quite effective in dogs and cats.[6,24] It has recently been approved for use in children and will likely emerge as the primary drug of choice in veterinary medicine. It is administered at 10 mg/kg, three times a day for 10 to 17 days. To date, it has been associated with few side effects. Alternatively, calcium disodium EDTA is an effective metal chelator. It should be diluted to 10 mg/ml with 5% dextrose, then administered subcutaneously at 25 mg/kg, qid, for 2 to 5 days. Another agent, D-penicillamine has also been used, most commonly as a follow-up agent after treatment with calcium

disodium EDTA. D-penicillamine is administered orally at 110 mg/kg/day (divided every 6 to 8 hours) for 1 to 2 weeks. If toxicity to D-penicillamine develops, as evidenced by vomiting, CNS depression, and anorexia, the dose should be reduced.

ZINC

Sources
Sources of zinc include zinc nuts, pennies minted after 1981, and zinc oxide-containing products (e.g., diaper rash ointments, cosmetics).[25,26]

Signs
Acute zinc oxide poisoning results in severe vomiting, CNS depression, and lethargy, with diarrhea occurring less commonly. Subacute or chronic elemental zinc poisoning may result in anorexia, vomiting, diarrhea, CNS depression, pica, hemolysis, regenerative anemia, spherocytosis, an inflammatory leukogram, icterus, and renal failure.

Diagnosis
Diagnosis is based on the history of exposure, development of compatible clinical signs, and the presence of radiodense material within the GI tract. Hypocupremia may be present, presumably from zinc antagonism of the GI absorption of copper. Blood and tissue levels may confirm a clinical diagnosis, but care should be taken to collect samples in containers appropriate for trace mineral analysis.

Treatment
As with lead ingestion, removing the source of zinc, either through emesis or surgery, is important. Supportive care and chelation therapy with calcium disodium EDTA are also indicated.[26] Of note, animals with zinc poisoning appear to have high postoperative complication rates. One should also anticipate that serum zinc concentrations would decrease rapidly after removal of the source.

IRON

Sources
Sources of iron are multivitamins and other iron-containing medications. Animals should be monitored for possible clinical signs of iron toxicosis if elemental iron has been ingested in excess of 60 mg/kg. Potentially lethal doses of iron are in the range of 200 to 250 mg/kg.

Signs
Clinical signs observed shortly after ingestion are characterized by certain acute GI effects: vomiting, abdominal pain, diarrhea, hematemesis, and melena. These signs may resolve within 6 to 24 hours after ingestion. Many poisoned animals do not progress beyond this stage; however, life-threatening signs associated with multisystem failure may occur 1 to 3 days after ingestion.

Management
Treatment of animals that have ingested large amounts of iron includes the use of an emetic if ingestion was less than 2 hours. This is followed by administration of activated charcoal plus a saline or osmotic cathartic. If potentially toxic amounts (>60 mg/kg) of iron were ingested, gastric lavage with magnesium hydroxide at 5 to 10 times the dose of elemental iron has been shown to be effective. Whole-bowel irrigation with a polyethylene glycol electrolyte solution may also be effective for decontaminating the GI tract after iron ingestion. Finally, deferoxamine, a chelating agent, should be considered after large ingestions of iron. It is administered 15 mg/kg/hour IV.[27]

SECTION III

Techniques

CHAPTER 71

Clinical Genetics

Urs Giger

Recent developments in molecular and human genetics have increased the interest in using this tool in the diagnosis, management, and control of hereditary disorders. Genetics has emerged as an important discipline in small animal practice for several reasons. Effective preventative measures have reduced the frequency of infections, nutritional disturbances, and intoxications. Furthermore, life-saving advances in medicine and surgery have increased the chance of survival of companion animals and thus tend to raise the recognition of genetic defects. Inbreeding practices to preserve desirable traits in certain breeds favor the occurrence of recessively inherited diseases. Technologic advances have allowed the recognition and characterization of the clinicopathologic, biochemical, and molecular basis of many hereditary diseases. In the past, genetics played a large role in a few patients; however, today hereditary disorders and genetic predispositions to diseases are critical in small animal practice for most patients. Specific hereditary disorders are covered under chapters of individual organ systems. This chapter on clinical genetics reviews the general characteristic clinical features of hereditary diseases in small animals, the various modes of inheritance, the screening of specific tests used to reach a diagnosis, as well as the management of these diseases and control in future generations. The importance of genetic counseling is addressed (i.e., providing information for pet owners and breeders of animals afflicted with hereditary disorders, concerning the consequence of such disorders and the ways in which they can be prevented by informed breedings). Furthermore, the recent completion of the human and canine genome sequence and initiative for a feline genome sequence have greatly facilitated the research of single-gene and complex inherited diseases. The field of *genomics* is the study not only of single genes but also of the organization, function, and interaction of all genes in the genome, including their interaction with environmental factors.

FREQUENCY

Because of the increased awareness (on the part of breeders, pet owners, and veterinarians) of genetic defects and improved diagnostic abilities in clinical practice, the number of reported hereditary diseases in small animals is rapidly growing. Originally, diseases with apparent clinical manifestations affecting the appearance and gait of an animal were recognized. Thus it is not surprising that skeletal malformations, skin and eye abnormalities, and neuromuscular defects were more frequently reported than disorders involving internal organs. Furthermore, clinicians now recognize that animals with recurrent or chronic infections or immune-mediated diseases may have a genetic defect that dysregulates one of their immune functions. Other genetic predispositions of certain animals, families, or breeds to develop disorders such as hip dysplasia, gastric torsion, adverse drug reactions, and cancer have been clearly established.

At present, approximately 430 hereditary diseases in dogs and 180 disorders in cats have been adequately documented. By comparison, several thousand hereditary disorders have been accumulated in the compendium known as *Online Mendelian Inheritance in Man* (OMIM) by Victor McKusicks. Practically all hereditary diseases described in small animals have also been seen in humans and generally represent close homologues.

Although any genetic defect may occur in any animal, many have been documented only in one family or breed. In some breeds, the frequency of a particular disorder and the mutant allele may reach high proportions. This may be due to a "founder" effect in which one or more of the founders of a small ancestral group was a carrier or even affected, or it may be as observed in several smaller breeds in which a "popular sire" was later determined to be a carrier of a mutant gene. Unfortunately, genetic disease frequencies are generally not available or are severely biased because of data collection. For instance, the prevalence of hip dysplasia may differ greatly depending on methods used to reach a diagnosis and whether a registry requires or only encourages recording of every examined animal. Large-scale randomized screening programs and open registries with data on genetic diseases in certain breeds have rarely been established. In people, a disease occurrence of 1 in less than 500 individuals is considered a high-frequency disorder. In companion animals, many hereditary diseases appear to occur in 1% to 10% of certain breed populations. Recently, resources have become available to obtain genetic information. In addition to the list of hereditary diseases and associated breeds in the appendices of this book, other published lists organized by breed or disease are available. A list of genetic diseases in all species with references assembled by Frank W. Nicholas, known as *Mendelian Inheritance in Animals* (MIA), can be obtained online on Cambridge University's website. The most comprehensive and updated searchable information on canine hereditary traits, however, is Donald F. Patterson's *Canine Genetic Disease Information System*, available in book format.

INHERITANCE

Genetic diseases are caused by chromosomal alterations or gene mutations. Disease-causing mutations are heritable changes in the sequence of genomic deoxyribonucleic acid (DNA) that alter the expression, structure, and function of the coded protein. The *genotype* refers to the animal's genetic makeup (reflected by its DNA sequence), whereas the *phenotype* relates to the entire makeup of an animal (determined both genetically and environmentally). The molecular genetic defect is now known for more than 40 hereditary disorders in small animals (Table 71-1). Among the disorders caused entirely or partly by genetic factors, three main types are recognized: (1) chromosomal, (2) single gene, and (3) complex or multifactorial disorders. For approximately half of the

Table • **71-1**

Examples of Hereditary Disorders Characterized at the Molecular Genetic Level

DISORDER	BREED
Hematologic Disorders	
Elliptocytosis (band 4.1) deficiency	Mixed breed dog
Pyruvate kinase (PK) deficiency	Basenji, West Highland white terrier, Cairn terrier, Beagle, Eskimo toy, Dachshund, Abyssinian, Somali, DSH cat
Phosphofructokinase (PFK) deficiency	English springer and American cocker spaniel, mixed breed dog
Hemophilia A (Factor VIII)	Mixed breed, Irish setter
Hemophilia B (Factor IX)	Airedale terrier, Labrador retriever, mixed breed
von Willebrand disease	Doberman, Manchester terrier, Pembroke Welsh Corgi, Bernese mountain dog, Kerry Blue, Poodle, Papillon
vWD type 1	German shorthair, wirehair pointer
vWD type 2	Dutch Kooiker, Scottish terrier, Shetland sheepdog
vWD type 3	Basset, Pembroke Welsh corgi
Severe combined immunodeficiency (SCID)	Irish setter, red and white setter
Leukocyte adhesion deficiency (LAD)	Brittany spaniel
Complement component 3 deficiency	
Hereditary Eye Diseases	
Progressive retinal atrophy	Irish setter, red and white setter
PRA dominant	Bull mastiff, English mastiff
PRA type A	Miniature schnauzer
PRA X-linked	Samoyed, Siberian husky
PRA red 1	B phosphodiesterase
PRA red 1a	Sloughi
PRA red 3 (pred)	Cardigan Welsh Corgi
Progressive cone dysplasia	Chesapeake Bay and Labrador retriever, English cocker spaniel, Portuguese water dog, Australian cattle dog, Miniature and toy poodle, Entlebuchers, American Eskimo, Nova Scotia Duck Tolling Retrievers
PRA pred (linkage)	Briard
Stationary night blindness	German short haired pointers
Con (retinal) degenerative	
Neuromuscular Diseases	
Shaking puppy syndrome	English springer spaniel
Dystrophin muscular dystrophy	Golden retriever, Rottweiler, DSH cat, mixed breed
Mucopolysaccharidosis type I	Plott hound
type IIIA	Wirehaired dachshund, New Zealand Huntaway dog
type IIIB	Schipperke
type VI	Siamese cat (two mutations), Miniature pinscher, miniature Schnauzer
type VII	German shepherd, mixed breed, DSH cat
Alpha mannosidosis	Persian, DSH cat
Gangliosidosis GM1	Siamese, Korat cat, Portugese water dog
GM2	Korat cat
Globoid cell leukodystrophy (Krabbe)	West Highland white and Cairn terrier
Glycogenosis type IV	Norwegian forest cat
Alpha fucosidosis	English springer spaniel
Neuronal ceroid lipofuscinosis	English setter
Myotonia congenita	Miniature schnauzer
Narcolepsy	Doberman, Labrador retriever, dachshund
Ivermectin toxicity (MDR-1 gene)	Collie, Sheltie, Australian cattle dog
Deafness	German short haired pointers
Hepatic Diseases	
Congenital hypothyroidism with goiter	Toy fox terrier
Hyperchylomicronemia	DSH cat
Glycogenosis type Ia	Maltese
Copper toxicosis	Bedlington terrier
Cobalamin malabsorption	Giant Schnauzers
Renal Diseases	
Cystinuria type I	Newfoundland, Labrador retriever
Renal adenocarcinoma and nodular dermatitis	German shepherd (linkage)
X-linked nephropathy	Samoyed
Polycystic kidney disease	Persian and other cats

A list of test laboratories is available at www.vet.upenn.edu/penngen.

disorders suspected to be of a genetic nature, however, the mode of inheritance remains unknown. These molecular genetic changes include point mutations, deletions, and insertions in the DNA sequence that result in a missense or nonsense sequence with an altered codon sequence. A codon is a three base sequence of DNA or RNA that specifies a single amino acid.

The dog has 76 autosomes (38 pairs) and 2 sex chromosomes (78XX or 78XY), whereas the cat has 38XX or 38XY. The human genome project has facilitated progress in canine and feline gene mapping. Furthermore, the canine genome sequence is nearing completion. Through physical and genetic mapping strategies, genes have been assigned to and localized along a chromosome, and new genes can be identified.

Chromosomal Disorders

Chromosomal disorders are caused by an excess or deficiency of genes contained in a chromosome or chromosomal segment. Understandably, such defects may result in severe, often lethal clinical syndromes. Although alterations of autosomes have only rarely been reported in small animals—some had syndromes with multiple defects—they are commonly reported in infants and are often responsible for fetal losses. In contrast, abnormalities involving the X and Y chromosomes leading to sex development disorders are well recognized. The best example is the tricolored (calico, tortoiseshell) male cat with testicular hypoplasia and an XXY chromosome set. However, not every sex developmental disorder is due to a defect in the sex chromosomes (e.g., XX sex reversal reported in various canine breeds).

Single-Gene Traits

The inheritance of a single-gene defect is often called *Mendelian trait* and involves one mutant gene (allele) at a single locus. When an animal has a pair of identically mutant genes (alleles), it is said to be *homozygous* (a homozygote), whereas when only one of the alleles is mutated, it is said to be *heterozygous* (a heterozygote) at that gene locus. The pattern of inheritance depends mainly on two factors: (1) whether the mutation is located on an autosome (autosomal) or on the X chromosome (X linked) and (2) whether the phenotype, the observable expression of a genotype as a disease trait, is dominant (i.e., expressed when only one chromosome of a pair carries the mutation) or recessive (i.e., expressed when both chromosomes of a pair carry the mutation). Therefore it is the phenotype rather than the mutant gene or protein that is dominant or recessive. In humans most diseases are dominantly inherited, whereas recessive traits resulting from inbreeding practices are more commonly been in small animals.

Autosomal Recessive Inheritance

Autosomal recessive inherited traits are common in small animals. The parents of affected animals must carry the mutant allele. Because they are generally asymptomatic carriers (heterozygotes), they are called *obligate carriers*. Typically one fourth of males and females in a litter are likely to be affected. Phenotypically normal offspring may be in a ratio of 2:1, either carriers (heterozygotes) or free of the mutant allele ("clear," homozygous normal). Although the parents could also be affected, diseased animals generally are not used for breeding, unless they remain unrecognized because signs do not develop until later in life (late-onset diseases).

X Chromosomal Recessive Inheritance

In X chromosomal recessively inherited disorders, males who are hemizygous for the X chromosome are either affected or normal, whereas females are typically carriers (one normal and mutant allele on X chromosome). When heterozygous females (carriers) are mated to a normal male, half of their male offspring will be affected and half of their female offspring will be phenotypically normal carriers (whereas the other males and females will be "clear"). The mutant X chromosomal gene is never passed on from the sire to a male offspring but is transmitted by an affected male to all of its female offspring (obligate carriers). Affected females would occur only if a carrier female is mated with an affected male. Heterozygous females are usually unaffected, although some manifestations may occur because of X chromosomal inactivation. In addition, an X-linked dominant trait may need to be considered but has been reported only in Samoyeds with a specific glomerulonephropathy. X-linked disorders should not be confused with sex-limited disorders, such as diseases related to the primary and secondary sex organs. Y chromosomal diseases have not been reported in animals.

Autosomal Dominant Inheritance

In autosomal dominant conditions, the disease appears in every generation. An affected animal generally has one affected parent unless this animal has a new mutation in the gamete of a phenotypically normal parent or when the disease is variably expressed (nonpenetrant in parent). *Penetrance* refers to the likelihood that an animal carrying a particular mutation will exhibit an altered phenotype. Males and females are equally likely to transmit the disease to an offspring of either sex. Because affected animals are generally heterozygous, half of all offspring will be affected. Affected animals generally are not used in breeding programs, hence rapidly eliminated. Furthermore, homozygous states of dominant traits are often lethal and thus result in fetal loss or stillborns.

Mitochondrial Inheritance and Imprinting

Mitochondrial inheritance is a rare and atypical hereditary disorder involving mitochondrial DNA. Because all mitochondrial DNA is transmitted from the ova (mother), all offspring from an affected female (but none from an affected male) will be diseased. In humans, several neuromuscular diseases are known to be associated with mutations in mitochondrial DNA. In dogs, some myopathies may be caused by a mitochondrial defect.

Imprinting is another non-Mendelian mechanism for single-gene disorders. Here the effects of certain genes depend on whether they are inherited through the maternal or paternal parent. In companion animals this phenomenon has not yet been documented.

Complex or Multifactorial Inheritance

A number of developmental disorders resulting in congenital malformations are caused by complex or multifactorial inheritance, as well as other disorders in adult animals. Rather than having one single-gene error, several major and minor gene defects (polygenic) in the genetic information, together with certain environmental factors, can produce or predispose to a serious illness. Hip and other dysplasias and certain congenital heart defects (conotruncal defect) are examples, and the degree to which a trait (e.g., hip dysplasia) is genetically determined may greatly vary between breeds (heritability). Thus the hereditary nature of a particular disease may be suggested or established by a certain familial occurrence, breed predilection, breeding studies, established mode of inheritance, identified gene defect, or a combination of these factors.

CLINICAL SIGNS

Hereditary defects can involve any gene and hence, any organ. Therefore the clinical signs of hereditary diseases are extremely variable and may mimic acquired disorders. Some typical features, however, may raise our suspicion of a genetic disorder.

In contrast to infectious diseases, intoxications, and nutritional imbalances that generally affect an entire litter, hereditary diseases often involve only a few in a litter. Furthermore, the age of onset of clinical signs for a particular gene defect is rather specific and independent of environmental factors.

Most genetic defects cause clinical signs early in life. Fetal resorptions, late abortions, and stillborns may be caused by genetic traits but are rarely determined. Most puppy and kitten losses occur during the first week of life, shortly after the maternal homeostatic system can no longer compensate for an endogenous defect and are generally not shown to the veterinarian as they are considered of the usual losses by breeders. Some neonatal kitten losses have recently been attributed to blood type incompatibility: Type A and AB kittens born to Type B queens develop life-threatening neonatal isoerythrolysis when nursing and absorbing anti-A–containing colostrum during the first day of life. Certain congenital malformations may also not be compatible with life, such as severe cleft palates and hernias. The term *congenital* only implies that the disease is present at birth, however, and does not necessarily mean it is hereditary.

A common problem in puppies or kittens that have problems due to hereditary conditions is *failure to thrive*. These animals lag behind their healthy littermates in their development; they do not gain weight at a normal rate and are generally lethargic. They often fade (hence the term *fading puppy or kitten syndrome)* and finally die. Failure to thrive should not be confused with *growth retardation*, which refers to a proportionally stunted growth that may or may not be associated with other clinical signs. In addition to these relatively unspecific clinical signs, some hereditary defects may cause specific clinical manifestations. Easy to recognize are malformations that involve any part of the skeleton and can lead to disproportionate dwarfism, gait abnormalities, facial dysmorphia and other malformitives. A large number of hereditary eye diseases have been described in dogs, some of which are not recognized until adulthood. Neuromuscular signs may vary from exercise intolerance to ataxia and seizures. Defects of many other internal organs are associated with unspecific clinical signs. Many disorders cause an isolated typical sign, whereas others produce a characteristic overall pattern of anomalies known as specific *syndromes*.

Clinical manifestations of hereditary diseases are extremely variable, ranging from benign to debilitating and lethal. They are usually chronic, progressive (i.e., once an animal shows signs, it probably will not recover), and often cause death at an early age. A few hereditary defects, however, result in intermittent or recurrent problems, such as hereditary bleeding disorders and primary immunodeficiencies.

Diagnostic Tests

Diagnostic tests generally are required to support or confirm the diagnosis of a genetic disorder. Radiology and other imaging techniques may reveal skeletal malformations or cardiac anomalies. Ophthalmologic examination may further define an inherited eye disease; although some are not recognized before several years of age. Routine tests such as complete blood count (CBC), chemistry screen, and urinalysis may suggest some specific hematologic or metabolic disorders or rule out many acquired disorders. Furthermore, clinical function studies may better define a GI, liver, kidney, or endocrine problem. Histopathology or electron microscopy of a tissue biopsy (or both) from an affected animal or from the necropsy of an affected littermate or relative may give the first clue as to a genetic defect.

A few laboratories provide special diagnostic tests that allow a specific diagnosis of an inborn error of metabolism. *Inborn errors of metabolism* include all biochemical disorders due to a genetically determined, specific defect in the structure, function, or both of a protein molecule. Aside from the classical enzyme deficiencies, genetic defects in structural protein receptors, plasma and membrane transporters, and other proteins covered by this definition will result in biochemical disturbances. The laboratory approach is to detect the failing system or to determine the specific protein or gene defect. Disorders of intermediary metabolism typically produce a metabolic block in a biochemical pathway leading to product deficiency, accumulation of substrates, and production of unusual substances via alternative pathways. The most useful specimen to screen for biochemical derangements is urine because abnormal metabolites in the blood will be filtered through the glomeruli but fail to be reabsorbed (because no specific renal transport system exist for most abnormal metabolites).

Once the failing system has been identified, the defect can be determined at the protein level. These protein assays include the classic enzyme function tests and immunologic assays. Because most enzymes are present in abundant amounts, no major functional abnormalities are generally observed unless the enzyme activity is severely reduced, usually to less than 20% of normal value. Thus homozygously affected animals have very low-protein activity, quantity, or both, often in the range of 0% to 10%. These tests may also be used to detect carriers (heterozygotes) that typically have intermediate quantities at the protein level (30% to 70%) but no clinical signs. Unfortunately, protein assays are labor intensive and require submission of appropriate fresh tissue or fluid (and a control sample) under special conditions to specialized laboratories. The section of Medical Genetics at the School of Veterinary Medicine of the University of Pennsylvania performs tests to diagnose known conditions and to study potential new disorders (www.vet.upenn.edu/penngen).

The molecular defect has been identified for over three-dozen hereditary diseases in companion animals; thus DNA screening tests have been developed. These tests are mutation specific and can therefore only be used in animals suspected of having the exact same gene defect. Small animals within the same or a closely related breed will likely have the same disease-causing mutation for a particular disease (e.g., phosphofructokinase deficiency in English springer and American Cocker spaniels), as will mixed breed dogs due to mother-son or father-daughter matings with one parent. However, dogs, cats, and unrelated breeds of species with the same disorder will likely have different mutations, as shown with X-linked muscular dystrophy and erythrocyte pyruvate kinase deficiency in various breeds of dogs and cats.

DNA tests have several advantages over other biochemical tests. The test results are independent of the age of the animals; thus tests can be performed long before an animal is placed in a new home and before clinical signs become apparent. DNA is stable, and only the smallest quantities are needed. Therefore no special shipping arrangements are necessary as long as one follows the specific instructions for biologic products. DNA can be extracted from any nucleated cell (e.g., blood, buccal mucosa [cheek swabs], hair follicle, semen, formalinized tissue). For instance, blood can be sent in an EDTA tube, or a drop of blood can be applied to a special filter paper for DNA extraction. Buccal swabs can be obtained with special cytobrushes. This method should not be used in nursing animals, or only hours after nursing and rinsing the oral cavity with water. The DNA segment of interest is amplified with appropriate forward and reverse primers and polymerase chain reaction (PCR). The mutant or normal allele (or both) is identified by DNA size difference directly on a gel (in case of deletions or insertions) or after restriction enzyme digestion for point mutations or other suitable test systems to differentiate normal and mutant allele. These tests are generally simple and accurate as long as appropriate techniques and controls are used, but human errors in identifying samples can still occur. Furthermore, they can be used not only for the detection of affected animals but also for carriers. Such testing is extremely

valuable to select breeding animals that will not cause disease or further spread the disease-causing allele. For instance, phosphofructokinase deficiency was recognized to cause intermittent anemia and myopathy in English springer spaniels, and a DNA-based test became available in the early 1990s. There were still 4% and 1% carriers in the field trial and conformation lines, respectively, in the first randomized survey performed in 1998. If an animal with all the desirable qualities is found to be a carrier, it could be bred to a clear animal (homozygous normal) because this would not result in any affected offspring. However, offspring would need to be tested, and only clear animals would be used in subsequent breedings.

For many inherited disorders the defective gene remains unknown; however, for a few, a polymorphic DNA marker that is linked to the disease-causing mutant allele has been discovered (see chapter on genome). Such linkage tests were first developed for copper toxicosis in Bedlington terriers and are now available for some forms of retinopathy, in various breeds and renal carcinoma with nodular dermatitis in German shepherds. They are accurate for a particular animal as long as an affected animal is in its family (informative family). At present, mutation-specific and linkage tests are available only for single-gene defects in small animals. However, complex genetic traits may also soon be approached by these methods.

Prognosis and Therapy

Because the clinical consequences of the many hereditary disorders vary greatly, it is not surprising that the prognosis for survival and quality of life ranges from excellent to grave. The clinical course and outcome for a particular defect is rather similar among affected animals. Some defects are recognized as a breed characteristic (e.g., fold ear in Scottish folds and lack of tail in Manx [both dominant traits]) or an incidental finding (e.g., microcytosis in Akitas), whereas others are progressive and lead to severe organ dysfunction and death (e.g., many lysosomal storage diseases).

At present the therapeutic options in the treatment of hereditary diseases are limited, and ethical principles need to be carefully considered. Although several structural malformations can be surgically corrected (e.g., cryptorchism, hernias, hepatic shunts, patent ductus arteriosus [PDA]), these animals should not be shown or bred. In a few cases a deficient protein, cofactor, substrate, or metabolite can be supplemented to correct the defect. For instance, vitamin B_{12} deficiency in cachectic and lethargic giant schnauzers and Border collies with an ileal receptor defect can be helped by monthly cobalamin injections. Pancreatic enzyme supplementation and daily insulin injections are used to manage animals with exocrine or endocrine pancreatic insufficiency, respectively. Fresh frozen plasma is administered in the treatment of hereditary coagulopathies and von Willebrand's disease whenever animals excessively bleed. Other enzyme and protein replacements are also experimentally attempted.

Although kidney transplants have been established in clinical practice for chronic renal failure in cats, they have not been applied in animals with hereditary (juvenile) renal disorders. Several hereditary disorders of hematopoietic cells have been experimentally corrected by bone marrow transplantation (e.g., pyruvate and phosphofructokinase deficiency, cyclic hematopoiesis, and interleukin-2 [IL-2] receptor defects). Furthermore, bone marrow transplantation is being attempted to deliver functional cells or active proteins to other tissues including liver, bone, and brain (e.g., in lysosomal storage disease). Finally, gene therapy, the integration of a functional gene into the patient's own defective cells, will likely be clinically feasible in the twenty-first century. Experiments in rodent models have provided encouraging results. However, effective gene therapy has proven more difficult in larger mammals, and the technology needs to be further improved to achieve persistent and regulated gene expression in larger mammals including humans, dogs, and cats. One of the first and most promising canine gene therapy experiments has been the correction of mucopolysaccharidosis type VII in neonatal puppies with a retroviral vector carrying the beta-glucuronidase gene; these treated animals remain ambulatory, whereas affected animals become tetraparetic by a few months.

Control

Much more important than the treatment of hereditary disorders is the control of these traits in breeding programs. Thus to reduce the frequency or altogether eliminate a genetic defect, the further spread of the mutant gene has to be prevented in a family or entire breed. It is obvious that affected animals of any genetic disease should not be used for breeding. This approach is simple and effectively eliminates disorders with a dominant trait. For recessively inherited disorders, however, the elimination of affected animals is not sufficient to markedly reduce the prevalence of a defect within a breed, kennel, or cattery. It may be safest not to breed any related animals of affected animals, as requested by some kennel clubs; however, this practice may (because of inbreeding and narrow gene pools in some breeds) eliminate all breeders in an entire kennel or cattery and severely reduce the genetic diversity of a breed. Thus it will be pivotal to detect carriers (heterozygotes) and truly "clear" animals (homozygous normal). Obligate carriers can be readily identified for autosomal (both parents of affected) and X chromosomal recessive (mother of affected) disorders. As mentioned previously, for some diseases, reliable carrier detection tests are available, and many breeders know about them and inform the veterinarian. For instance, carriers have half-normal (~ 50%) enzyme activity by functional assays or have a normal *and* mutant DNA sequence for the diseased gene on a DNA test. Breeders should therefore be encouraged to screen their animals before breeding for known genetic diseases whenever carrier tests are available. Their availability is also listed on several websites including www.vet.upenn.edu/penngen. Unfortunately, many breeders mistrust these newer tests; either they were disappointed by inaccuracy of early tests, such as the radiographic examination for hip dysplasia, or they fear that the results may become public and could hurt their business. Thus breeders need to be educated by well-informed veterinarians. If a particular carrier needs to be used because of a narrow gene pool and many desirable traits, it should only be bred with a homozygously normal (clear) animal; all its offspring need to be tested, and only clear animals should be used in future breedings. If no carrier tests are available, a test mating between the dog in question and a known affected or carrier could be performed, and as long as no affected offspring and at least 5 healthy puppies or 11 healthy kittens, are born to "clear" an animal of a carrier state. For many breeders this approach is ethically unacceptable because it may produce affected animals.

In conclusion, it is exciting to learn about recent advances in the understanding of hereditary disorders and genetic predispositions in small animal practice, be it the advances in diagnostic approach to a hereditary disease, understanding of its pathophysiology, or its control. In addition to the clinician's responsibility to suspect a genetic disease and to appropriately diagnose it with modern, specific techniques, clinicians must become involved in the control of these disorders in the breeders' kennels or catteries. Practitioners thus can make an important contribution toward controlling the further spread of mutant genes and reducing future suffering of animals.

CHAPTER • 72

Abdominocentesis and Diagnostic Peritoneal Lavage

Elke Rudloff

Sterile procedure: There should be no gross evidence of intra-abdominal mass lesions, and the urinary bladder must be empty before the procedure. If the animal is unable to void voluntarily, careful manual expression or urinary catheterization is performed.

Surgical scrub required: The ventral abdominal skin from the xyphoid to pubis region is clipped free of hair and surgically prepared.

Conscious sedation: The clinician uses intravenous butorphanol 0.4 mg/kg or hydromorphone 0.2 mg/kg and diazepam 0.2 mg/kg; this is more important for diagnostic peritoneal lavage (DPL) than for centesis.

Local anesthesia required: Up to 4 mg/kg of lidocaine is used in the region where the needle or catheter is placed.

If an *abdominocentesis* is to be performed, the animal can be standing or in lateral recumbency. Ultrasound-guided centesis of any fluid pocket is the preferred method for fluid collection. If ultrasound is unavailable, a four-quadrant tap should be performed. In each of the four abdominal quadrants, an 18 to 22 gauge 1-inch needle or over-the-needle catheter is percutaneously inserted. Sample yield is maximized if fluid is allowed to flow out of the needle under the influence of gravity and not aspirated. A negative tap *does not* rule out the presence of intra-abdominal pathology.

If a DPL is to be performed, the animal should be placed in left-lateral recumbency or in a ventrodorsal position to avoid traumatizing the spleen.

Catheter placement for DPL: When using an over-the-needle catheter (Figure 72-1), the clinician should make a small skin incision at the site of the skin block and insert the catheter just through the body wall. There will be a slight pop as the peritoneum is penetrated. The catheter should then be rotated and advanced over the needle until it is fully inserted. If the catheter does not advance easily, it may still be in the subcutaneous tissue or against an organ and should be repositioned.

Peritoneal lavage catheters (Figures 72-2 and 72-3) are usually placed using a Seldinger technique, with instructions contained in the kit. The kits contain all the materials necessary (except for the fluid to be infused), including local anesthetic, drapes, and disinfectants.

When placing a catheter, the following points should be kept in mind:

- If fluid freely drains from the catheter, samples should be collected (Figure 72-4).
- If no fluid drains, the clinician should infuse 20 mL/kg of warmed isotonic replacement crystalloid (e.g., 0.9% sodium chloride, Ringer's lactate solution) and clamp the infusion set. Then the animal should be gently rolled back and forth and turned on its side. The infusion set should then be opened, and the first few milliliters should be allowed to drain out of the catheter before collecting samples.
- If an abdominal bleed is suspected, the catheter can be sutured in place to permit evaluation of follow-up samples. If septic peritonitis is suspected, the catheter can be left in place until surgical intervention to permit periodic lavage to dilute and drain septic material. If an aseptic peritonitis or pancreatitis is suspected, the catheter can be left in place to permit periodic abdominal lavages to dilute and drain inflammatory mediators.

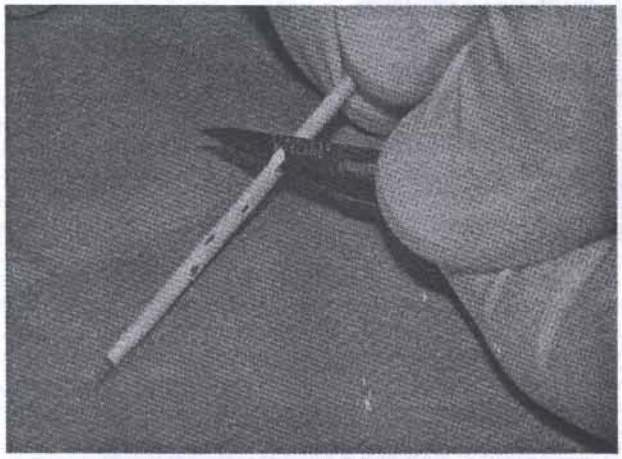


Figure 72-1 Over-the-needle abdominal catheter. Small side holes (two to four) are carefully cut into a 14- to 18-gauge 2-inch catheter 2 mm apart with a scalpel blade. The edges of the holes are kept smooth to prevent the catheter from barbing and possibly breaking.

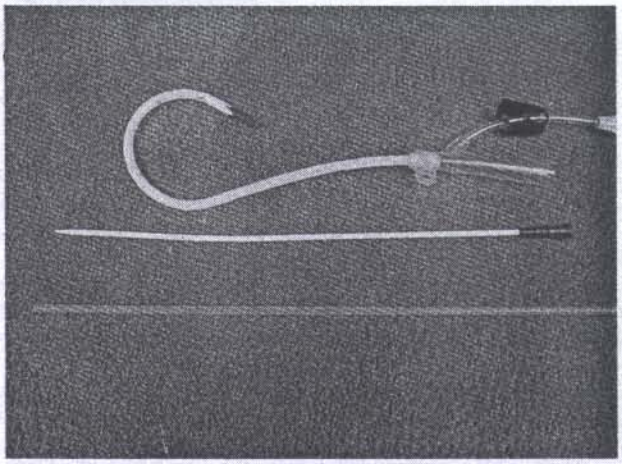


Figure 72-2 Manufactured abdominal drains. *Top to bottom:* Arrow abdominal drainage catheter, Arrow peritoneal lavage catheter, pediatric peritoneal dialysis catheter. (Arrow, International, Reading, PA.)

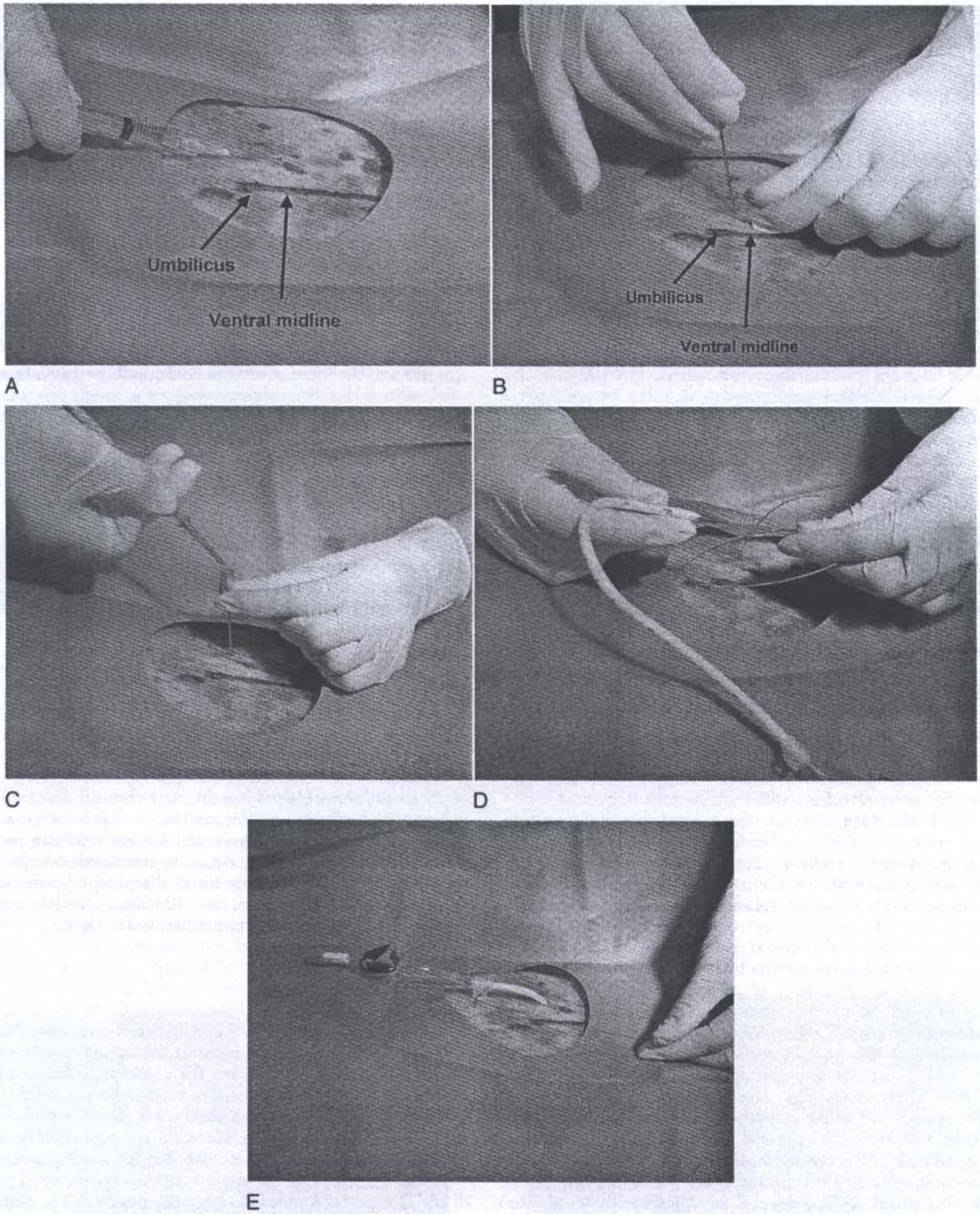


Figure 72-3 A, Placement of an abdominal drain via Seldinger technique. The animal is placed on its back and the ventral abdomen surgically prepared. Local administration of 2% lidocaine is injected lateral to the umbilicus at the site of catheter insertion. B, Placement of an abdominal drain via Seldinger technique. A sterile 1½- to 2-inch needle is placed into the peritoneal cavity at the locally anesthetized site. C, Placement of an abdominal drain via Seldinger technique. The J-wire is fed through the needle into the abdomen and the needle is removed leaving the J-wire in place. D, Placement of an abdominal drain via Seldinger technique. The catheter is fed over the J-wire into the abdomen. The J-wire is grabbed as it comes out of the proximal end of the catheter, and the catheter is fed into the abdomen until all the holes are contained within the abdominal cavity. E, Placement of an abdominal drain via Seldinger technique. The J-wire is removed and the catheter secured to the skin.

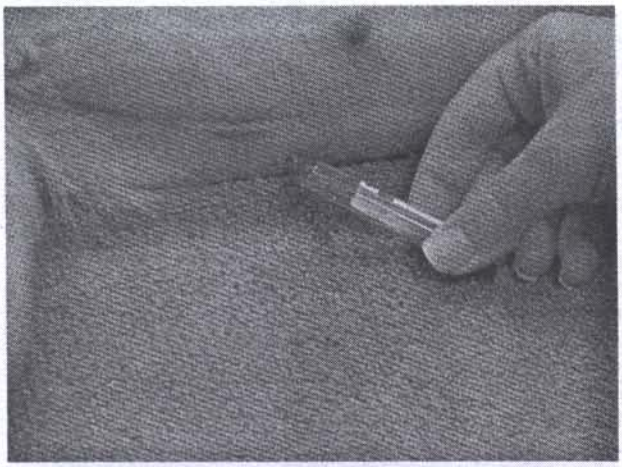


Figure 72-4 Collection of abdominal fluid samples for cytologic and chemical analysis.

- Complete removal of the fluid is not always possible or necessary; it may be used to partially replace calculated fluid deficits when peritonitis is not present.
- If the catheter is to be removed, the skin is pinched around the catheter while it is removed and a temporary dressing is placed on the area.
- Cytology: The presence of vegetable or meat fibers, intracellular bacteria, or toxic neutrophils is an indication for surgical exploration and culture submission.
- Special laboratory tests required: The packed cell volume (PCV) of the abdominal fluid can be compared with the peripheral PCV and serially monitored if abdominal hemorrhage is suspected. A white blood cell (WBC) count greater than 1000/mm^3 is diagnostic for peritonitis. If chemical analysis reveals that the creatinine or potassium level (or both) in the abdominal fluid is higher than the peripheral blood, a urinary tract rupture is suspected. If the total bilirubin of the fluid is greater than that of peripheral blood, a leaking biliary system is suspected.

CHAPTER • 73

Abdominal Ultrasound: Aspirations and Biopsies

Wendy D. Fife

INTRODUCTION

Ultrasonography has many advantages, including its ability to detect parenchymal changes within organs and define the origin and extent of lesions. Abnormalities detected with ultrasonography are often nonspecific, with a great deal of overlap in the appearance of various disease processes. Ultrasound-guided fine needle aspirates or tissue-core biopsies are therefore often required for cytology or histopathology to reach a definitive diagnosis. The use of ultrasound guidance when obtaining diagnostic samples allows for real-time monitoring of needle placement so that a selected portion of an organ or a focal mass lesion may be sampled. Ultrasonography allows for the assessment of nearby vessels or other structures to be avoided and can be used to reassess the patient after the biopsy procedure for evidence of complications, such as hemorrhage. Ultrasonography and ultrasound-guided biopsies are noninvasive and rarely require general anesthesia when compared with surgery.

INDICATIONS

Percutaneous ultrasound-guidance may be used to obtain diagnostic samples or to provide therapeutic intervention. Fine needle, large-gauge needle, or tissue-core biopsies are chosen based on the size and type of lesion to be sampled. Biopsy samples of a specific organ may be warranted in cases of diffuse parenchymal abnormalities, (focal loss of parenchymal homogeneity) or mass lesions, or in the case of a normal ultrasonographic appearance of an organ when the results of other diagnostics indicate organ dysfunction. Therapeutic uses of ultrasonography include the drainage of intra-abdominal or intrathoracic cysts, abscesses, or fluid, or to instill local chemotherapeutics or other chemical therapy.

MATERIALS

Sector or linear-array transducers may be used, depending on the depth of the structure to be biopsied. Linear-array transducers provide superior resolution for more superficial structures, whereas sector transducers are used to biopsy deeper tissues. The lesion to be biopsied should be placed within the focal zone of the transducer to allow for the best resolution. Some transducers are equipped with biopsy guides, and separate guides are available for attachment to conventional transducers. The guides function to keep the needle in the plane of the ultrasound beam (Figure 73-1).

Dedicated biopsy transducers and those equipped with biopsy guides often display electronic markers on the display screen. The lesion or tissue to be biopsied is placed between the markers and the needle is inserted with its position continuously monitored. Dedicated biopsy transducers are more expensive and specialized than conventional transducers or transducer biopsy guides and are rarely used in veterinary medicine.

The size and type of needle to be used depends on the size of the lesion being sampled and the type of sample desired.

The smallest needle that will provide a diagnostic sample should be used because larger needles may be associated with higher complication rates, such as hemorrhage. Fine needle samples most commonly yield samples for cytology, whereas histologic evaluation requires a tissue-core biopsy. Fine needle samples are commonly obtained when the organ being sampled has a diffusely abnormal appearance or when a small lesion (<1 cm) is being sampled. Tissue-core biopsies may be preferred in the case of a large mass or when histopathology is necessary. In many cases, a fine needle aspiration may be obtained first and a tissue-core biopsy pursued if the sample is inconclusive or nondiagnostic.

For fine needle aspiration, 20- to 25-gauge needles are typically used. In the case of the freehand technique, standard injection needles are used. A longer needle (e.g., 3½ inch) is required if a transducer guide is used. This length is necessary to pass through the biopsy guide and into the tissue. In the case of a tissue-core biopsy, a 14- to 18-gauge needle is used. Manual and automated biopsy devices are available. A manually operated Tru-Cut® needle requires two hands to operate, so two people are required for the procedure: one to place the transducer and another to operate the biopsy device. The operator is able to control the depth of the needle and the length of tissue to be sampled. Several types of semiautomatic and automatic biopsy devices have been developed. The inner cutting needle is manually advanced to the desired depth with a semiautomatic device. The outer cutting shaft, which is spring loaded, is then triggered. The exact depth of tissue biopsied is manually controlled. The inner cutting needle and outer shaft of an automatic device are initially advanced manually, 1.5 to 2.0 cm superficial to the tissue to be biopsied. Automatic biopsy guns automatically advance the cutting needle and external shaft when triggered. Caution is advised when using an automatic biopsy gun; the inner cutting shaft advances a specific distance (15 to 20 mm) beyond the external shaft to acquire the tissue sample when it is triggered. Most automatic biopsy guns accept disposable needles of varying sizes, and the distance the cutting shaft will advance can be adjusted to control the length of tissue sampled. This is particularly useful in cats and in the case of small lesions. This gun is reusable and can be sterilized. Individual disposable spring-loaded automatic and semiautomatic biopsy needles are available in various sizes.

TECHNIQUE

The needle should not enter more than one organ or pass through an organ, and a separate needle should be used for each organ sampled. Multiple samples of an organ or lesion are usually obtained.

The freehand technique can be used, in which case the transducer is operated with one hand and the needle with the other (Figures 73-2 and 73-3). This allows for greater flexibility in the approach to the structure of interest but requires hand-eye coordination and practice. The entire length of the needle must be kept within the ultrasound beam, and the tip must be localized. Moving the needle gently up and down while fanning the region with the ultrasound probe may aid in locating the needle tip. Under no circumstances should the location of a needle be determined by moving the needle side to side within an organ. This causes unnecessary tissue trauma. Roughening the outer needle shaft prior to introduction will create an irregular interface to increase sound reflection and sonographic visualization. Commercially available Teflon or other highly reflective-coated needles are available to enhance visualization. Use of a larger-gauge needle will facilitate visualization but may increase the risk of complication. The needle tip should be placed at the focal zone of the transducer to enhance resolution. Injection of a small amount of air or sterile saline may help localize the needle tip. After needle placement, and stylet removal in the case of a spinal needle, a syringe or extension tubing and syringe are attached to the needle. If the lesion is fluid filled, fluid is then aspirated. If large amounts of fluid are to be aspirated, a three-way stopcock is attached. For cytologic samples, aspiration is performed as the needle is moved slightly up and down within the tissue or lesion. Some individuals prefer to simply move the needle up and down within the tissue, without aspiration, to obtain a cytologic sample. This technique may provide less blood contamination within the sample and has been shown to yield diagnostic results. Fine needle samples may be obtained with the stylet in place as the needle is advanced (Figures 73-4 and 73-5). Once the needle is placed at the desired depth, the stylet is removed and the sample is acquired. This may be particularly useful in the case of traversing fat within the falciform ligament to obtain a liver aspirate in the cat. Without a stylet, the sample may consist of fat only, which may be improperly interpreted as hepatic lipidosis.

Use of a needle guide requires less dexterity, but once the needle enters the skin, the probe cannot be moved. Transducer guides also cause the angle of the needle relative to the ultrasound beam to be fixed, thereby limiting the angle at which the surface of the patient can be approached and prohibiting biopsy of superficial structures.

Patient Preparation

The patient is usually placed in dorsal recumbency on a padded trough. An intravenous catheter is placed in the case of a tissue-core biopsy so that intravenous sedatives can be administered. In the case of a very small lesion or a lesion in close proximity to large vascular structures, general anesthesia may be required. The use of some drugs should be avoided, including those that cause splenic enlargement or panting.

Depending on the tissue being sampled, the patient's clinical status, and the type of biopsy being performed, screening of the patient's coagulation status is recommended. For fine needle aspirations, coagulation-screening profiles are not routinely performed unless the lesion to be sampled is extremely vascular or the patient is at an increased risk of bleeding.

Specific Biopsy Sites

Fine needle aspiration and tissue-core biopsies of the liver are commonly done. Fine needle aspiration is performed when sampling focal masses that are complex or highly vascular, whereas a tissue-core biopsy is preferred in the case of a focal solid–appearing mass. In cases of diffuse hepatic disease, a fine needle aspirate may be done first and often yields a diagnosis in cases of specific diseases, such as lymphoma or hepatic lipidosis. Other diffuse hepatic diseases may require a tissue-core biopsy for a definitive diagnosis. The left-lateral aspect of the liver is generally the safest area to sample because it is the largest and the gallbladder and hilar vessels can be avoided. If a focal lesion is in a different location, or if the liver is small, sampling of another portion of the liver may be warranted. If the liver is small or located cranially, an intercostal approach is sometimes used, being cautious to avoid lung tissue. General anesthesia and positive pressure ventilation may also be used to displace the liver caudally for easier access. Multiple biopsies are routinely obtained.

The gallbladder may be sampled in cases of acalculous cholecystitis for culture and cytology. A transhepatic approach and a 22-gauge needle are used. The transhepatic approach is reported to decrease the risk of bile leakage.

Diffuse infiltrative splenic diseases, such as lymphoma and mast cell disease, and focal splenic masses are common indications for aspiration. Needle biopsy without aspiration

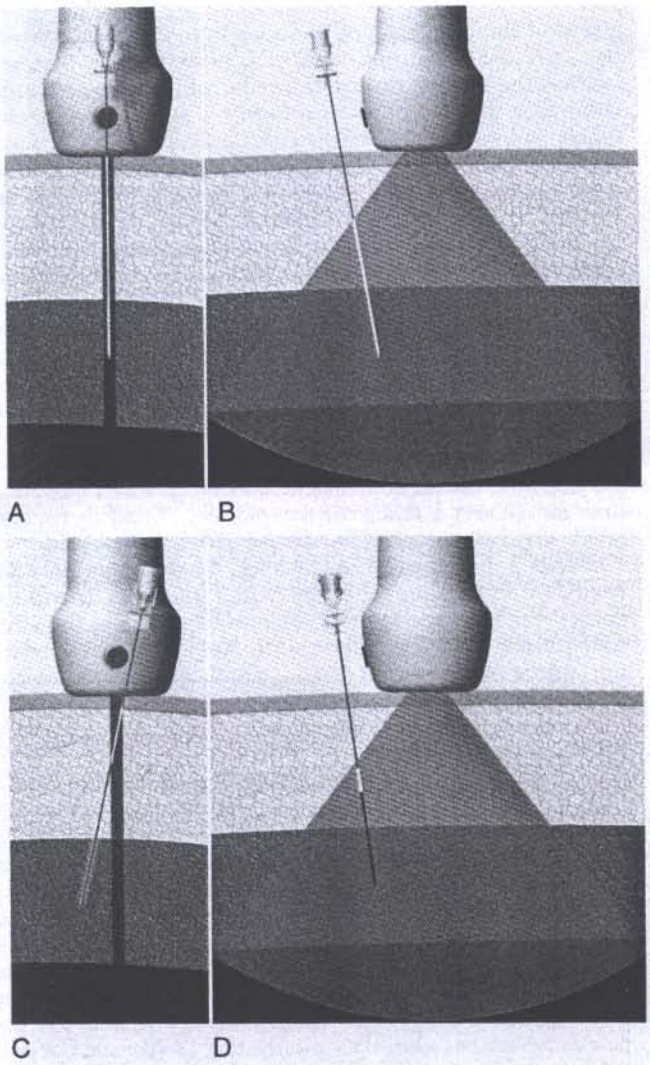


Figure 73-1 The angle of the biopsy instrument relative to the plane of the ultrasound beam is essential to visualize the tissue being sampled with the freehand method. **A** and **B**, Proper alignment of the biopsy instrument and ultrasound beam, with the two-remaining parallel the entire length of the needle. **C** and **D**, Improper alignment of the needle relative to the ultrasound beam. Only a small segment of the length of the needle can be seen as it intersects the plane of the beam. The tip of the needle and therefore the tissue being sampled cannot be seen. The white portion of the needle represents that which transects the path of the scanning plane and is therefore visualized.

may decrease the potential for blood contamination in splenic samples. If the aspiration technique is used, aspiration should be discontinued if blood appears in the hub of the needle. Complications due to splenic aspirates are extremely rare, but caution should be used when sampling complex, cavitary masses, such as those seen in splenic hemangiosarcoma. If fine needle samples of the spleen are nondiagnostic, a tissue-core biopsy of a solid mass lesion or the solid portion of a complex lesion may be indicated.

Renal biopsy may be performed in cases of diffuse renal disease or focal renal masses. Fine needle aspirates are usually performed if diffuse disease such as lymphosarcoma is suspected, whereas tissue-core biopsies are required to diagnose glomerular and tubular diseases and renal mass lesions. Sampling of the left kidney is preferred in cases of diffuse bilateral renal disease due to its relatively caudal location and easier access. The caudal cortex of the kidney should be sampled (including glomeruli but avoiding the medulla and hilar vessels). The biopsy plane should be directed laterally to avoid puncturing the renal hilus, caudal vena cava, or aorta. Feline renal biopsies are commonly done by manually stabilizing the kidney close to the ventral or lateral skin surface while performing a core biopsy of the lateral cortex with or without direct ultrasound guidance. Complications are rare and in most cases self-limiting but may include intra-abdominal hemorrhage or hemorrhage manifested as hematuria. Small dogs and cats may have an increased risk of hemorrhage and cats with hypertension are at particular risk. The animal's packed cell volume (PCV) should be monitored for several hours after the procedure. Renal biopsies should not be performed indiscriminately because fatal hemorrhage can occur.

Urinary bladder masses are commonly identified ultrasonographically. They are usually readily accessible for aspiration with a 21- or 22-gauge needle. In cases of transitional cell carcinoma, percutaneous biopsy often yields a diagnostic sample, but seeding of the tumor into the abdomen and subcutaneous tissues can occur. Ultrasound-guided urinary catheter placement and vigorous suction is a viable diagnostic alternative and avoids the potential for seeding of tumor cells.

Percutaneous biopsy of the prostate may be indicated when parenchymal abnormalities or prostatomegaly are identified. Fine needle aspiration of fluid-filled cysts or cavities within the prostate may be obtained for culture and cytology. These lesions may occur in association with prostatitis or neoplasia. If neoplasia is suspected, a tissue-core biopsy should be performed. The biopsy is obtained from the caudal abdomen, lateral to the prepuce. Adjacent vascular structures, such as the aorta and caudal vena cava, should be avoided. If the prostate is small or caudally located, the pubic bone may interfere.

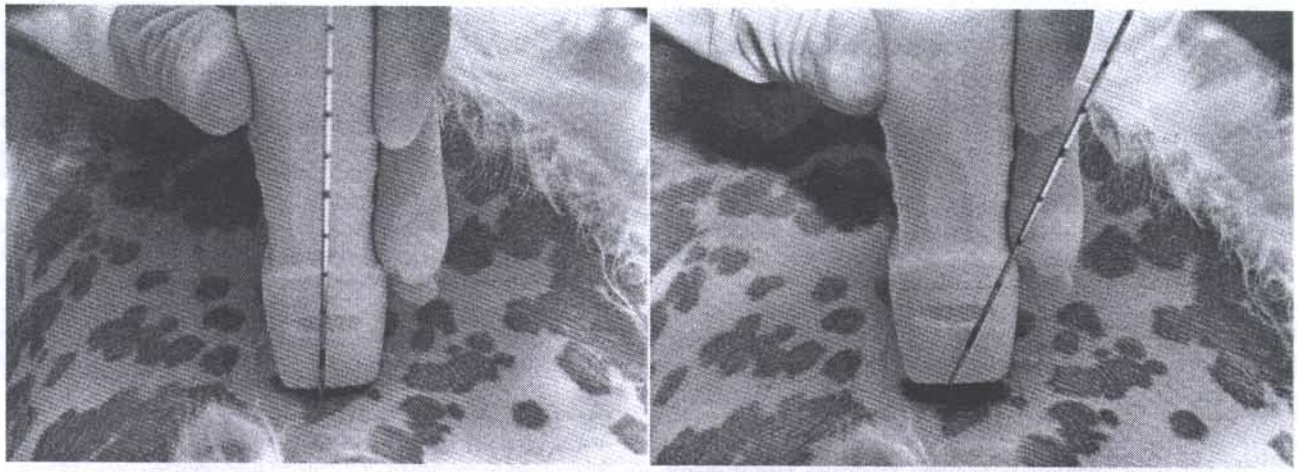
The pancreas may be aspirated to differentiate between pancreatitis and pancreatic neoplasia. Secondary pancreatitis is an uncommon complication. Infection may develop in conjunction with pancreatic neoplasia, so false-negative diagnoses may occur.

Other abdominal structures that may be aspirated or biopsied include enlarged intra-abdominal lymph nodes and gastrointestinal (GI) masses. Aspiration of adrenal masses has been reported in veterinary medicine but is uncommonly performed; blood pressure alterations and severe hemorrhage may occur in the case of pheochromocytoma. Close proximity to the caudal vena cava and aorta are additional risks.

Ultrasound-guided percutaneous drainage of intra-abdominal abscesses is performed in people as an alternative to surgical treatment. This technique may be useful in veterinary patients. With the patient under sedation, the abscess cavity is drained using a 20-gauge or larger needle. Samples are submitted for culture and cytology. Follow-up ultrasound examinations, possibly in conjunction with repeated abscess drainage, are done. The procedure may reduce morbidity and mortality associated with abdominal abscesses treated surgically.

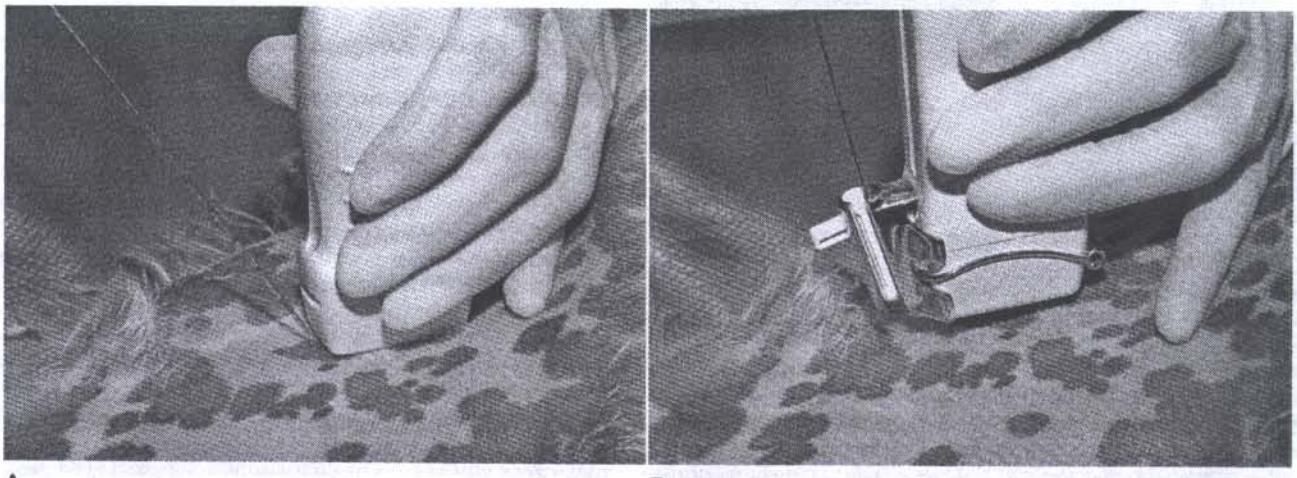
Contraindications and Complications

Complications related to ultrasound-guided biopsy procedures are uncommon. The risk of complication varies based upon the size of the needle being used and the location of the lesion. A 22- to 25-gauge needle should be used when possible, and larger gauge and tissue-core biopsies pursued if samples are nondiagnostic. Hemorrhage is minor and self-limiting in most instances. The results of physical examination and



A B

Figure 73-2 Freehand biopsy technique. The ultrasound probe is held in one hand and the biopsy instrument in the other hand. The biopsy instrument must be maintained within the plane of the ultrasound beam. **A,** Proper alignment of biopsy instrument relative to ultrasound beam. **B,** Improper alignment, with the biopsy instrument angled relative to the ultrasound beam. This will not allow proper visualization of the biopsy instrument within the scan plane.



A B

Figure 73-3 **A,** Freehand biopsy technique. The instrument is held with one hand and the biopsy instrument, in this case a Biopty® gun, is held with the other. The angle of the biopsy needle relative to the transducer is not fixed. **B,** Biopsy with guide attached to transducer. In this case, an external metal guide is attached to this sector transducer. The angle of the biopsy needle relative to the probe is fixed.

laboratory testing when necessary will identify patients at increased risk for hemorrhage. Color Doppler imaging is recommended when available to assess the vascularity of tissues and adjacent structures before the biopsy is performed and to monitor for hemorrhage in the postbiopsy period. The risk of peritonitis associated with penetration of the bowel is small in cases of fine needle aspiration, but bowel should be avoided with larger-gauge needles and tissue-core biopsies. Seeding of a tumor along a needle tract is also rare but has been reported in cases of transitional cell carcinoma in the canine urinary bladder. As with any procedure, adequate restraint and sedation are necessary to minimize risk to the patient.

FUTURE TRENDS

Ultrasonographic-guided percutaneous antegrade pyelography has been used to confirm obstructive uropathy and the site of obstruction in the dog and cat. This procedure does not

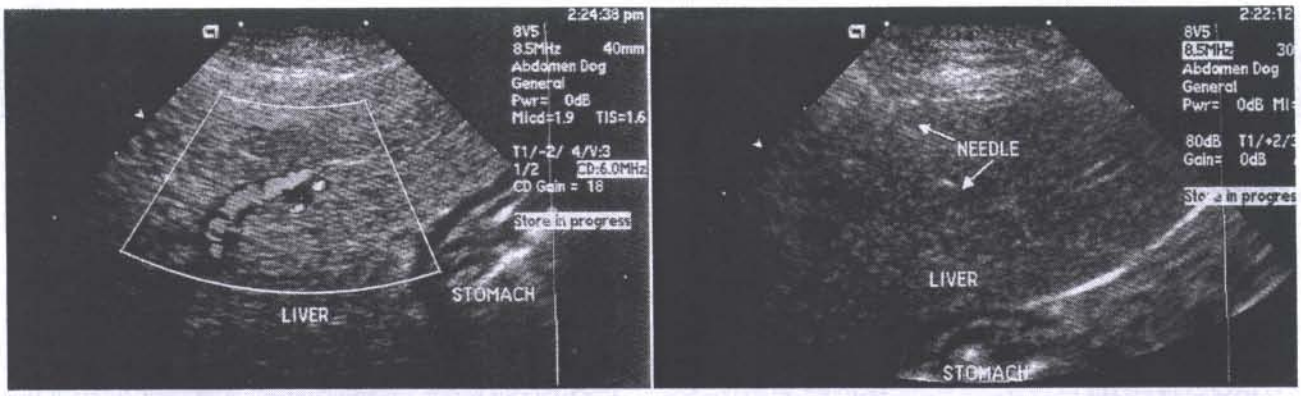


Figure 73-4 Fine needle aspirate of the liver using a sector transducer. A, Color Doppler identifies blood flow in hepatic vessels, which are to be avoided by the path of the biopsy needle. B, The entire length of the needle can be seen coursing through the hepatic parenchyma as a linear hyperechoic structure *(arrows)*.

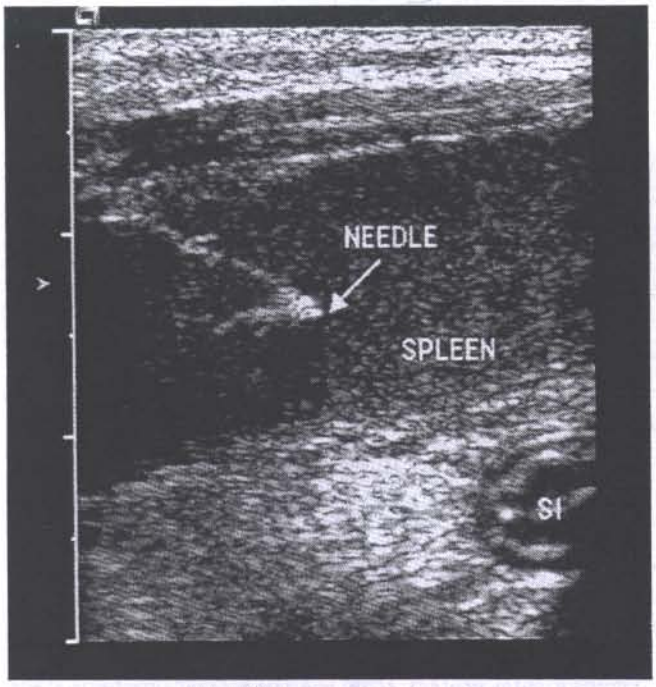


Figure 73-5 Fine needle aspirate of the spleen using a linear transducer in a cat with splenomegaly. A linear transducer is useful for biopsy of superficial structures. The entire length of the needle can be seen. The needle tip is causing distal acoustic shadowing due to its high degree of echogenicity. *SI*, Small intestinal segment.

require the intravenous administration of iodinated contrast medium as it does with excretory urography (EU). A 22-gauge spinal needle is introduced into the renal pelvis via the lateral cortex, to avoid hilar vessels, and nephropyelocentesis is performed by withdrawing 4 to 6 ml of urine. The clinician then injects 2 to 4 ml of iodinated contrast medium into the renal pelvis and radiographs are performed. This procedure is useful in animals with poor renal function and resultant inadequate pyelogram phase during EU to diagnose a ureteral obstruction. The possible nephrotoxic effects associated with intravenous contrast administration are decreased. Transcutaneous pyelocentesis can also be used to collect urine for culture when pyelonephritis is suspected and cystocentesis samples yield a negative culture.

Local administration of pharmaceuticals can be performed with ultrasound guidance. Percutaneous injection of ethanol has been used to treat thyroid and parathyroid disease in veterinary patients. Local chemotherapeutics have been placed with ultrasound guidance in cases of abdominal neoplasia.

Endoscopic and laparoscopic ultrasonography are being used in people to evaluate structures more directly and to obtain aspirates and biopsies. These procedures are less invasive and quicker than open surgical biopsies. The necessary equipment is expensive and not yet widely available in veterinary medicine.

CHAPTER 74

Arthrocentesis and Arthroscopy

Mark C. Rochat

ARTHROCENTESIS

Synovial fluid is a dialysate of plasma combined with hyaluronic acid produced by type 2 (B) synoviocytes. The viscosity of normal synovial fluid provides lubrication, shock absorption, and joint stability. Arthropathy results in loss of integrity of the synovial membrane and introduction of inflammatory mediators into the joint. Inflammatory cells and infectious agents release hyaluronidase and other matrix metalloproteinases, resulting in breakdown of hyaluronic acid. Loss of normal hyaluronic acid leads to loss of synovial fluid viscosity, improper cartilage nutrition, and decreased shock absorption.

Arthrocentesis is the process of withdrawing synovial fluid from a joint by use of a hypodermic needle and syringe. Arthrocentesis is a secondary diagnostic tool that should be preceded by a thorough history, physical and orthopedic examination, and diagnostic imaging studies. Diagnostic imaging studies should be performed prior to arthrocentesis because artifacts such as hematomas may be created, leading to difficulty in interpreting the diagnostic images.

Arthrocentesis is indicated for characterizing the nature of arthropathies. The source of lameness can usually be isolated to a specific joint by history, as well as physical and orthopedic examination. Rarely, joint effusion, pain, or other signs of arthropathy cannot be readily identified, and the animal has vague and often diffuse lameness. This is common in immune-mediated polyarthropathies. In these situations, arthrocentesis is indicated as a screening tool when historical information supports a diagnosis of polyarthropathy. Multiple joints should be aspirated to enhance the likelihood of identifying the arthropathy. The carpus and hock are commonly involved in immune-mediated disease but can be difficult to aspirate due to their small size. On occasion, arthrocentesis yields a definitive diagnosis. For example, the presence of *Ehrlichia* morulae in intra-articular monocytes is diagnostic for joint sepsis due to ehrlichiosis. More often, arthrocentesis reveals the general cellular pattern and characteristics of the synovial fluid and joint environment, allowing broad classification of the arthropathy. Arthrocentesis is also the primary method of monitoring response to therapy for immune-mediated polyarthropathies.

Arthrocentesis may require brief heavy sedation or anesthesia to allow safe aspiration of synovial fluid while minimizing the risk of injury to intra-articular structures or articular cartilage if the animal is fractious, painful, or energetic. Aseptic technique is required. To perform arthrocentesis, the animal is positioned in lateral recumbency with the affected limb uppermost. A 20- to 25-gauge needle attached to a 3- to 5-cc syringe is inserted with the clinician's dominant hand, while the opposite hand stabilizes the limb and joint. Proper orientation of the needle to safely enter the joint is facilitated by palpation of the joint during flexion and extension, reviewing diagrams illustrating proper needle placement (Figure 74-1), or by viewing skeletal specimens. The needle is inserted and gentle vacuum applied with the hand that inserts the needle and syringe. The needle is advanced until synovial fluid enters the syringe. Use of a 3- to 5-cc syringe allows the operator to achieve an adequate degree of suction while using one hand to insert the syringe and needle. The needle should be withdrawn if blood is encountered, and a new needle and syringe should be used for a second aspiration attempt. Hemarthrosis secondary to trauma does occur in small animals but is uncommon. Aspirated blood is usually a contaminant and should clot. Generally as much as 1 to 2 ml of fluid should be aspirated if possible, but the application of excessive negative pressure or aspiration of large volumes of fluid may increase the risk of aspirating blood, thereby ruining the sample. After the fluid is collected, negative pressure is released and the needle withdrawn. If no synovial fluid is obtained, the needle is redirected after reviewing the angle of placement. If the needle is properly aligned but little or no synovial fluid is obtained, the needle may be plugged with soft tissue or hematomas or there may be insufficient fluid for aspiration as is true with normal joints.

Aspirated fluid should be immediately transferred to an EDTA tube, if a sufficient amount of fluid was aspirated (0.5-cc fluid for a 3-cc EDTA tube). Smears of the synovial fluid should also be made and air-dried prior to submission. If sufficient synovial fluid remains for bacterial culture and susceptibility, it can be inoculated at room temperature for 24 hours in a sterile red tube top with blood culture media at a 9:1 ratio. If only a small amount of fluid (1 drop) remains in the needle hub, 0.5 cc of blood culture media can be aseptically aspirated in a separate syringe, the needle with residual synovial fluid placed on the syringe, and the media flushed through the needle into a sterile red top tube and incubated as previously described.

Prepared slides and the EDTA tube should be submitted to a clinical pathology laboratory for evaluation. Synovial fluid characteristics that should be evaluated include volume, color, turbidity, total protein, total cell count, cell differential, viscosity, mucin clot test, and cytologic exam for cellular characteristics, infectious organisms, neoplastic cells, crystals, and other abnormalities (see Figure 74-2). Synovial fluid characteristics for cats are extrapolated from dogs. If immediate results are needed, some aspects of synovial fluid analysis can be determined in the clinical setting. Some appreciation of color, turbidity, and viscosity can be made when the fluid is expelled onto the glass slide. Cytologic examination of the fluid will provide a rough estimate of the cellularity of the sample, the types of cells present, and specific cellular characteristics such as inclusions or organisms, cytoplasmic granules, nuclear changes, phagocytosed cellular debris, and vacuolation. Other findings such as crystals may be identified. Cytologic examination is the single best test for determining the nature of the arthropathy if the amount of fluid obtained limits the extent of the fluid analysis. Complications are rare and generally limited to articular cartilage injury, hemorrhage, and iatrogenic infection.

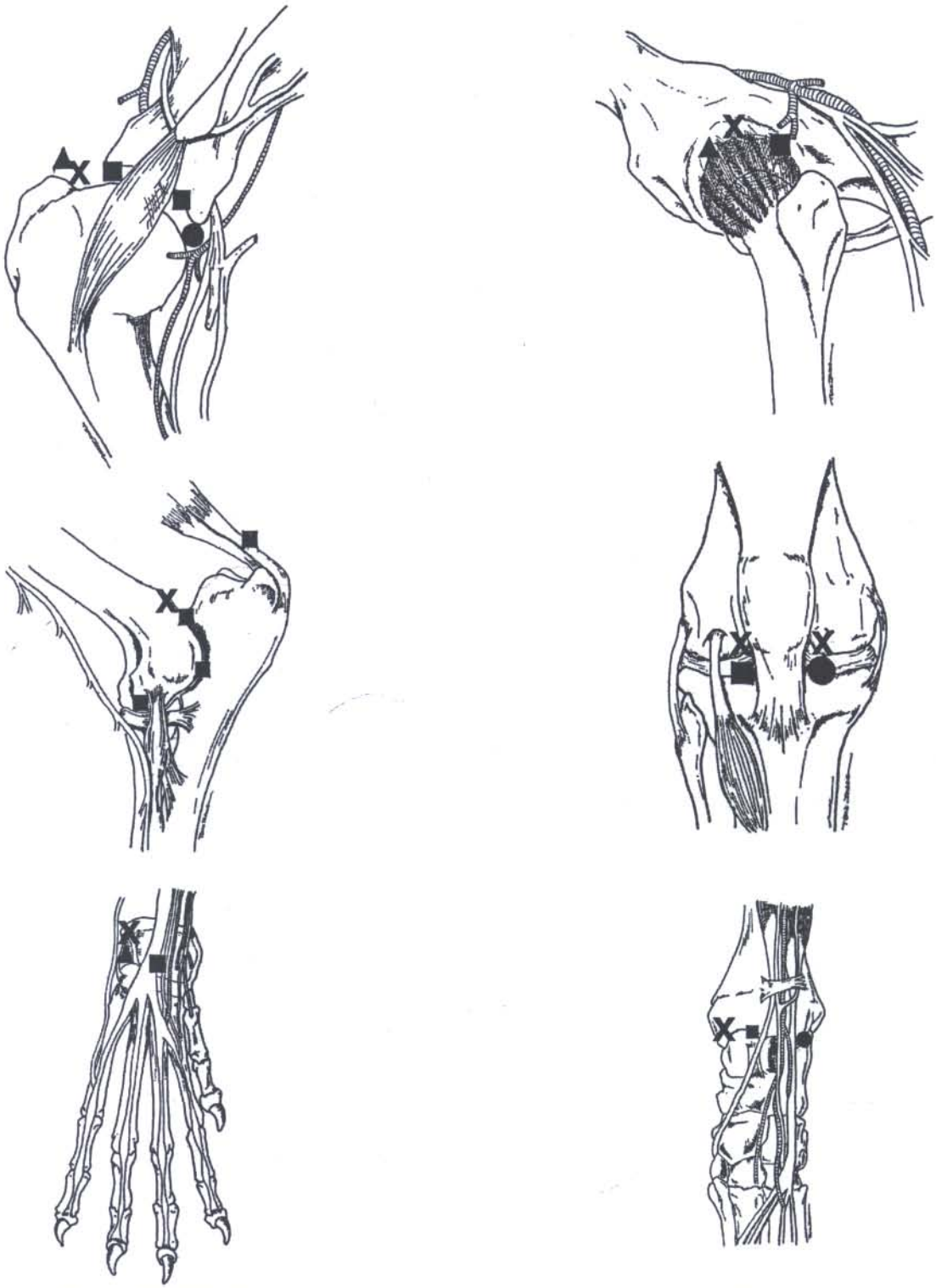


Figure 74-1 Sites for arthrocentesis (X), egress portal (▲), arthroscope portal (■), and instrument portal (●) for the large joints of the appendicular skeleton.

ARTHROSCOPY

Arthroscopy is the process of examining and treating joint disorders by use of a small fiber-optic telescope. The advantages of arthroscopy are a minimal degree of invasiveness, decreased recovery times from surgery, visualization of a greater percentage of the joint surfaces than what is possible by arthrotomy, and improved visualization of joint pathology. The disadvantages of arthroscopy are the expense of the associated equipment, steep learning curve to master the technique, and limitation of the technique to the shoulder, elbow, carpus, hip, stifle, and hock joints of medium to large breed dogs.

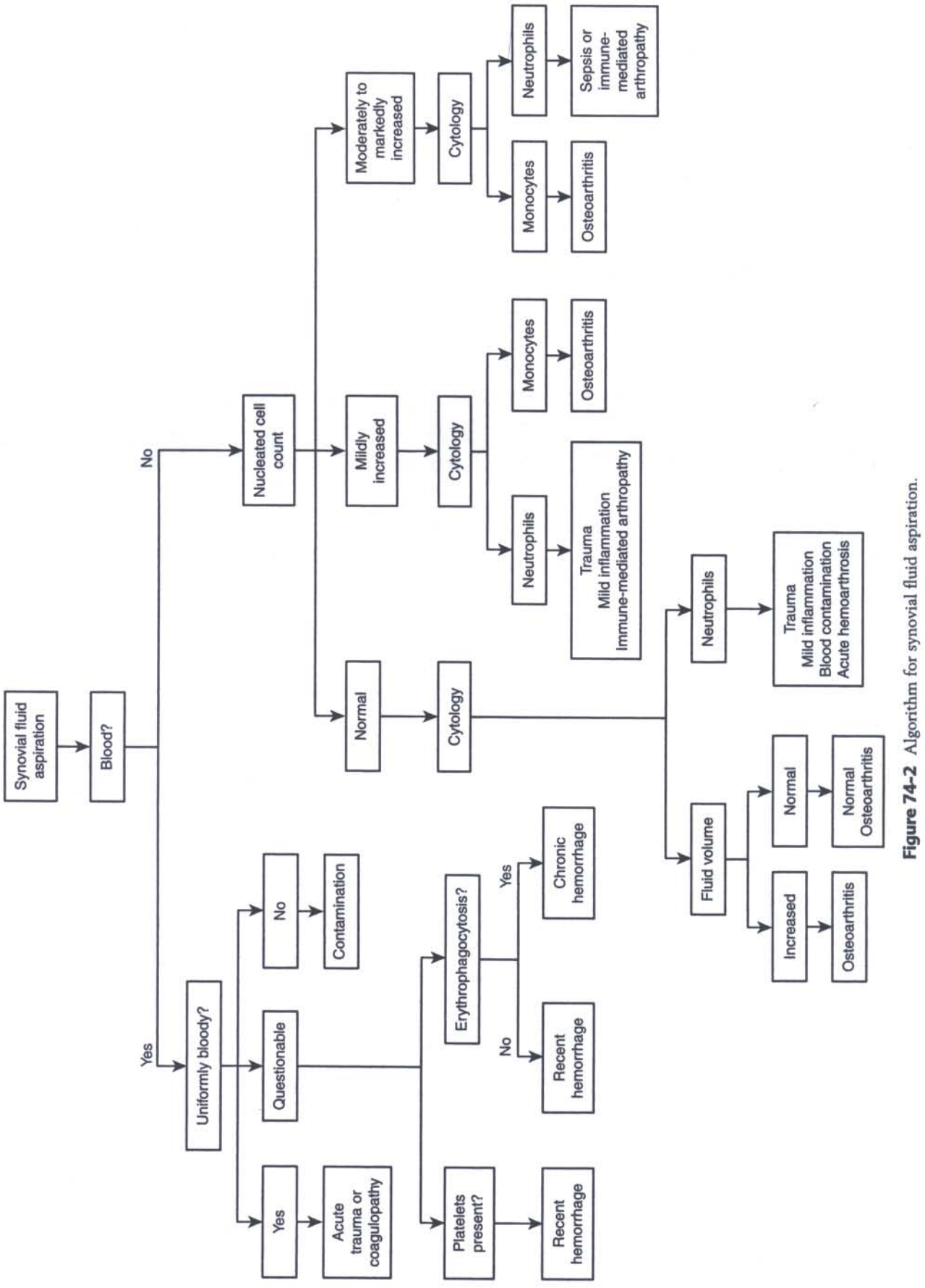


Figure 74-2 Algorithm for synovial fluid aspiration.

Arthroscopy is indicated for characterizing ill-defined arthropathies of the previously mentioned joints by synovial biopsy and visualization of the pathology. Arthroscopy is also indicated for treating a limited number of joint diseases including osteochondritis dissecans, bicipital tenosynovitis, fragmented medial coronoid process disease, cranial cruciate ligament disease, and stifle meniscal injury. As the science and instrumentation of arthroscopy improves, other techniques for addressing various arthropathies may also be treated by arthroscopic methods.

The basic principles of surgery are observed whenever arthroscopy is performed. Canine arthroscopy must be performed with the patient under general anesthesia. The patient is clipped and prepared in the same fashion as for an arthrotomy. Strict adherence to principles of aseptic technique should be observed throughout the procedure. Perioperative antibiotics are unnecessary due to the minimally invasive nature of the procedure and the continuous irrigation of the joint surfaces. The instrumentation required for arthroscopic surgery in dogs is not extensive but somewhat delicate and very expensive. A complete discussion of arthroscopic instrumentation and technique is presented elsewhere.

Complications observed with arthroscopy include failure to properly create an arthroscopic or instrument portal, damage to intra-articular structures, premature dislodgement of the arthroscope, collapse of the joint capsule secondary to excessive fluid extravasation, hemorrhage from inadvertent puncture or injury of periarticular vessels or the stifle intra-articular fat pad, damage to the arthroscope from excessive bending forces applied to the arthroscope, neurologic injury, infection, and inability to adequately explore or treat the joint disease. The incidence of complications is, for the most part, directly related to the experience of the participating arthroscopist.

CHAPTER 75

Artificial Insemination in the Dog

Catharina Linde-Forsberg

Success rates in having dogs conceive after artificial insemination (AI) are dependent on a number of factors. These include the timing of the AI relative to the time of ovulation, how many times during estrus the AI is performed, the quality of the freshly ejaculated semen, how that semen was handled, and the AI technique used. This chapter will only deal with AI techniques.

AI TECHNIQUES IN THE DOG

Methods for AI in bitches include vaginal deposition of semen and transcervical intrauterine deposition, surgical intrauterine deposition, and intrauterine insemination by laparoscopy. The canine vaginal tract consists of the vulva, the vestibule, the vagina, the narrow paracervical region, the cervix, and the fornix (Figure 75-1).

Significantly higher whelping rates (range, 30% to 50%) are obtained with both fresh, chilled, and frozen-thawed dog semen when inseminated into the uterus, as opposed to when it is deposited in the vaginal tract. For frozen-thawed semen, litter size is also significantly increased by intrauterine AI. It has been estimated that 10 times as many spermatozoa are required to obtain similar results by vaginal AI as by intrauterine AI. For these reasons intrauterine AI should always be attempted in the dog. The problems faced in attempting to catheterize the canine cervix relate to its relative inaccessibility.

Palpation of the Cervix

To obtain good results using AI in the bitch, it is absolutely essential to learn location of the cervix by abdominal palpation so that semen can be deposited correctly and so that the bitch is not injured during the insemination procedure. The bitch should have an empty stomach and bladder to facilitate palpation. While training to palpate the cervix, the rigid single-use plastic canine AI catheter is introduced into the vagina of the patient. The introduction of the catheter is facilitated if the vulva is elevated to just below the anus (such as when the bitch stands for the male dog). By inserting the catheter along the left or right side of the vestibulum, the centrally located urethral opening can be avoided. Because the urethral opening of the bitch is located at the pelvic brim, it is surprisingly easy for the plastic AI catheter, or a thin rigid endoscope, to be unintentionally introduced into the urinary bladder. Apart from the hazards of perforating the bladder with the catheter, it is obvious that no pregnancy would follow AI of the bladder. Thus the correct position of the catheter should always be checked by palpation before depositing a semen dose. If the catheter is in the urinary bladder, the cranial part of the vagina and the cervix can be palpated above the catheter. The walls of the urinary bladder usually are thinner than the walls of the vagina and the tip of the catheter stands out more distinctly, therefore, than if it were in the vagina. When the tip of the catheter is introduced just cranial to the pelvic brim, its position should be checked by palpation. Cranially the vagina in most bitches slopes slightly downward. However, in some breeds, especially the sight hounds that have a very arched loin, the vagina may have a more dorsal direction (see Figure 75-1). The cranial end of the catheter should now be lowered closer to the abdominal wall to make it more accessible to palpation. In large or obese bitches and in bitches with large and pendulous mammary glands, it may be easier to grasp the cervix by

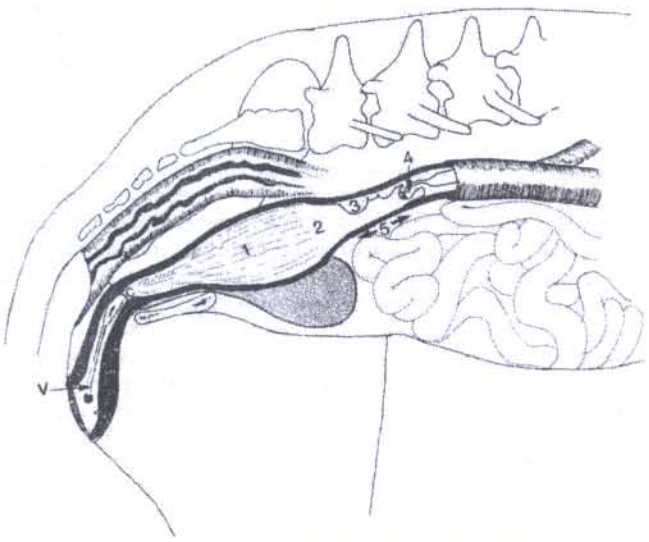


Figure 75-1 Schematic drawing of the canine caudal reproductive tract. **1,** Plicate area of vagina; **2,** rugose area of vagina; **3,** dorsal median fold of paracervix (number is placed on caudal tubercle of dorsal median fold); **4,** vaginal cervix; **5,** paracervix and paracervical area (*v,* single permanent ventral median fold in vestibule; *c,* cingulum at vaginovestibule junction). (From Lindsay FEF: The normal endoscopic appearance of the caudal reproductive tract of the cyclic and non-cyclic bitch: post-uterine endoscopy, *J Small Anim Pract* 24:1, 1983, with permission.)

palpation via the flank, which is usually thinner than the ventral abdominal wall. The tip of the catheter should then be lowered and also deflected toward the left flank (if the left hand is used for palpation). When the catheter tip can be palpated and its correct position in the vagina thus checked, it is carefully introduced further, under continued palpatory control, until it reaches the paracervical area. This is the narrow, cranial portion of the vagina created by the dorsal, median postcervical fold that can be palpated as a 1- to 2-cm long, usually somewhat firm structure. It ends at the cervix, which in a bitch in estrus is a 0.5- to 1.5-cm hard, rounded-to-ovoid, freely movable structure (see Figure 75-1). The rigid plastic AI catheter, which has a diameter of 5 mm, may be too wide to be introduced into the paracervical area in some bitches, especially those of the smaller breeds or those that have not given birth to a litter of pups. Consequently, it is usually not possible to pass the outer protecting sheath of the Scandinavian catheter, which has a diameter of 10 mm, into the paracervical area (Figure 75-2). Once the cervix has been identified, the corpus uteri and the uterine horns can be palpated in front of this structure. This can be achieved by lowering the tip of the catheter and closing the tip of the thumb against that of the index finger above the catheter, then lifting the cranial end of the catheter in such a way that the cervix and the uterine horns are pulled upward between the fingers. Their size and consistency then become evident. (This method of palpating the uterus is also useful for early pregnancy detection and to examine bitches with suspected pyometra.)

VAGINAL INSEMINATION

Vaginal AI involves using a rigid plastic single-use catheter (20- to 45-cm long and 5 mm in diameter) that is introduced into the cranial vagina and as close to the cervix as possible. With the catheter in place in the cranial vagina, the syringe containing semen is attached and the hindquarters of the bitch then elevated before infusing the semen. After deposition of the semen dose, the catheter is withdrawn and the bitch is held with elevated hindquarters for 5 to 10 minutes to facilitate the transport of spermatozoa toward the oviducts. The bitch should also be feathered around the vulva and perineal region to stimulate uterine contractions. Spermatozoa may reach the tip of the uterine horn within 30 seconds to 1 minute during a natural mating and within about 30 seconds to 2 minutes after a vaginal AI if the bitch is held with elevated hindquarters. Vaginal AI with the bitch standing horizontally may prevent the transport of spermatozoa into the uterus and oviducts.

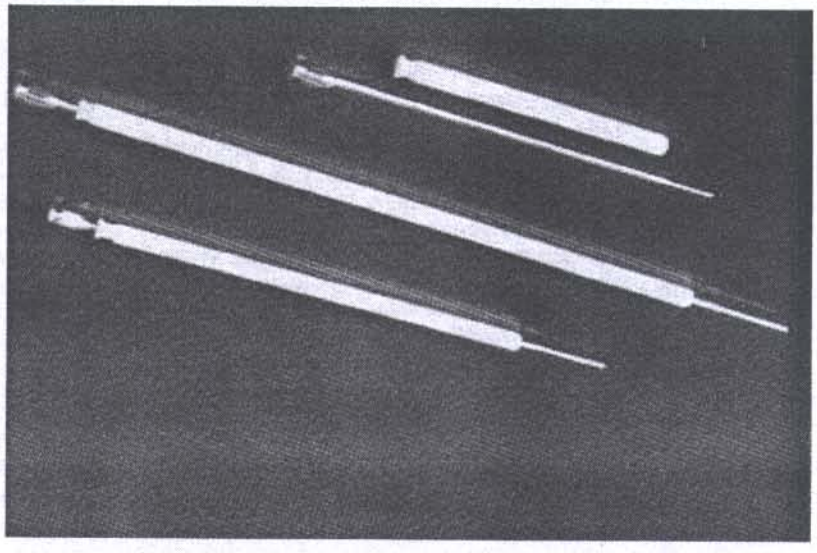


Figure 75-2 The three sizes of the Scandinavian AI catheter for dogs. (The Scandinavian catheters can be obtained from the Norwegian Fur Breeders' Association, PO Box 136, Økern, N-0509 Oslo 5, Norway. Phone: +47-23-25 81 00; Fax: +47-22-64 35 91.)

INTRAUTERINE INSEMINATION USING THE SCANDINAVIAN CATHETER

The Scandinavian catheter consists of a 3-mm wide steel catheter with a 1- to 2-mm diameter tip. It comes in three different lengths (20, 30, and 40 cm) and is used together with an outer protecting nylon sheath that is 10 mm in diameter (see Figure 75-2). The medium sized catheter fits most small- and medium-sized bitches.

Intrauterine AI with the Scandinavian catheter is performed with the bitch standing on the floor or on a table. Sedation is rarely needed. On the contrary, most bitches in estrus freely accept this type of handling. If light sedation is necessary (in a large, obese, or nervous bitch), 1- to 3-mg/kg xylazine intramuscularly or intravenously can be used. The nylon sheath is first introduced into the vagina as far as possible. If lubrication should prove necessary, a small amount of liquid paraffin or Vaseline, which are not spermicidal, can be used. If the nylon sheath is introduced together with the inner steel catheter, the tip of the steel catheter must be placed so that it is completely protected by the nylon sheath. The cranial end of the nylon sheath is palpated in front of the pelvic brim as previously described. If the tip of the sheath is lowered closer to the abdominal wall, the cervix usually can be palpated a few centimeters in front of and above the catheter. In large or obese bitches it may be easier to palpate and grasp the cervix via the flank. The steel catheter is then introduced through the sheath until its tip reaches the ventral fornix. The cervix is fixed between the thumb and the index finger and, by applying a slightly downward traction at the corpus uteri, it is tilted so that the angle of the cervical canal becomes more horizontal. The tip of the steel catheter is then carefully withdrawn while pushing it repeatedly against the surface of the cervix in search of the opening of the cervical canal. In most cases the sensation when this opening is found can be described as the sensation of touching cartilage (i.e., "crispy"). Once the opening has been found, the catheter should be fixed and the cervix worked against the catheter. The cervical canal is 5- to 10-mm long and not always completely straight (see Figure 75-1). Thus slight pressure may have to be applied, while rotating the catheter to ease it through. In most bitches the tip of the catheter can easily be felt in front of the cervix in the corpus uteri. In some bitches, however, the sensation is not as distinct. In a few bitches the catheter can only be introduced halfway through the cervix, which is usually sufficient. The syringe containing semen is firmly connected to the catheter, and the semen is slowly infused into the uterus while pressure is applied with thumb and index finger around the cervix to prevent backflow. Sometimes a resistance to infusion occurs because the opening of the catheter may be pressed too hard against the endometrial mucosa. Slight downward traction at the corpus uterior of the cervix usually alleviates resistance and allows semen to be infused. (To check that the catheter really is in the uterus, 1 to 2 ml of physiologic saline can be infused. If the catheter is in the right position in the uterine body, the fluid can easily be infused. If, on the other hand, the catheter is in the paracervical region, there will be an almost immediate backflow of saline between the catheter and the nylon sheath). After intrauterine deposition of the semen, the catheter is withdrawn; to minimize backflow of semen and to facilitate uterine transport of spermatozoa toward the oviducts, the bitch should be held with elevated hindquarters for 5 to 10 minutes after the AI while being feathered around the vulva and perineal region to stimulate uterine contractions and sperm transport.

To learn this technique requires some practice, but once learned it is a quick procedure, usually being accomplished within minutes. Once learned, less than 5% of attempts are unsuccessful. It is recommended that, initially, organ specimens be obtained for training purposes and anatomic study. It is also advised that first attempts be made in medium-sized, calm, lean bitches that have given birth to one or more litters. They are usually considerably easier to catheterize. Perforations may occur if the catheter is introduced blindly or with force. Provided that the catheterization is performed under careful palpatory control, however, the technique is completely safe. (This technique can also be used for procedures such as intrauterine infusion of contrast medium for hysterographic examinations of the bitch with suspected pyometra.) Some bitches are more difficult to catheterize, particularly those belonging to some of the giant breeds, as well as obese or nervous animals. Should transcervical catheterization fail and the decision be made to deposit the semen in the vagina, a change should be made to the single-use vaginal catheter to avoid a backflow of semen between the nylon sheath and the steel catheter.

INTRAUTERINE INSEMINATION USING ENDOSCOPIC VISUALIZATION OF THE CERVIX

Transcervical intrauterine insemination on the standing, nonsedated bitch can also be accomplished with the aid of a rigid fiber-optic endoscope (i.e., a cystourethroscope) that is 23 to 29 cm in length and 4 mm in diameter with an oblique viewing angle of 25 to 30 degrees, together with a stainless steel sheath (23 French gauge) (Figure 75-3). A dog urinary catheter, 6 to 8 French gauge, is passed through the operating channel of the sheath. The endoscope is introduced into the vagina and advanced past the vaginal folds and into the narrow paracervical area until the external os of the cervical canal can be visualized. To guide the endoscope through the sometimes tortuous vaginal vault, it can be quite helpful to let the urinary catheter lead the way by a few centimeters, thus indicating the right direction. Similar to use of the Scandinavian catheter, it can also be established (by abdominal palpation) whether the tip of the endoscope is correctly positioned in relation to the cervix. If the lumen in the paracervix is very narrow, the catheter may have to be introduced along one side of the dorsal median fold. The urinary catheter is then manipulated into the cervical opening and further into the uterus by a pushing and twisting movement. If the opening of the

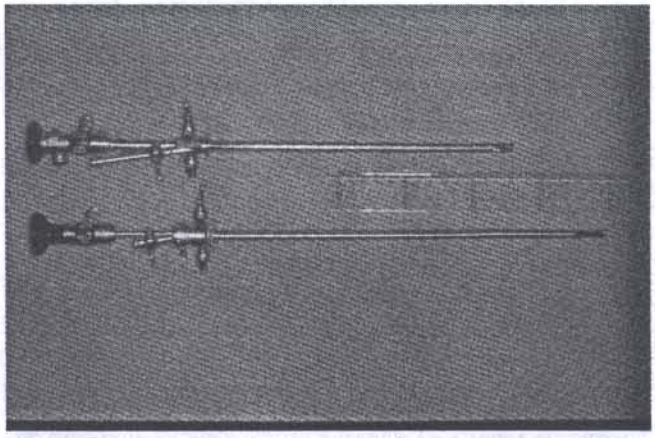


Figure 75-3 Transcervical intrauterine insemination can also be accomplished with the aid of a rigid fiber-optic endoscope connected to a cold light source and a canine urinary catheter (6 to 8 French gauge). The endoscope comes in different lengths.

cervical canal is directed away from the endoscope and thus out of sight, the cervix can be manipulated by pushing it with the tip of the rigid endoscope or with the catheter while moving the instrument from side to side below the cervix. After semen has been deposited into the uterus, the catheter and the endoscope should be removed and the bitch kept with elevated hindquarters for 5 to 10 minutes.

A significant advantage of this technique is that it allows direct visualization of the cervical opening. However, it involves manipulation of the scope and catheter and requires some practice. Although the equipment is expensive, it should be a good investment for practitioners specializing in canine reproduction and AI to obtain at least one endoscope of medium size, which will fit most breeds. The endoscope is also a great help when training to perform transcervical catheterization with the Scandinavian catheter.

INTRAUTERINE INSEMINATION USING SURGERY

Surgery to effect intrauterine insemination is still widely used. The bitch should be under general anesthesia and in dorsal recumbency. The ventral abdomen is clipped, and after routine surgical preparation a 4- to 6-cm incision is made midway between the pubis and the umbilicus through the linea alba. The uterus is elevated through the incision, and the needle of the syringe containing the semen is inserted into the lumen of the uterine body at a 45-degree angle with the bevel of the needle up. The semen is slowly injected into the uterus. It should flow easily with obvious distention of the uterine horns. If it does not, the needle should be repositioned. A piece of saline-moistened gauze is held over the injection site after the needle is withdrawn. After 1 minute the gauze is removed, the uterus replaced into the abdomen, and the wound closed using routine methodology. To avoid backflow of semen the bitch should be positioned with its rear elevated as she recovers from anesthesia. Whether it is ethically acceptable to resort to surgery to achieve pregnancies is debatable. The method, although advocated by some, is considered by many to be unethical and unacceptably stressful for the bitch. Two obvious disadvantages are (1) the general risks for infection and other complications associated with surgery and (2) the limited number of surgical AIs that can be performed in a given bitch. The method is also costly and time consuming.

INTRAUTERINE INSEMINATION USING LAPAROSCOPY

Abdominal laparoscopy should offer a somewhat more acceptable alternative to full surgery for AI in the dog; however, this method has not met with acceptance from practitioners, most likely because they are more used to the surgical technique.

CHAPTER 76

Diagnostic Blood Pressure Measurement

Rebecca L. Stepien

Acute blood pressure (BP) measurement is required to diagnose hypertension or hypotension or to exclude these diagnoses as a cause for clinical signs in a patient. Multiple BP measurement techniques are available; each is associated with advantages and disadvantages.

PATIENT SELECTION

Blood pressure measurements are assessed as one part of a clinical evaluation that includes the patient history, physical examination findings, results of other diagnostic testing, and evaluation of concomitant medications, including anesthetics and sedatives. Many BP measurement techniques have test characteristics that require low diagnostic cutoff values for maximum sensitivity to hypertension (maximum opportunity to correctly identify an abnormally high value). Unfortunately, low diagnostic cutoff values also are associated with increased numbers of false-positive diagnoses. As a result, many BP measurement techniques are best able to correctly identify truly hypertensive patients as abnormal when the test is applied to patient populations with clinical signs or diseases likely to be associated with systemic hypertension. Routine "screening" BP measurements in clinically normal patients may assist the clinician in establishing a typical baseline BP value for an individual patient, but abnormally high BP values obtained from clinically normal patients must be viewed with caution due to the high incidence of false-positive readings in this patient population.

INDICATIONS FOR BLOOD PRESSURE ASSESSMENT

Blood pressure assessment is indicated in cats suspected of having or already diagnosed with diseases commonly associated with systemic hypertension (i.e., renal insufficiency or thyrotoxicosis); in cats presenting with clinical signs consistent with systemic hypertension; and in cats that have unexplained left ventricular hypertrophy. The most common reason for clinical presentation of hypertensive cats is ophthalmologic abnormalities. Although other causes of intraocular hemorrhage (e.g., coagulopathy) and retinal detachment (e.g., inflammatory disease) should be ruled out, immediate measurement of

systemic BP guides the course of the diagnostic evaluation in these patients. For cats with neurologic signs in addition to ophthalmologic signs, diagnosis of critical levels of hypertension and immediate therapy can lead to rapid improvement in BP and relief of clinical signs.

Systemic BP should be assessed in cats whenever auscultatory cardiac abnormalities (e.g., gallop rhythms, left-sided systolic murmurs) and radiographic, electrocardiographic, or echocardiographic findings are consistent with hypertrophic myocardial disease involving the left side of the heart. Systemic hypertension (and hyperthyroidism in cats over 8 years of age) should be excluded by appropriate testing before a diagnosis of idiopathic hypertrophic cardiomyopathy is made. Early recognition of abnormal BP typically leads to evaluation for other systemic diseases, especially renal insufficiency.

Ophthalmologic abnormalities may also be seen in cases of canine hypertension, but systemic hypertension in dogs is most often diagnosed when BP is evaluated as part of the clinical workup of dogs with systemic diseases known to be associated with hypertension. In dogs, the diseases most frequently associated with elevations in BP are protein-losing renal diseases or chronic renal failure of any etiology, hyperadrenocorticism, diabetes mellitus, and pheochromocytoma. As with cats, systemic hypertension should be ruled out as a cause of left ventricular thickening of unknown etiology. Lastly, BP should be evaluated in cats or dogs with intracranial neurologic signs.

Dogs and cats that present with clinical signs of low cardiac output (e.g., weak peripheral pulses, cold extremities), shock, blood loss, or obtundation should be evaluated for hypotension. In some cases, hypotension is diagnosed clinically based on the constellation of history, presenting signs, and suspected clinical diagnosis (see Shock, Chapter 124). Accurate measurement of BP is important in any hypotensive patient to confirm the diagnosis and to provide baseline data for monitoring the response to therapy. BP evaluation methods differ in their sensitivity to low BP. Automated noninvasive techniques (i.e., oscillometric techniques) may fail to detect a pulse when hypotension is present, and operator-reliant techniques for pulse detection (e.g., Doppler sphygmomanometry) can be unreliable if the pulse signal is difficult to discern. Of the methods typically used in acute BP measurement, arterial cannulation is the most accurate method of documenting hypotension.

CHOOSING A BLOOD PRESSURE MEASUREMENT TECHNIQUE

Acute Diagnostic Blood Pressure Measurement

Detection of systemic hypertension may lead to additional testing for an underlying disease condition. In such cases, it is advantageous to perform BP measurement acutely (i.e., during a clinical examination or diagnostic evaluation), rather than hospitalizing patients and placing indwelling arterial catheters. When a technique to measure BP in a particular animal is chosen, specific issues to be considered include the availability of equipment, the availability of "normal" values to use for comparison, the skill and experience of the person making the measurement, and specific issues related to the animal (e.g., size, obesity, temperament).

The accuracy and usefulness of the measurement technique chosen ultimately depends more on attention to detail and use of applicable normal values (i.e., generated with the same technique as the one in use) than on which technique is used. Although multiple studies have addressed correlation or lack of correlation between invasive and noninvasive techniques in both dogs and cats, few studies are available that address the ability of these techniques to discern "normal" from "abnormal" in a conscious clinical population. Therefore assessment of BP values obtained may involve comparisons with normal values or comparison with values known to be associated with clinical signs.

Continuous Blood Pressure Monitoring: Conscious Patients

The monitoring of BP over time requires either continuous measurement (arterial catheterization) or repeated measurements, recorded automatically (oscillometric or photoplethysmographic techniques) or manually (Doppler sphygmomanometric methods). Arterial catheterization has the greatest number of advantages in conscious patients. Blood pressure obtained via arterial cannulation is accurate when the technique is used correctly and the values obtained are objective and repeatable (no manual pulse detection is required). A particularly important advantage is that the system can be secured to continue BP measurement when the animal moves. The major disadvantages are the technical skills and equipment required to maintain an arterial catheter and transducer system. Noninvasive methods are commonly used to take serial BP measurements in conscious animals. Although noninvasive BP measurements appear to be technically simple to obtain, they are subject to marked inaccuracy with animal movement, poor pulse pressure, arrhythmia, or inconsistent technique. When repeated BP measurements are obtained using these methods, cuff size and positioning, as well as limb position, should be identical for the repeated recordings.

Continuous Blood Pressure Monitoring: Anesthetized Patients

Blood pressure monitoring by most clinical methods is accurate and repeatable in anesthetized animals. The primary confounding problem of patient movement is absent in these patients, which renders them ideal subjects for BP measurement. Nonetheless, differences between values obtained by invasive methods (arterial catheterization) and noninvasive methods have been documented in numerous studies of dogs and cats. These studies indicate that numeric values obtained by means of noninvasive methods often underestimate true BP. In the case of anesthetized animals, this may result in an erroneous diagnosis of hypotension, but it seldom leads to the more dangerous error of overestimating BP in these patients.

BLOOD PRESSURE MEASUREMENT TECHNIQUES

Arterial Puncture or Arterial Cannulation ("Invasive" or "Direct" Technique)

Direct BP measurement involves advancing a needle attached to a pressure transducer directly into an artery to measure BP. This procedure may be performed acutely to obtain instantaneous BP readings, or BP can be measured over time through the use of an indwelling arterial catheter instead of a needle. Invasive BP measurements are typically used during anesthetic procedures, in critical care patients when ongoing BP information is desired, or to document or exclude hypertension acutely as a clinical diagnosis in dogs. Acute arterial puncture is seldom used for clinical diagnosis of hypertension in cats.

Direct BP measurement is usually performed by means of puncture of the femoral artery in dogs. Use of local anesthesia is strongly recommended for this procedure and is well tolerated by most dogs. The patient is gently restrained in lateral recumbency. Approximately 5 minutes prior to arterial puncture, 1 to 2 mL of 2% lidocaine hydrochloride is injected subcutaneously over the area in which the femoral pulse is palpated. A 22-gauge, 1-inch needle is attached to a transducer and flushed with heparinized saline, ensuring that no bubbles remain in the transducer. The transducer is zeroed at the level of the sternum in the laterally recumbent dog. The femoral

pulse is palpated in the femoral triangle, and the needle is carefully advanced into the femoral artery (Figure 76-1) until a satisfactory pressure waveform is recorded on the monitor screen. A sample of the tracing is recorded, and the needle is withdrawn. Firm pressure is applied to the area of arterial puncture for a minimum of 5 minutes after measurement. The patient should be monitored for at least 1 hour after the procedure for any complications related to hematoma formation. Systolic, diastolic, and mean BP values from five consecutive cardiac cycles during normal sinus rhythm are averaged to obtain a representative value for the patient. When use of an arterial catheter is preferred, the catheter is usually inserted into the dorsal pedal artery. A local anesthetic may be used as described previously.

Oscillometric Technique

Oscillometric BP measurement involves the use of an automated detection system and a cuff that is wrapped around a limb or tail over an artery. The cuff is inflated automatically to a pressure that causes occlusion of the artery and then slowly deflated. The machine detects oscillations in the vessel wall as the occlusion is eased, and the pressure at which oscillations are maximal is recorded as the mean arterial pressure. Systolic and diastolic pressures are then calculated by the monitor using algorithms specific to the technique. This technique uses data from many cardiac cycles to render a single reading and is therefore unsuitable for use in animals with rapidly changing BP.

Oscillometric BP measurement methods are more accurate in dogs than in cats. This measurement method may return inaccurate results if the patient is not motionless (e.g., trembling), has a weak or irregular pulse, or has a small artery (i.e., most cats). Use of a cuff of appropriate size is extremely important to ensure accurate measurements. Cuff width should be approximately 40% of the circumference of the limb or tail in dogs and approximately 30% of the appendage circumference in cats. When used on the tail, the cuff is wrapped snugly high on the tail head with the dog in sternal or lateral recumbency. Although tail cuffs can be used in standing animals, animal movement often interferes with accurate measurement. Limb cuffs are wrapped around the forelimb distal to the elbow or around the mid-metatarsus at the level of the superficial plantar arterial arch (Figure 76-2). To maximize accuracy, the cuff should be at the level of the heart during readings; therefore lateral or sternal recumbency is preferred, and use in standing patients is not recommended. In cats, tail cuffs return more repeatable measurements than limb cuffs, but the accuracy of oscillometric BP measurements obtained by this method is questionable. Typically, the cat rests in sternal recumbency during readings (Figure 76-3).

In all cases, best results are obtained when the patient is minimally restrained and soothed during the procedure. A short acclimation period prior to measurement is recommended. A series of at least five readings are obtained at approximately 1-minute intervals. Any readings that are clearly erroneous are discarded. The multiple readings are then averaged to obtain a representative result.

Oscillometric techniques are valuable in anesthetized dogs and cats to monitor trends in BP. Because the animal is immobilized and BP shows less variability over time, repeatable and accurate readings can be obtained over time in both dogs and cats.

Doppler-Ultrasonic Technique (Doppler Sphygmomanometry)

Doppler ultrasonic flow detection through the use of a piezoelectric crystal allows detection of flow in a peripheral artery. Hair is clipped just proximal to the palmar metacarpal pad at the level of the superficial palmar arterial arch for forelimb measurement; over the dorsal pedal artery for hindlimb measurement; or on the ventral aspect of the tail for tail measurement. An occluding cuff (sized as outlined for oscillometric techniques) is placed proximal to the point of flow detection (mid-radius in the forelimb, proximal to the hock in the hindlimb, or proximal to transducer placement on the tail), and measurements are obtained with the cuff at the level of the heart. Ultrasonic coupling gel is placed on the concave surface of the Doppler transducer, and the transducer is held in position during measurements (Figure 76-4) or fixed in position using adhesive tape. An audible pulse signal is obtained, and the cuff is inflated with a bulb attached to a pressure gauge. The cuff is inflated to a pressure no less than 40 mm Hg above the audible cutoff point of the signal. The cuff is then slowly deflated, and the pressure at which the Doppler signal is again audible is recorded as the systolic pressure. The cuff is deflated further, and the pressure at which

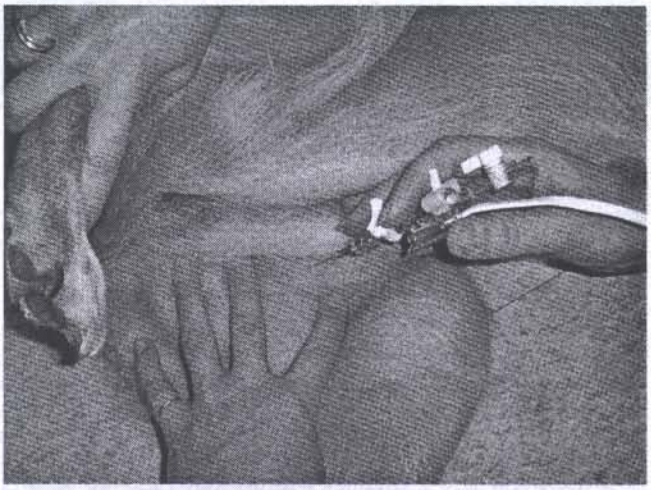


Figure 76-1 Invasive BP measurement via direct arterial puncture in a dog. A 22-gauge needle (with an attached pressure transducer, previously flushed with heparinized saline and zeroed) is advanced into the femoral artery at the level of the palpable pulse in the femoral triangle.

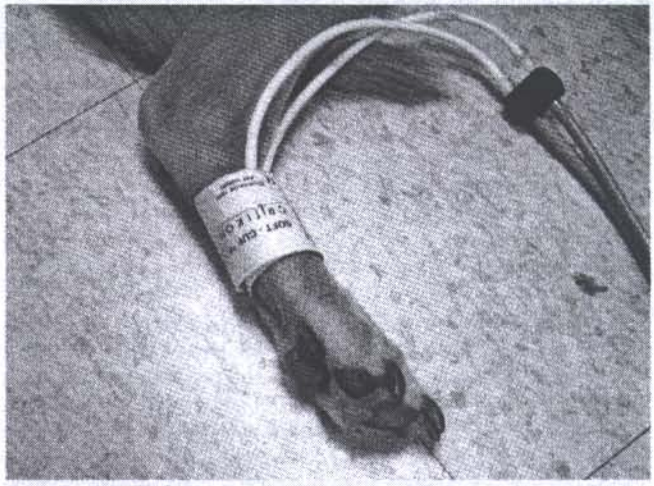


Figure 76-2 Correct cuff placement for oscillometric measurement of BP via the dorsal pedal artery in a dog. The cuff tubing is attached to the oscillometric BP monitor for readings.

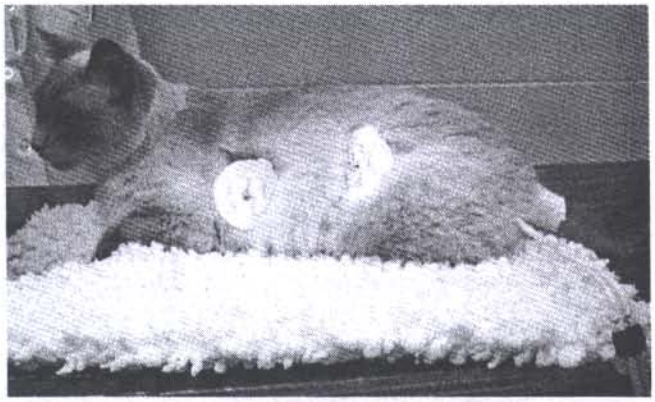


Figure 76-3 Correct placement of a tail cuff for oscillometric readings in a cat. The cat is relaxed and minimally restrained in sternal recumbency.

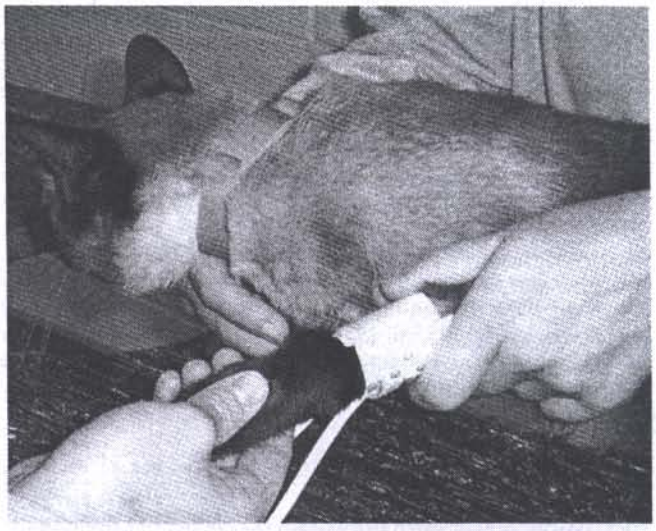


Figure 76-4 Measurement of BP via Doppler sphygmomanometry from the forelimb of a cat. Note that the inflatable cuff is at the same level as the heart in the sternally recumbent animal.

the audible signal abruptly changes in pitch or becomes muffled is recorded as the diastolic pressure.

The Doppler flow detection system of BP measurement is considered the most accurate and repeatable of studied noninvasive BP measurement techniques in conscious cats. It is frequently used in dogs but may provide spurious high readings in some individuals. When abnormal readings are obtained by this method from dogs, care should be taken to make sure the abnormal readings are repeatable over multiple measurement periods. The advantages of this technique include flexibility with regard to motion, low pressure, small vessels, or the presence of arrhythmias, as well as speed of measurement. The rapidity of the measurement techniques allows for prompt assessment of changing BP, but meticulous attention must be paid to obtaining strong, audible signals in order to obtain the most accurate BP readings. This technique is also the most operator dependent of the techniques discussed. Accurate identification of diastolic pressures improves with operator practice, and BP measurement using Doppler ultrasonic flow detection techniques is most accurate if a few well-trained individuals in a practice are responsible for this diagnostic test and perform the test frequently.

Photoplethysmography

Photoplethysmographic techniques measure blood volume by attenuation of infrared radiation. The blood volume is held constant by a microcomputer-based servosystem so that cuff pressure equals intra-arterial pressure. The cuff is positioned distal to the hock or at the tail head, and a visible waveform is used to assess the strength of the signal. Because the equipment is designed for use on the human finger, it is most suitable for cats or small dogs. Skin pigment may interfere with readings. This technique has not been studied extensively in conscious dogs and cats but appears to be as accurate as other noninvasive techniques in anesthetized animals.

CHAPTER • 77

Techniques for Bone Marrow Aspiration and Biopsy

Leo J. "Ty" McSherry

Peripheral blood abnormalities are the most common indications for the evaluation of bone marrow. These include poorly or nonregenerative anemia, persistent or unexplained neutropenia, unexplained thrombocytopenia, or any combination of peripheral cytopenias. A persistent leukocytosis or thrombocytosis, dysplastic changes, or the inappropriate presence of immature hematopoietic cells in the peripheral circulation are additional indications for bone marrow evaluation. Bone marrow can be used to stage neoplasia, evaluate lytic bone lesions, or determine the cause of unexplained hypercalcemia or hyperproteinemia, especially hyperglobulinemia, as may relate to lymphoma, multiple myeloma, or some systemic infections. Less commonly, bone marrow can be evaluated to help determine the cause of fever of unknown origin or evaluate total body iron stores.

Contraindications to bone marrow aspiration or biopsy are few and are generally related to the use of sedation or restraint. Hemorrhage is an uncommon complication, even in severely

thrombocytopenic animals, and severe or unexplained thrombocytopenia is a common indication for marrow evaluation. Peripheral neutropenia is also a common indication for marrow evaluation; however, infection is unlikely because the aspirate, biopsy, or both is performed as a sterile procedure. The potential complications associated with hemorrhage or infection are minimal and should not dissuade the clinician from evaluating the marrow if indications to do so are present.

With the possible exception of a Petri dish or watch glass, most hospitals will have the necessary materials for bone marrow aspiration and biopsy. These include aspiration or biopsy needle, sedation or anesthesia, microscope slides, anticoagulant, scalpel blade (no. 11, no. 13), Petri dish or watch glass, 12-cc syringe, hematocrit capillary tubes, 2% lidocaine, and surgical scrub.

BONE MARROW ASPIRATION

Three types of aspiration needles are available: (1) the Illinois sternal, (2) the Jamshidi, and (3) the Rosenthal. These are available in 15- and 18-gauge sizes, 1 to 1½ inches in length. The 18-gauge needles are typically used in cats and small dogs, whereas the 15-gauge needles are reserved for dogs greater than 20 pounds. The Illinois sternal needles have a removable plastic cap (designed to hold the stylet in place during placement of the needle) and a removable needle guard. However, the plastic cap and needle guard necessitate the use of gas sterilization. The Jamshidi needles are stainless steel, durable, and may be heat sterilized; however, they lack a removable cover or needle guard.

The use of adequate sedation or general anesthesia will greatly facilitate the collection of bone marrow. Many authors describe collection with nothing more than a local anesthetic, and this may be all that is necessary or permissible in stoic animals or those at a high risk of anesthetic complications. Aspiration is a painful procedure, however, and a struggling or anxious animal will likely interfere with collection of an adequate sample. Sedation or anesthesia is suggested.

The use of an anticoagulant, although not necessary, is recommended and allows for the preparation of high-quality slides. It also allows time to complete the procedure before slides need to be prepared. Anticoagulant can be prepared by injecting 0.35 cc of sterile saline into a 3-ml lavender top tube containing EDTA, withdrawing the solution, and then reinjecting it into a second EDTA tube. This should yield approximately 0.5 cc of a 2.5% EDTA solution. Alternatively, a 5% solution of EDTA may be prepared using the dry reagent by a local or compounding pharmacy. The dry reagent is inexpensive and available through many pharmaceutic companies. This is a practical and recommended alternative for hospitals that regularly perform bone marrow aspiration. A volume of 0.5 to 1.0 ml is recommended per collection.

Three sites are commonly used for the collection of bone marrow: (1) the proximal humerus, (2) the iliac crest, and (3) the trochanteric fossa. The proximal humerus is an easily accessible site in dogs and cats of all sizes. It has little overlying tissue and provides a fairly large area for placement of the needle. Its disadvantages include its proximity to the head and the thick, rounded cortex. The greater tubercle is easily palpated, and the needle is inserted into the flat area of the craniolateral aspect of the humerus distal to the greater tubercle. The needle is inserted perpendicular to the long axis of the humerus (Figure 77-1).

The iliac crest is easily accessible in thin dogs or those in good body condition, as well as in large cats. It should be avoided in large or obese animals because it may be difficult to palpate or to seat the needle due to a large amount of overlying tissue. The iliac crest is the widest and most dorsal aspect of the wing of the ilium (Figure 77-2). The trochanteric fossa may be used in cats or small dogs. The trochanteric fossa is medial to the greater trochanter. The greater trochanter is palpated, and the needle inserted medial to it (into the trochanteric fossa). The needle is inserted parallel to the long axis of the femur (see Figure 77-2). The trochanteric fossa is generally avoided in well-muscled or obese animals due to a significant amount of overlying tissue.

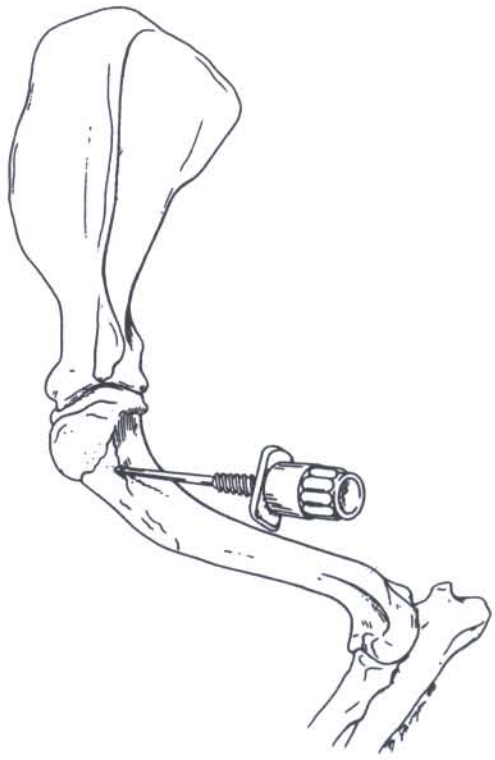


Figure 77-1 The needle is inserted perpendicular to the long axis of the humerus. (From Grindem CB: Bone marrow biopsy and evaluation, *Vet Clin North Am Small Anim Pract* 19:669, 1989.)

After sedation the animal is placed in lateral recumbency for collection from the proximal humerus, or it can be placed in either lateral or sternal recumbency for collection from the iliac crest. In nonsedated animals, lidocaine is used to block the surgically prepared site, beginning with the periosteum. The needle is then slowly withdrawn while blocking the overlying tissues and finally the skin. The sterile aspiration needle, scalpel blade, and 12-cc syringe are placed on the sterile glove field. Sterile gloves are worn, and 0.3- to 0.5-cc of anticoagulant is drawn into the 12-cc syringe that is then placed again on the sterile field. A small stab incision is made in the skin. The incision only need be wide enough for the aspiration needle.

The site of collection can be localized using one hand. The aspiration needle should be firmly seated in the palm of the hand and the needle held securely between the thumb and index finger. The plastic needle guard on the Illinois sternal needle has a small lip on which the thumb and index finger can be placed to grip the needle securely and to apply firm pressure. A tendency exists to hold the needle as if it were a pen. This should be avoided because it does not allow sufficient pressure to be applied to advance the needle through the cortex. In addition, if using the Jamshidi aspiration needle, pressure should be applied to the top of the stylet to prevent it from being dislodged while placing the needle. This is accomplished by holding it firmly in the palm of the hand.

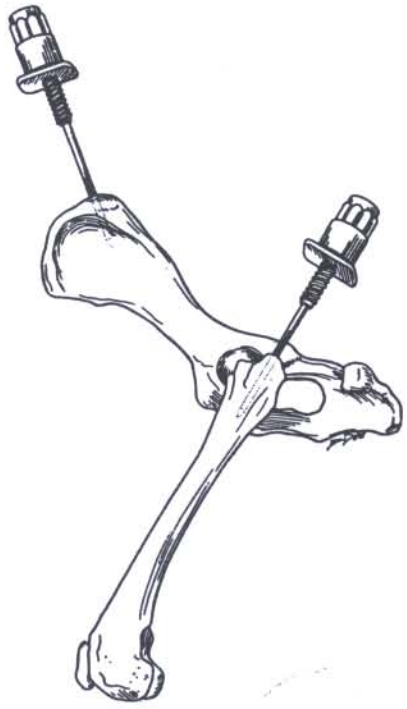


Figure 77-2 The needles are inserted medial to the greater trochanter and parallel to the long axis of the femur. (From Grindem CB: Bone marrow biopsy and evaluation, *Vet Clin North Am Small Anim Pract* 19:669, 1989.)

The aspiration needle is placed through the stab incision down to the periosteum. With the needle seated on the bone, firm clockwise-counterclockwise rotational pressure is applied to advance the needle. Frequently a slight decrease in resistance occurs when the needle enters the marrow cavity. When approaching the proximal humerus in cats, the needle may suddenly "pop" into the marrow cavity. When the needle has been properly positioned, it should feel very firmly seated, as might a nail in a block of wood. During advancement, the needle may occasionally and suddenly slide off the cortex into the surrounding soft tissue. This is especially common when approaching the proximal humerus and to a lesser degree the iliac crest. The needle will be freely movable in the subcutaneous tissues and not be firmly seated. Should this occur, the clinician should simply withdraw the needle to the level of the cortex, again seat the needle, and begin rotational pressure. When approaching the iliac crest, it is useful to have an assistant place counterpressure against the distal femur at the level of the stifle.

Once the needle is seated, the clinician should remove the top (if using an Illinois sternal needle) and stylet and place them on the sterile field. Next, a 12-cc syringe should be attached. While holding both the aspiration needle and syringe with one hand, the clinician should make several firm aspirations by rapidly pulling the plunger back. Marrow can appear after the first attempt at aspiration; however, several attempts could be necessary before marrow appears in the syringe. A total volume of 1 or 2 cc is collected if possible. If anticoagulant has been used, the syringe is removed from the needle and gently rocked to mix the marrow and anticoagulant. The sample may then be set down and the needle removed before preparing slides. Should no marrow appear in the syringe after vigorous aspiration, the syringe is removed from the needle and the stylet replaced. The needle is then advanced slightly using the same pressure with which it was placed, and aspiration is reattempted. Occasionally while approaching the iliac crest, the needle may be advanced too far into the opposite cortex. Unsuccessful attempts at aspiration will result. The needle should then be slightly withdrawn before again attempting aspiration.

After mixing the marrow and anticoagulant, the sample is expelled into a Petri dish or watch glass. The Petri dish or watch glass may be gently shaken or tilted to allow visualization of the marrow spicules. Marrow spicules appear as small, irregular white or gray particles that may adhere slightly to the dish or glass. These are collected using a hematocrit capillary tube or pipette. Only a small amount of sample needs to be collected in the capillary tube to prepare an adequate slide. The sample is placed on one end of a glass slide. A second slide is overlain on the bottom slide and the sample permitted to spread briefly between the slides. Digital pressure on the top slide is typically not necessary and is discouraged because cell lysis can result. The top slide is then smoothly but rapidly pulled down the length of the bottom slide and the sample air-dried.

If anticoagulant is not used, the slide must be prepared immediately after successful aspiration. Bone marrow clots very rapidly, and a clotted sample will not allow adequate slides to be prepared. As soon as marrow appears in the syringe, negative pressure is released and both the aspiration needle and syringe are removed. It is important to have several clean glass slides laid out prior to collection. The clinician should rapidly place a few drops of sample near the top of each of the slides. An assistant should then follow closely, preparing slides as the clinician goes down the row. It is difficult to prepare several slides by oneself because the marrow is likely to clot before the smears can be prepared. Several slides should be prepared and submitted. The preparation of 12 to 15 slides should result in several diagnostic slides and would permit additional testing or special staining should this be necessary to identify a poorly differentiated leukemia. In addition, accurate interpretation of the marrow is dependent upon the findings of a concurrent complete blood count (CBC), and a CBC (or current CBC results) should always be submitted with the aspirates.

BONE MARROW BIOPSY

Bone marrow biopsy is indicated if repeated attempts at aspiration are unsuccessful, if evaluating for metastatic neoplasia, or if evaluating lytic bone lesions resulting from neoplasia, inflammation, or infection. Unsuccessful aspiration resulting in a dry tap may result from myelofibrosis, myelophthisis, hypoplasia or aplasia, or technical error. Bone marrow may be collected immediately after aspiration and may be collected from the same site or a distant site. Collection from separate sites may increase the likelihood of identifying metastatic neoplasia. Concurrent aspiration and biopsy is beneficial in that aspirated samples may occasionally be insufficient, necessitating histologic evaluation. Additionally, marrow biopsy immediately after aspiration may prevent the need for an additional anesthetic procedure should the aspirates be insufficient for a diagnosis.

Patient preparation, sites of collection, and approach are similar to those described for aspiration. Biopsy is considerably more painful, and good sedation or (preferably) anesthesia should be used. Jamshidi bone marrow biopsy needles are 11 to 13 gauge and 3 to 4 inches long. The 13-gauge needles are typically used in cats and dogs less than 20 lb. Due to the larger size of these needles, the wing of the ilium may be too thin to be used in cats or very small dogs.

The biopsy needle is seated on the cortex and advanced using the same clockwise-counterclockwise rotational pressure that is used to place the aspiration needle. It is beneficial

to lay the index finger along the shaft of the needle while advancing the needle to stabilize it while it is rotated. With the needle firmly imbedded, the stylet is removed and the needle is advanced an additional inch or more using the same rotational pressure to collect an adequate sample. The biopsy fragment must be broken loose using several 360-degree twists in both directions, and the needle is withdrawn. The biopsy fragment is pushed out the top of the needle in a retrograde fashion using the wire that accompanies the needle. The biopsy needle is tapered, and attempting to push the sample out the tip will crush it and damage the sample. The collection of a sufficient sample will allow the core to be sectioned and part submitted for culture if an infectious process is suspected. The biopsy fragment is typically submitted in formalin; however, consulting the surgical pathology service may be beneficial because other fixatives are occasionally preferred. Biopsy samples should not be submitted in the same packaging as cytology preparations because the formalin vapors can interfere with the staining quality of cytologic preparations.

CHAPTER 78

Brain Biopsy

Richard A. LeCouteur
Peter J. Dickinson

Neoplastic, vascular, infectious, or inflammatory diseases of dogs and cats frequently result in focal brain involvement. In affected animals, results of ancillary diagnostic investigations, such as cerebrospinal fluid (CSF) analysis and electroencephalography, may be within normal limits or may provide only "indirect" evidence of the presence of a brain lesion. The use of computed tomography (CT) and magnetic resonance imaging (MRI) has enabled accurate detection of many focal brain lesions. Although CT and MRI are sensitive in determining location, extent, and relationships to adjacent structures of brain lesions, both have limited specificity. Non-neoplastic lesions (such as those seen in association with infectious, inflammatory, or vascular diseases) may mimic the CT or MRI appearance of a neoplasm. In most instances, results of CT or MRI provide only a broad list of differential diagnoses for a focal brain lesion. An accurate histologic diagnosis of an intracranial lesion is critical before recommending a specific management or treatment strategy, and the need remains to obtain an intraoperative neuropathologic diagnosis from tissue samples obtained from the lesion.

OPEN BRAIN BIOPSY

Open brain biopsy may be appropriate in certain clinical situations in which cortical architecture needs to be preserved, for leptomeningeal sampling, for superficially located lesions, and when a decompressive craniectomy with good cortical visualization may be helpful in addition to obtaining a biopsy sample.

For superficial brain lesions, a craniectomy is performed, the dura is opened, the lesion is located, and a specimen of affected brain is excised using a no. 11 scalpel blade. For more deep-seated brain lesions, freehand fine needle (22 gauge) aspiration, or Tru-Cut® biopsy (using a 14-gauge Tru-cut biopsy needle, Travenol Laboratories Inc., Deerfield, IL), CT-guided freehand Field-Lee needle biopsy (using a 13-gauge Field-Lee brain biopsy needle, V. Mueller, Chicago, IL), or ultrasound-guided Menghini needle brain biopsy techniques (using a 16-gauge Menghini biopsy needle, Miltex Corp., Lake Success, NY) have been reported for use in dogs after a limited craniectomy.

Although open brain biopsy techniques usually are accompanied by low morbidity and mortality, these techniques are no longer recommended for deep-seated brain lesions. Stereotactic brain biopsy procedures are preferred, as they have been shown to work safely and effectively in a consistent manner in a large number of cats and dogs.

STEREOTACTIC BRAIN BIOPSY

With the advent of CT and MRI, and the development of CT-guided stereotactic frames, closed stereotactic brain biopsy has become the standard of care in people. Essentially all closed methods rely on the three-dimensional CT-generated coordinates identifying the lesion location. These coordinates are used to plot the optimal trajectory and depth needed for a biopsy needle to reach a target and obtain a diagnostic tissue sample.

Technical impediments exist to the direct application of most human stereotactic systems to dogs and cats. Most commercially available systems use a cumbersome head-frame, designed specifically for the human skull, and require dedicated, expensive computer software for the planning phase. Several different systems for image-guided stereotactic brain biopsy have been reported for use in dogs and cats.

Stereotactic biopsy begins with proper patient selection. The possibility of non-neoplastic disorders such as infection, cerebral infarction, or vasculitis, must be considered and investigated with other tests in appropriate patients prior to biopsy. When the differential diagnosis list is long and may include neoplasms and inflammatory lesions, the appropriate handling of tissue samples should be discussed with a neuropathologist in advance of the procedure. All patients should be tested for coagulation parameters (prothrombin time [PT], partial thromboplastin time [PTT]) prior to the procedure and should have a platelet count greater than 100,000. Patients should not receive aspirin products for 1 week before surgery.

General anesthesia is required for stereotactic brain biopsy. Biopsy generally is done on the CT-scanner table. For those lesions not well identified on CT images, MRIs that demonstrate a lesion may be used for comparison to localize the lesion on CT images, using well-defined anatomic landmarks (e.g., lateral ventricles). Axial CT images are used to define the CT coordinates of reference markers and the biopsy

target. Dorsal or sagittal images may be used for trajectory planning. An entry point should be selected that is associated with a low risk for neurologic deficit or hemorrhage (e.g., avoidance of dorsal sagittal sinus). Ependymal puncture should be avoided where possible. A small craniotomy (2- to 4-mm diameter) is made by means of a twist drill, the dura mater is punctured with an 18-gauge needle, and biopsies may be done with a side-cutting aspirator biopsy needle (using a T 19.S biopsy needle, Ohio Medical Instruments, Cincinnati, OH) with a 10-mm side opening. On average, two or three specimens are removed. It is important to biopsy several regions of the intracranial lesion using a single trajectory.

The intraoperative goal should be to confirm by means of smear or touch preparations whether tissue satisfactory for an eventual diagnosis has been obtained. A specific histologic diagnosis may require routine formalin fixation and paraffin embedding of the biopsy tissue. At the conclusion of the biopsy procedure, the needle is withdrawn in increments to assess any possibility of hemorrhage. In the case of hemorrhage, blood should be permitted to egress from the needle spontaneously until the bleeding stops. An immediate postoperative CT scan should be obtained.

Although stereotactic brain biopsy is minimally invasive (compared with open biopsy techniques) and designed for low risk, complications may rarely occur. Morbidity may include seizures, hemorrhage, new neurologic deficits, brain infection, tumor seeding, and lack of a definitive diagnosis.

Handling the Intraoperative Specimen

The intraoperative specimen must be processed rapidly and carefully to provide timely and accurate diagnostic information. For large specimens, cytologic analyses (touch imprints, smears) may be done in conjunction with frozen sections. Cytologic analyses alone may be done in situations where access to frozen sections is difficult or when the biopsy specimen is small.

The clinician can make a smear (or "squash") preparation by placing a small fragment of tissue at one end of a standard glass microscope slide. The end of another glass slide is placed over the tissue, mild pressure is applied to the slides, and the slides are gently and rapidly pulled apart to produce a smear. The slides are fixed immediately in 95% alcohol and stained with a rapid hematoxylin and eosin stain. Other techniques include fixation of the specimen in alcohol followed by toluidine blue, Giemsa, or Papanicolaou staining, or air-drying the specimen prior to Romanovsky or Wright's staining.

The clinician may take touch imprints by pressing a glass slide briefly to the surface of the fresh (unfixed) biopsy specimen. Small fragments first may be blotted to remove excess blood or fluid. The slides are fixed and stained in a similar manner to the smear preparations.

Frozen sections provide superior architectural detail for the intraoperative interpretation of biopsy specimens. They are done by placing carefully oriented tissue fragments on a cryostat chuck and freezing them in a viscous freezing medium (such as OCT), either within the cryostat with use of coolant spray and a metal heat extractor or by snap freezing in supercooled isopentane or 2-methylbutane. Frozen sections are cut and thaw mounted on glass slides. They may be either fixed immediately in alcohol or air-dried before fixation. The sections then are stained with a rapid hematoxylin and eosin stain.

With results of one of the rapid tests outlined previously, a decision may be made regarding the need for further biopsy specimens to define the exact nature of the lesion (e.g., if results from an initial specimen are inconclusive) or the need for additional specimens for completion of specialized techniques (e.g., culture and sensitivity testing for a suspected inflammatory or infectious disorder).

Most intracerebral biopsy specimens may be safely fixed in 10% neutral buffered formalin and processed for hematoxylin and eosin staining. Small samples (1 to 2 mm) may be adequately fixed in 1 to 2 hours, whereas larger specimens may require overnight fixation. If any doubt exists as to the appropriateness of the fixative, a neuropathologist should be consulted immediately. Although technical improvements in immunohistochemical staining permit accurate assessment of samples after formalin fixation and paraffin embedding, immunohistochemical-staining assessment of ultrastructural detail using electron microscopy requires fixatives containing glutaraldehyde.

CONCLUSION

Treatment options based on empiric observations of brain lesions in dogs and cats may compromise clinical outcome. Regardless of lesion location, size, or appearance, a histologic diagnosis is necessary for optimal treatment. Although stereotactic brain biopsy techniques require specialized equipment and instrumentation, they should be considered a standard option in the diagnostic workup of dogs or cats with definable brain lesions on CT or MRI.

CHAPTER 79

Muscle and Nerve Biopsy

Peter J. Dickinson
Richard A. LeCouteur

Biopsy of muscle and nerve is an essential consideration in the diagnosis and therapy of neuromuscular diseases in small animals. Examination of the specific components of the motor unit, as well as of sensory and autonomic nerves, permits definition and classification of the underlying pathology.

MUSCLE BIOPSY

Conventional biopsy and formalin fixation techniques, as used with most organ systems, severely limit the quantity and quality of information that may be obtained from muscle specimens. The development of specialized enzyme histochemical

techniques, using frozen skeletal muscle biopsy specimens, has greatly increased the understanding both of normal muscle and of the underlying pathologic processes of many neuromuscular diseases.

Selection of Muscle

The selection of a muscle for biopsy is guided by a number of criteria:

1. The muscle should be affected by the disease process but should not be end-stage. This choice may be based on electrophysiologic data, including abnormal electromyographic (EMG) results and clinical abnormalities suggesting muscle involvement (atrophy, hypertrophy, apparent pain, weakness).
2. The muscle should be easily identified surgically, with low associated morbidity, and with fibers oriented in a single direction.
3. Specimens should be harvested from muscles for which there is previous interpretive experience. Standard muscles include the lateral head of the triceps brachii (distal third), vastus lateralis (distal third), cranial tibial (proximal third), and temporalis muscles. Biopsy specimens from both a thoracic and a pelvic limb muscle, or other distant locations, are necessary to permit diagnosis of generalized neuromuscular disease.
4. Muscle biopsy specimens should be harvested from a site remote to tendinous insertions and aponeuroses.
5. Specimens should be free of artifacts induced by previous disease, intramuscular injections, and EMG needle insertion.
6. Some specialized procedures may require biopsy specimens from specific muscles or regions within muscles. For example, diagnosis of congenital myasthenia gravis is based on the demonstration of decreased numbers of acetylcholine receptors in biopsies of external intercostal muscle.

Open Muscle Biopsy Procedure

Open biopsies are done most often under general anesthesia following electrodiagnostic investigations. After routine surgical preparation, the skin and fascia overlying the muscle are incised, allowing visualization of the orientation of the myofibers. A sample for fixation is harvested first. Two incisions are made with a No. 11 scalpel blade, parallel to the direction of the myofibers and approximately 2 cm long, 0.25 cm apart, and 0.5 cm deep. Specialized muscle clamps are placed at either end of the incised strip of muscle (to minimize myofiber contraction), and the isolated muscle is freed from the surrounding muscle with a scalpel blade or scissors. This specimen is immersed immediately in fixative, usually glutaraldehyde (either sodium phosphate–buffered glutaraldehyde or Karnovsky's fixative). Clamps may be removed after 24 hours following fixation. If a specialized muscle clamp is not available, the specimen may be sutured to the wooden stem of a cotton-tipped applicator. Samples for freezing and routine histochemical staining (approximately 0.5 to 1 cm in cross section and 1 to 1.5 cm long) may be harvested from adjacent muscle. It is not necessary to maintain these specimens in a stretched position. Handling of the specimen should be kept to a minimum to reduce artifact. Wound closure is routine. External dressings are not necessary. Complications (infection, hematoma) are uncommon and usually are the result of animals interfering with the biopsy site. Collection of a muscle biopsy specimen may be contraindicated in patients with significant coagulopathies.

Percutaneous Muscle Biopsy Procedure

Percutaneous needle or punch muscle biopsy is not recommended routinely due to the limited size and poor orientation of the biopsy specimens obtained.

Specimen Processing and Transport

Ideally, muscle biopsy specimens should be frozen immediately or transported to specialized laboratories for processing and interpretation. Specimen blocks are mounted on thin cork squares using tissue-embedding media, with the muscle fibers oriented vertical to the cork, and frozen for approximately 20 seconds in isopentane (2-methylbutane) cooled to approximately −150° C in liquid nitrogen. Proper freezing of the sample is critical for preservation of morphologic detail and prevention of artifacts. Frozen blocks may be stored in airtight containers at −80° C or in liquid nitrogen storage vessels. For biopsy specimens that are to be transported to specialized laboratories for processing, one fact cannot be overemphasized: *the quality of the information that will be obtained depends on the quality of the biopsy specimen that arrives at the laboratory.* Before a biopsy procedure is performed, the laboratory's specific instructions for selection, handling, and transportation of the specimen should always be obtained. Nonfrozen specimens should be wrapped in saline-moistened swabs that have been thoroughly wrung dry; the specimens then should be placed in an airtight container and maintained at 4° C using cold packs. The specimen container should be wrapped in a layer of newspaper to insulate it from the cold packs to prevent partial freezing of the specimen. Specimens should be shipped so as to reach the laboratory within 30 hours and should not arrive at the laboratory during a weekend. Muscle specimens to be used for biochemical analysis, such as carnitine quantitation, and glutaraldehyde-fixed specimens may be transported in a container separate from the chilled biopsy specimen. Many laboratories request that 5 cc of the animal's serum be shipped with the muscle biopsy specimen.

NERVE BIOPSY

Selection of Nerve

As with muscle selection, certain guidelines should be followed in the selection of a nerve for biopsy:

1. The nerve should be affected by the disease process, as evidenced by abnormal results on electrophysiologic investigations or by neurologic abnormalities in areas innervated by the nerve (atrophy, hypotonia, hyporeflexia, paresis, sensory deficits).
2. If the disease process is generalized, a nerve should be selected that (1) is easily biopsied with low morbidity, (2) has established normal electrophysiologic and morphometric data available, and (3) innervates a muscle that may be routinely biopsied.

Biopsy of the mixed (motor/sensory/autonomic) common peroneal nerve is recommended when generalized neuromuscular disease is suspected. This nerve is relatively easy to identify and biopsy because it is flat and contains prominent fascicles. Other mixed nerves that may be biopsied easily are the tibial nerve (pelvic limb) and the ulnar nerve (thoracic limb). When a predominantly sensory neuropathy is suspected, biopsy of cutaneous sensory nerves, such as the caudal cutaneous antebrachial nerve or the caudal cutaneous sural nerve, may be appropriate. Biopsy of nerve roots via laminectomy may be necessary when pathology is restricted to the most proximal portions of the peripheral nervous system. If both dorsal and ventral nerve roots are affected, biopsy of the dorsal nerve root is preferred. Biopsy of cranial nerves is infrequently done, largely due to the inaccessibility of these nerves.

Nerve Biopsy Technique (Common Peroneal)

The common peroneal nerve may be palpated on the lateral aspect of the distal femur just caudal to the proximal tibia. A 6 to 8 cm incision is made over this region, exposing the

fascia of the biceps femoris muscle. After the nerve has been palpated through the fascia, a small incision (4 to 5 cm) is made in the fascia while the fascia is elevated with a pair of rat-toothed forceps to prevent inadvertent damage to the nerve. The nerve may be seen as it passes over the lateral head of the gastrocnemius muscle. A 5-0 or 6-0 silk suture is placed through the caudal one fourth to one half of the nerve at the proximal end of the biopsy site, allowing minimal gentle traction as a 3 to 4 cm fascicular biopsy is excised using fine iris scissors. Severely diseased nerves may be markedly reduced in size and may appear almost translucent. Care should be taken to dissect as much fat and fascia from around the nerve as is possible. Wound closure is routine. External dressings normally are not required. Some animals may exhibit proprioceptive deficits, with knuckling of the distal pelvic limb on the side of the biopsy. This usually resolves within 3 to 4 days, and long-term deficits are uncommon.

Nerve Specimen Processing

The nerve should be placed immediately into fixative (usually glutaraldehyde). Contraction artifact is minimized by (1) pinning the nerve at either end to a piece of balsa wood; (2) suturing the nerve at either end onto the wooden stem of a cotton-tipped applicator; or (3) suspending the nerve in fixative with a stainless steel weight. The sample then may be transported to the laboratory in a sealed screw-top bottle. A nerve specimen also may be frozen in liquid nitrogen if specialized biochemical analysis is required. Specimens collected in this manner may be used for plastic embedding, teased fiber preparations, or electron microscopy.

CHAPTER 80

Buccal Mucosal Bleeding Time

Catharina Brömel

Examination of the patient with a suspected bleeding disorder includes assessment of vascular response and platelet function with formation of the platelet plug (primary hemostasis) and of the coagulation cascade leading to formation of fibrin and stabilization of the plug (secondary hemostasis). Persistent hemorrhage from superficial cutaneous injuries and mucosal surfaces (nasal, gingival, gastrointestinal, genitourinary) and formation of petechiae or ecchymoses are characteristic indicators of abnormalities in primary hemostasis. Primary hemostasis can be evaluated through quantitative measures (platelet estimate from blood smear, platelet count, mean platelet volume) and qualitative measures (von Willebrand factor [vWF] concentration and in vitro platelet function tests, such as aggregometry, aperture closure time, and flow cytometry). The buccal mucosal bleeding time (BMBT) is an in vivo, easily performed screening test for evaluation of primary hemostasis in dogs and cats.

Abnormalities in secondary hemostasis can cause hematomas, hemarthrosis, and bleeding into the pleural and peritoneal cavities. These abnormalities are identified by coagulation screening tests (prothrombin time, activated partial thromboplastin time, activated coagulation time, fibrinogen), proteins induced by vitamin K absence or antagonism (PIVKA), and individual coagulation factor assays.

Determination of the BMBT requires two people and can generally be performed without sedation in dogs. The materials needed are (1) a bleeding time device, such as the Simplate II R (Organon Teknika Corp., Durham, North Carolina), shown in Figure 80-1; (2) a gauze strip approximately 5 cm wide; (3) circular filter paper; and (4) a stopwatch.

The animal is placed in lateral recumbency. The upper lip facing the examiner is everted to expose the buccal mucosa, and the gauze strip is tied around the maxilla and mandible to cause moderate venostasis of the buccal mucosa (in sedated cats, the gauze strip can be tied through the open mouth around the cranium). The tear-away tab (see Figure 80-1) of the single or dual-blade spring-loaded bleeding time device is removed. The device is placed evenly against the exposed mucosal surface rostral to the gauze, with care taken to avoid visible blood vessels. The trigger is depressed, resulting in one or two standardized 5 mm by 1 mm mucosal incisions. The stopwatch is started at the time of trigger activation, and the device is removed from the mucosa. The filter paper is used to blot the blood in 5 second intervals about 2 mm from the incision; care is taken to avoid disrupting platelet plug formation by touching the incision (Figure 80-2). The blood should be prevented from reaching the animal's mouth, because this causes agitation. Blotting and the stopwatch are stopped upon complete cessation of hemorrhage, when blood is no longer absorbed by the filter paper. The BMBT is the time elapsed between mucosal incision and cessation of hemorrhage. If two incisions are made, bleeding generally stops at the same time at both sites. If not, the time should be recorded when the first incision ceases to bleed.

Published reference ranges for the BMBT are 1.4 to 3.5 minutes in dogs and 1.5 to 2.5 minutes in cats. For clinical purposes in dogs, a BMBT of less than 4 minutes is considered normal.

BMBT measurement is not indicated in animals with thrombocytopenia (less than 70,000/μL), because an abnormal result would be expected. Other causes of a prolonged BMBT are von Willebrand's disease (vWD), thrombocytopathies, and vascular disorders. Impaired platelet adhesion and aggregation are present in vWD, a hereditary deficiency of vWF that is reported in various dog breeds but is rare in cats. In a patient with a normal plasma vWF concentration and absence of thrombocytopenia, a prolonged BMBT suggests a defect in platelet function that can be congenital or acquired. Inherited thrombocytopathies (intrinsic platelet function defects) are rare. They include disorders of platelet membranes (e.g., Glanzmann's thrombasthenia in otter hounds and Great Pyrenees dogs) and disorders of platelet secretion (e.g., spitz and basset hound thrombopathy and platelet granule storage pool deficiency in American cocker

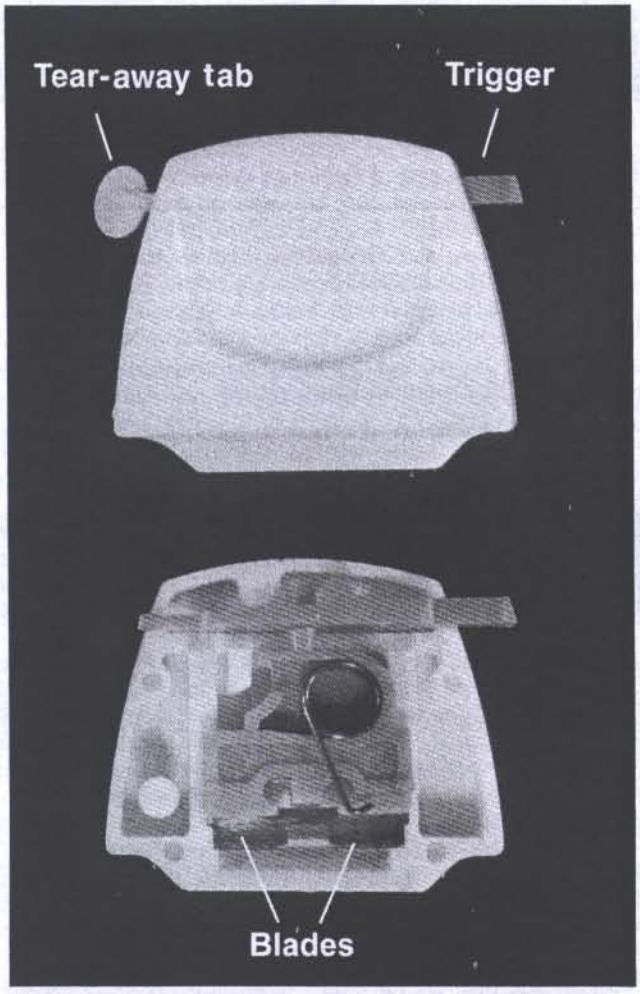


Figure 80-1 Disposable bleeding time device (Simplate II R). *Top*, Entire device. *Bottom*, Device with front cover removed, after tear-away tab has been removed and trigger pressed.

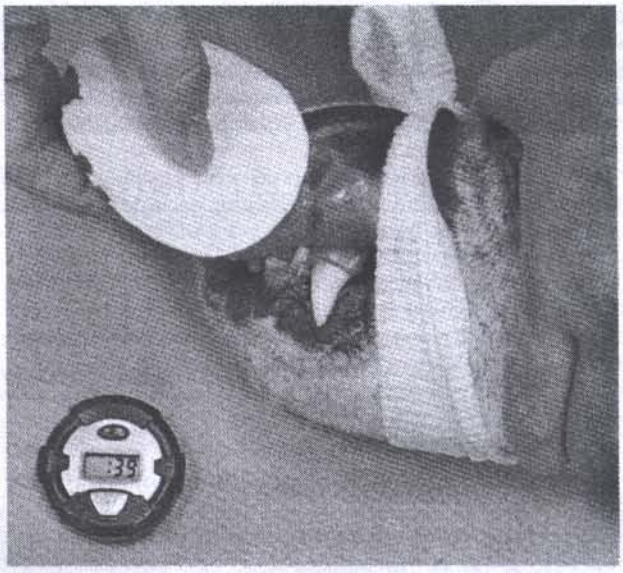


Figure 80-2 Determination of the buccal mucosal bleeding time in a dog.

spaniels and feline Chédiak-Higashi syndrome). These defects have been associated with a prolonged BMBT. However, not all conditions or agents that cause a platelet dysfunction are reported to result in an abnormal BMBT.

Acquired thrombocytopathies are seen in uremic animals, in whom the prolonged BMBT is primarily due to defective platelet adhesion. Platelet aggregation is not consistently altered in uremic animals. Uremic toxins are thought to play a role in the pathogenesis of this condition. A prolonged BMBT was noted after infusion of dextran 70 in dogs. Nonsteroidal anti-inflammatory agents interfere with platelet function through inhibition of cyclooxygenase 1 (COX-1), leading to decreased synthesis of thromboxane A_2, a platelet-aggregating and vasoconstricting factor. Aspirin was found to prolong the canine BMBT. Indomethacin did not prolong the BMBT in dogs; the same results were found for the weak COX-1 inhibitors carprofen and meloxicam. Reports on ketoprofen have been conflicting. Acquired thrombocytopathies associated with dysproteinemias and with disseminated intravascular coagulation (DIC) are thought to result from platelet coating by paraproteins and fibrin degradation products. Other causes of a prolonged BMBT include infectious diseases (feline retrovirus–induced thrombocytopathy, canine leishmaniasis and ehrlichioses e.g., *Ehrlichia canis, Ehrlichia platys*), myeloproliferative diseases, and vasculopathies, e.g., vasculitis and inherited vascular defects. Coagulation factor deficiencies do not produce an abnormal BMBT because functional primary hemostasis leads to the formation of an unstable platelet plug; however, rebleeding can occur.

The BMBT is a quick, useful cage-side test for evaluation of primary hemostasis. It requires minimal preparation and few materials, and it is fairly noninvasive, safe, cost-effective, and easy to perform. Results are available immediately, which allows efficient presurgical screening and repeated evaluation to assess response to treatment. The test can be used as a complement to in vitro function tests, which may not fully reflect platelet function in vivo. However, the BMBT procedure is affected by iatrogenic variables that could normalize the result. Reports on sensitivity and specificity for the detection of primary hemostatic disorders vary. A normal result does not eliminate a diagnosis of vWD or a platelet function defect, especially if the degree of dysfunction is mild. No correlation was found between the BMBT and plasma vWF concentration in dogs. The BMBT test is not standardized (e.g., degree of venostasis) and not reproducible. For any two readings in the same dog, the BMBT may differ by up to 2 minutes with one observer or between two observers. However, it is a valuable tool for the initial assessment of the patient with a suspected bleeding disorder, together with the signalment, medical history (e.g., congenital versus acquired thrombocytopathy), drug history, physical examination findings, and results of other hemostatic, biochemical, and hematologic parameters.

CHAPTER • 81

Jugular Catheterization and Central Venous Pressure

Darlene L. Riel

Catheterization of the jugular vein is a common method of achieving central venous access. Of the four general categories of intravenous access devices (winged needle, over-the-needle, through-the-needle, and multilumen catheters), the through-the-needle and multilumen catheters are favored for jugular catheterization. These catheters are available in a variety of lengths and diameters.

THROUGH-THE-NEEDLE CATHETERS

Through-the-needle catheters are catheters that are passed through a needle. The catheter is packaged in a protective plastic sleeve to prevent contamination. After catheter placement, the needle is withdrawn and a needle guard is applied to prevent trauma to the dog or cat and to protect the catheter from shearing.

MULTILUMEN CATHETERS

Multilumen catheters have two to five separate lumens in one catheter and are available in both the over-the-needle and through-the-needle designs. They are useful for administering two or more continuous infusions at the same time and/or for monitoring central venous pressure. Catheter placement is accomplished with the aid of a guide wire and a vein dilator.

JUGULAR CATHETERIZATION

Supplies and Patient Preparation for All Catheters

The catheterization supplies (Box 81-1) are gathered and arranged so as to be ready for use on a clean tray or countertop close to the patient. An appropriate-size catheter for the dog or cat is selected. The tip of the jugular catheter should reach the vena cava, close to the right atrium. The length to which the catheter should be inserted is determined by measuring from the expected catheter insertion site to the caudal edge of the triceps muscles.

Box • 81-1

Jugular Catheterization Supplies

- Clippers and antiseptic preparation solutions
- Through-the-needle catheter or multilumen catheter kit
- Antimicrobial ointment
- Sterile 2 × 2 gauze sponge
- Heparinized saline syringes
- Surgical drapes, if necessary
- Sterile gloves
- Small utility surgical set
- Suture material
- Injection cap (or caps) or T-port
- Bandage material
- Tape

Proper positioning of the dog or cat, usually in lateral recumbency, is crucial. An assistant should extend the patient's head and direct the front limbs caudally. The assistant should hold off the vein by pressing into the thoracic inlet. Placement of a bag of fluids, a sandbag, or rolled towels under the neck may help stabilize the vein. If the vein is not properly stabilized, it may roll laterally or crumple longitudinally. Hair should be clipped wide enough to prevent contamination during the catheterization procedure. Aseptic technique is used, and the site is prepared as would be a surgical site. Sterile drapes should be used if necessary.

Through-the-Needle Catheterization Technique

The operator should first inspect the through-the-needle catheter to make sure the catheter is retracted back into the needle and is not visible at the needle bevel. Grasping the needle firmly, with the needle bevel up, the operator inserts the needle through the skin and advances it subcutaneously parallel to the vein for at least 1.25 cm before it is introduced into the vein. Venipuncture is confirmed when a flash of blood is seen within the catheter. The operator then advances the needle well into the vein, holds the needle with one hand, and threads the catheter with the other hand by pushing the catheter hub within the protective plastic sleeve until the catheter hub is advanced into the needle hub. Pressure is applied at the catheter puncture site; the needle is backed out from the skin, and the plastic sleeve is disconnected from the needle. The needle is secured with a needle guard. If a wire stylet is present, it is removed from the catheter. The catheter then is capped with an injection cap or T-port. Placement is confirmed by successful aspiration of blood, and the catheter is then flushed with heparinized saline. The catheter is sutured close to the insertion site, and care is taken not to kink the catheter. The insertion site is covered with a sterile dressing. Finally, the catheter is secured with a stabilizing wrap.

Multilumen Catheter Technique

All the "pigtail" ports of the multilumen catheter are flushed with sterile heparinized saline, and injection caps are applied to all the ports *except* the most distal one. A No. 11 scalpel blade is used to make a full-thickness stab incision large enough to accommodate the vessel dilator (too small an incision makes it difficult to pass the dilator). The catheter introducer (usually an over-the-needle style catheter) is inserted, and the guide wire is fed through the catheter introducer and into the jugular vein. A length of wire is left exposed that is equivalent in length to the multilumen catheter. It is important that the operator control the wire so as to prevent contamination outside the sterile field and to prevent the wire

from slipping down the jugular vein. The catheter introducer is then withdrawn from the vein over the guide wire, leaving the guide wire in the vein. The vein dilator is threaded over the guide wire and advanced into the jugular vein to its full length. Some resistance is expected, and the dilator may need to be rotated or twisted to insert it into the jugular vein. Digital pressure is applied to minimize bleeding, and the dilator is removed from the vein and then withdrawn over the guide wire. *Care must be taken not to remove the guide wire!* The catheter is threaded over the guide wire until the operator can grasp the guide wire from the open pigtail injection port. The operator holds the guide wire and advances the catheter into the jugular vein to the predetermined length. Once the catheter is in place, the guide wire is removed, leaving the multilumen catheter in the vein. An injection cap is placed on the pigtail of the distal port, air is aspirated, and the port is flushed with heparinized saline. The catheter is then sutured in place, and the insertion site is covered with a sterile dressing. Finally, the catheter is secured with a stabilizing wrap.

CENTRAL VENOUS PRESSURE MEASUREMENT BY WATER MANOMETER

Central venous pressure (CVP) is a luminal pressure measurement taken from the intrathoracic portions of the cranial vena cava. The accepted normal range for CVP is 0 to 10 cm H_2O.

Supplies Needed for Central Venous Pressure Measurement

A catheter with the tip properly placed in the intrathoracic vena cava is required. The materials needed include a sterile bag of fluids with an attached fluid administration set, an intravenous fluid extension set, a three-way stopcock, and a water manometer.

Procedure

The dog or cat should be positioned in lateral or sternal recumbency. A water manometer is placed in the fluid line via a three-way stopcock and the extension set (Figure 81-1). The fluid administration set and the extension set are primed with sterile fluids from the fluid bag while the stopcock is in the "Off" position to the water manometer. There must be no air bubbles in the fluid lines. The primed extension set is attached to the patient's catheter. The stopcock at the bottom of the manometer should rest on the table or cage floor. The administration set is opened, again with the stopcock in the "Off" position to the manometer, to allow fluid to flow into the patient's catheter, thus ensuring that the catheter is patent. If fluid does not flow freely into the patient's catheter, a valid CVP measurement will not be obtained. Next, the stopcock is turned so that the "Off" position is now to the patient. The fluid will now fill the manometer, which is allowed to fill about three-quarters full. The stopcock then is turned "Off" to the fluids, allowing a pathway only from the fluid-filled manometer and the patient's catheter.

The level of fluid in the manometer falls until the hydrostatic pressure of the column of fluid reaches equilibrium with the hydrostatic pressure of the blood at the end of the catheter. Therefore it is essential to know where the catheter tip lies in relation to the manometer fluid column. When the animal is in lateral recumbency, the cranial vena cava lies near the midline, and the manubrium is a good reference point. When the animal is in sternal recumbency, the cranial vena cava is about at the level of the point of the shoulder or the scapulohumeral joint. With the stopcock resting on the tabletop or cage floor, a *zero reference point* is determined by a horizontal line drawn between the manometer and the appropriate external anatomic landmark (manubrium or scapulohumeral joint). The centimeter mark where the horizontal line intersects the manometer is the zero reference point. A carpenter's level fastened to a taut string is an excellent guide for the horizontal line from the anatomic landmark to the manometer. The difference between the equilibrium point reading and the zero reference point is the CVP measurement. For example, if the initial reading is 15 cm H_2O (where the fluid level stopped falling) and the zero reference point is 10 cm H_2O (horizontal line drawn between the external anatomic landmark and the manometer), the CVP is 5 cm H_2O. The presence of a well-placed, unobstructed catheter can be verified by the fluid column in the manometer, which will slightly oscillate up and down as the animal's heart beats or as the animal breathes. Readings are taken between ventilatory excursions. Trends in central venous pressure are more informative than single values. Each time a CVP measurement is obtained, the patient should be in the same recumbent position. The goal is to be consistent in taking the readings and to monitor the trends.

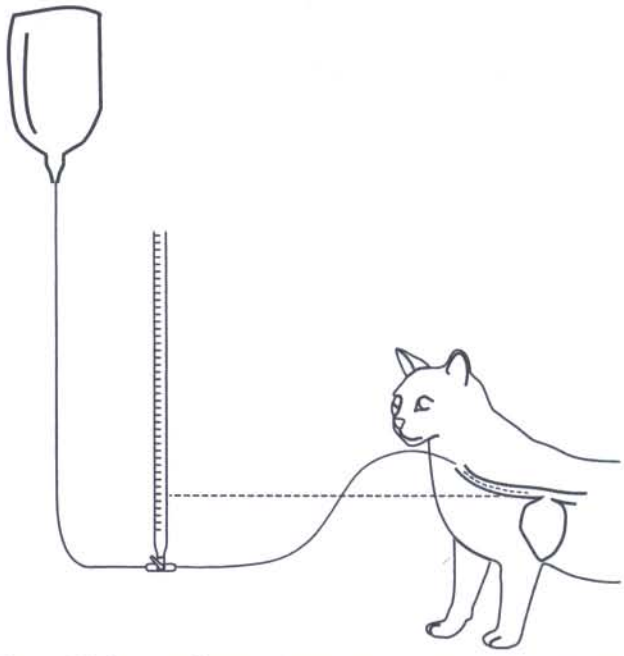


Figure 81-1 Setup for central venous pressure (CVP) assessment.

CHAPTER 82

Cerebrospinal Fluid Collection, Myelography, and Epidurals

Scott M. Anderson

CEREBROSPINAL FLUID COLLECTION

Cerebrospinal fluid (CSF) can be collected from the cerebellomedullary (CM) cistern or from the lumbar subarachnoid space. A larger volume of fluid is more easily obtained from the former, with less risk of iatrogenic hemorrhage.

Cerebellomedullary Cistern Collection

With the animal under general anesthesia, the operator clips and prepares the region for aseptic sample collection. If elevated intracranial pressure is suspected, the dog or cat is hyperventilated.

The animal is placed in lateral recumbency, with the neck flexed so that the long axis of the head is perpendicular to the spine. The spine and median plane of the head should be parallel to the table. Care should be taken to avoid hyperflexion of the neck, which can partially occlude the endotracheal tube and increase intracranial pressure by reducing jugular venous flow.

The midline is identified through palpation of the occipital crest. On the midline, just ahead of a line between the cranial edge of the wings of the atlas, a 22-gauge, 3.75 to 7.5 cm styletted spinal needle is inserted perpendicular to the long axis of the spine. In thick-skinned animals, a stab incision is made in the skin at the needle entry site so that the needle does not plunge into the spinal cord after being forced through the skin.

The needle is advanced slowly, in 1 to 2 mm increments. A pop and decreased resistance may be felt as the needle penetrates the dura. In cats and smaller dogs, this may be difficult to feel. The stylet then is withdrawn, and the operator checks for CSF flow. If none is seen, the stylet is replaced and the needle again is advanced in 1 to 2 mm increments, with the operator checking each time for CSF flow. If the needle strikes the occipital bone, it is "walked" off the caudal edge of the bone until it enters the CM cistern.

If no CSF flow is seen after further advancement, the operator should remove the stylet and withdraw the needle slowly, observing for CSF flow. If two unsuccessful attempts are made at CM cerebrospinal fluid collection, the operator should consider performing a lumbar tap rather than risking trauma to the cervical spinal cord.

If whole blood flows from the needle at any time, the needle should be withdrawn and the procedure repeated using a fresh needle.

Once CSF flow is seen, 0.5 to 2 mL is collected, depending on the animal's size, and the pressure is measured if desired. The jugular veins may be occluded to increase CSF flow. Aspiration with a syringe should be avoided, because this increases the risk of blood contamination. Only as much CSF as needed should be collected; removing a large volume of CSF may increase the risk of brain herniation (shift in intracranial contents), which is often fatal.

Blood in the CSF may be iatrogenic or pathologic. If blood is seen, the stylet is replaced for 1 minute, and sample collection is then resumed. Often the bleeding will have diminished. Iatrogenic hemorrhage often decreases as the fluid is collected. Therefore the first and second portions of the sample must be collected in separate tubes. If the degree of blood contamination is severe, an ethylenediamine tetra-acetic acid (EDTA) tube may be used to prevent clotting. Red blood cell contamination does not significantly correlate with the nucleated cell count or protein concentration.

If fluid analysis cannot be performed immediately, the addition of 30 µL of autologous serum per 250 µL of CSF has been shown to help preserve the structure of the cells in refrigerated CSF for up to 48 hours. If this process is used, a sample of unaltered CSF should also be submitted for determination of the protein concentration and total cell count.

If no flow can be obtained, the dog or cat may have suffered a brain herniation that is obstructing CSF flow. Attempts at CSF collection should be discontinued and hyperventilation instituted.

Lumbar Collection

For lumbar CSF collection, the animal is placed in lateral recumbency, with the hind legs pulled forward to flex the lumbar spine. A median or paramedian needle insertion site may be used. For a median puncture, the needle is inserted perpendicular to the spine just cranial to the L6 dorsal spinous process. For a paramedian placement, the needle is inserted slightly caudolateral to the L6 dorsal spinous process. The needle then is directed cranioventrally at an angle parallel to the plane of the dorsal intervertebral articulation (approximately 45 degrees to the spine). Fluoroscopy is helpful in confirming needle position.

The needle is advanced into the spinal canal. Aspiration of CSF from the dorsal subarachnoid space avoids needle-induced trauma to the spinal cord and is preferable, but obtaining fluid from this level is more difficult than obtaining it from the ventral subarachnoid space. Once the needle is felt to pass the articulation, the operator withdraws the stylet to check for CSF flow. If none is seen, the stylet is replaced and the needle is advanced in 1 to 2 mm increments, with the operator checking for CSF flow after each advance. Alternatively, the needle can be advanced until the tip contacts bone, and CSF then is withdrawn from the ventral subarachnoid space. The pathologist must be informed of the collection site: lumbar CSF has a slightly higher protein concentration and fewer cells than CSF collected from the CM cistern.

If no CSF is obtained, the needle is withdrawn in 1 mm increments, with the operator observing for CSF flow. If none is seen, collection at the L4 to L5 level can be attempted.

MYELOGRAPHY

Myelography (radiography after subarachnoid injection of a contrast medium) may be performed by either cervical (CM cistern) or lumbar injection. Cervical injection allows more

contrast medium to flow cranially into the cerebral ventricular system. In addition, a lesion causing severe cord swelling or compression may not allow the contrast medium to pass, resulting in only the cranial edge of the lesion being outlined. Lumbar injection, however, can be performed under pressure, forcing contrast medium past the lesion to outline the entire lesion and the full length of the spinal cord. For these reasons, a lumbar injection site is preferred.

The needle is placed as described above for CSF collection. Lumbar injection is typically done in the ventral subarachnoid space, because it can be difficult to position the needle tip in the dorsal subarachnoid space. Fluoroscopic guidance facilitates proper needle placement. CSF is collected prior to injection of the contrast media, because the CSF protein concentration and neutrophil count typically increase after myelography.

Use of a nonionic contrast medium (iohexal or iopamidol, 180 to 240 mg/mL) is advised. Metrizamide should not be used, because it poses a higher risk of complications, including seizures. A test injection of 0.2 mL of contrast medium should be performed, with fluoroscopic or radiographic confirmation that subarachnoid injection has occurred. The needle hub and injection set should be filled with contrast medium prior to commencing injection; this minimizes the appearance bubbles in the subarachnoid space, which may hamper interpretation.

Epidural leakage of contrast medium obscures the subarachnoid dye columns. If this is seen, the operator should withdraw the needle 1 to 2 mm and perform another test injection. If this does not produce opacification of the subarachnoid space, the operator should consider withdrawing the needle and selecting another injection site. Further incremental withdrawal could result in contrast medium being injected into the spinal cord parenchyma, with deleterious results.

After cervical injection and needle removal, the front half of the dog or cat is elevated to maximize the flow of contrast medium into the thoracic and lumbar subarachnoid space; lateral and ventrodorsal spinal radiographs are then obtained. Oblique views and dynamic studies may be helpful in some cases.

Transient exacerbation of neurologic impairment may be seen after myelography, particularly in large breed dogs, dogs with degenerative myelopathy, and dogs with chronic neurologic conditions. This usually resolves within a few days.

EPIDUROGRAPHY

Because the subarachnoid space typically does not extend to the lumbosacral junction, myelography is an unreliable means of assessing lesions caudal to L5. For this area, magnetic resonance imaging (MRI) scans are preferred. If MRI is not available, epidurography may be performed.

The tail base and dorsal sacral region are clipped and aseptically prepared. At any level from S3-CD1 through CD4-CD5, a 22-gauge, 2.5 to 7.5 cm styletted spinal needle is inserted on the midline perpendicular to the spine. With the needle tip on the floor of the spinal canal, 0.15 to 0.2 mL/kg of contrast medium is injected. With the needle in place, flexed, neutral, and extended lateral radiographs of the lumbosacral region are obtained. Supplemental injections of 0.1 mL/kg are given as needed for follow-up views. The needle then is removed, and a ventrodorsal radiograph is obtained.

Epidurography has no significant complications.

EPIDURAL ANESTHESIA

Epidural anesthesia may be administered as a single dose or may be given continuously through an indwelling catheter. To administer a single dose, a 20- to 22-gauge, 2.5 to 7.5 cm needle is inserted on the midline, perpendicular to the spine and slightly caudal to the L7 dorsal spinous process. A pop and decreased resistance are felt as the needle passes through the interarcuate ligament.

To verify that the needle tip is in the epidural space, sterile saline solution can be injected. There should be no resistance to injection if the needle tip has been properly placed. Alternatively, 3 to 4 mL of air may be injected. The bubbles produced do not significantly decrease the efficacy of the local anesthetic to be injected.

If CSF flow is obtained, the needle tip is in the subarachnoid space. This is uncommon, because the subarachnoid space typically does not extend to the L7 to S1 level. In this situation, a second attempt may be made to insert the needle into its proper epidural location. Alternatively, subarachnoid injection of a reduced dose of anesthetic may be performed (1 mL/10 kg body weight; that is, 50% of the epidural dose).

If blood flow is obtained, the needle should be withdrawn and another attempt made at proper placement. A local anesthetic should not be injected in this situation. Intravascular injection is contraindicated due to the risk of toxicity.

The selected local anesthetic can now be administered. Details of specific agents and dosages are beyond the scope of this chapter, but in general, approximately 1 mL/5 kg body weight is administered, to a maximum of 20 mL. For cesarean section, 1 mL/6 kg is reported to be sufficient. The anesthetic should be warmed to body temperature and injected over a 1-minute interval to minimize discomfort.

For continuous epidural anesthesia, a 17- or 18-gauge, 7.5 cm Touhy or Crawford needle is inserted and directed 30 degrees cranial, rather than perpendicular to the spine. The bevel is directed cranially. The catheter is advanced through the needle at least 3 cm into the epidural space, or farther, to the desired level in the lumbar or thoracic spine. If the catheter cannot be advanced, the operator injects a small amount of saline solution while again attempting to advance the catheter. If this fails, the needle and catheter are withdrawn simultaneously; if the catheter is withdrawn alone, it could be severed by the needle tip. If this occurs, most authors agree that surgery to retrieve the catheter fragment is not indicated.

Paresis of the nictitating membrane (the sympathetic innervation of which originates from T1 to T3) indicates blockade of spinal sympathetic outflow due to thoracic epidural anesthesia. This may produce hypotension, Horner's syndrome, and hypoglycemia. If the agent affects the cervical spinal cord, respiratory muscle paralysis can occur. In these cases, the thorax, neck, and head are elevated to decrease forward flow of the anesthetic agent and the patient is ventilated if necessary.

Other reported complications of epidural anesthesia include infection, seizures, insufficient or delayed onset of anesthesia, circulatory depression, Schiff-Sherrington–like reflexes, unilateral hind limb paresis, and partial anesthesia of the tail and perineum.

CHAPTER 83

Veterinary Diagnosis of Bacterial, Fungal, and Viral Disease

Janet E. Foley

INDICATIONS FOR TESTING

Infectious disease testing may be performed for a number of reasons; for example, to identify the etiology of an inflammatory disease, to follow up on a dog or cat with an infectious disease, to obtain an isolate for further testing (such as for antibiotic susceptibility), or to determine the risk of transmission of an infection to other animals or to people. Tests and interpretation vary, depending on the clinician's intent, therefore it is helpful to clarify the purpose for testing in each case. For example, if the goal is to determine whether an animal poses a risk to an immunocompromised human member of a household, it would be important to document active infection; thus culture or antigen-based tests would be used, not serology. It is important to evaluate test results in the context of the whole patient evaluation; documenting the presence of a pathogen does *not* prove that the pathogen is the cause of the animal's clinical signs.

TYPES OF TESTS: PROS, CONS, AND LIMITATIONS

Tests for infectious agents are either direct or indirect (Figure 83-1). *Direct tests* detect a pathogen, its nucleic acids, or its antigens. These tests include culture, polymerase chain reaction (PCR), antigen tests, and direct visualization. Direct methods may either document living (active) infection or may pick up an infection that no longer is active. Only culture documents that the infection is active at the time of sample acquisition, although cytology or histopathology can be suggestive. PCR or antigen tests may remain positive after effective treatment has been initiated; that is, after the target agent has died. For example, the blood of a bacteremic animal could be PCR positive for bacterial DNA for a few days after administration of antibiotics and after the animal has become culture negative. *Indirect tests* seek evidence of exposure to a pathogen by evaluating host response; these tests consist primarily of serology for specific host antibodies.

Good tests should be *sensitive* (high likelihood of detecting the infectious agent) and *specific* (low likelihood of a positive result if the agent is not present). Culture often is insensitive but highly specific. Bacterial culture often is negative in samples from animals recently started on antibiotics, and some agents may require days to weeks to grow in vitro. However, culture should be highly specific, depending on how well "positives" are further characterized in the laboratory. Culture has the additional advantages of providing an isolate for testing antibiotic, antifungal, or antiviral agents, molecular epidemiologic studies, and possible experimental infections. Culture sensitivity depends on sample handling (discussed below). *Many agents cannot be cultured*, therefore alternative methods for these organisms are critical and may be useful for improving sensitivity even for agents that can be cultured.

The "most direct" test is direct visualization, which also is insensitive, sometimes like looking for a needle in a haystack. Inflammation may be helpful in directing the attention of the clinical pathologist or microbiologist to the area containing organisms. Gram stains are useful in bacterial processes, because culture virtually always underestimates the number and diversity of bacteria, whereas a semiquantitative Gram stain can reveal both. Special stains, such as silver-based stains or calcofluor white (a fluorescent stain), can enhance spirochetes, some bacteria, fungi, and other organisms. Immunohistochemical stains use monoclonal or polyclonal antibodies raised against the pathogen to target areas in tissue where a pathogen is present, coupled with a technique for flagging the pathogen (usually either a fluorescent dye or a chemical chromogen).

PCR is emerging as a diagnostic powerhouse for bacterial, fungal, and viral infectious diseases. PCR is an iterated biochemical reaction performed in a *thermal cycler*, a machine that cycles repeatedly through a temperature series, so that a few target DNA fragments in a sample can yield millions of copies. Millions of same-size DNA fragments can be visualized on an electrophoretic gel. The trick to PCR is to find primers to start the reaction that anneal to a particular target and only that target. Thus *Hemobartonella felis* (now *Mycoplasma hemofelis*) primers should anneal only to *M. hemofelis* DNA and feline coronavirus primers only to feline enteric coronavirus (FECV) cDNA. There are several *universal primers*, which anneal to all bacteria or all filamentous fungi. After PCR is performed, the resulting fragment can be sequenced and the results checked against a data base to identify the bacterium or fungus present in the sample.

Even carefully designed PCR reactions occasionally have been found to amplify nontargets (when by chance, some other organism has a region of DNA to which the primers anneal), therefore it is important to verify PCR results with DNA sequencing, a DNA probe, a second PCR in another region of DNA, or some other method. Two other limitations of PCR are the feasibility of obtaining sufficient quality RNA or DNA from the clinical sample and inhibitors in the sample. RNA in viruses such as FECV, canine distemper, and others is prone to RNAse degradation and must be kept as cold as possible and processed rapidly in a laboratory using special techniques to protect the RNA. Delays in sample handling increase the rate of false-negative PCR results. DNA is more stable and can be shipped dried, frozen, at room temperature, in paraffin-embedded tissue, and so forth. Some pathogens are harder to "crack," in terms of obtaining DNA, particularly mycobacteria and many fungi. Blood, feces, ascitic fluid, ticks, and other samples have inhibitors that can make the reaction less sensitive. Also, PCR can become cross-contaminated with DNA in the laboratory, therefore positive results should be trusted only if the laboratory has excellent quality control and makes stringent use of negative controls.

Antigen tests are available for a few veterinary pathogens associated with high levels of antigen in a sample; some of these pathogens are feline leukemia virus (FeLV), *Cryptococcus neoformans*, and canine parvovirus. In other infections, such as feline immunodeficiency virus (FIV), antigen is insufficient to make such a diagnostic modality feasible.

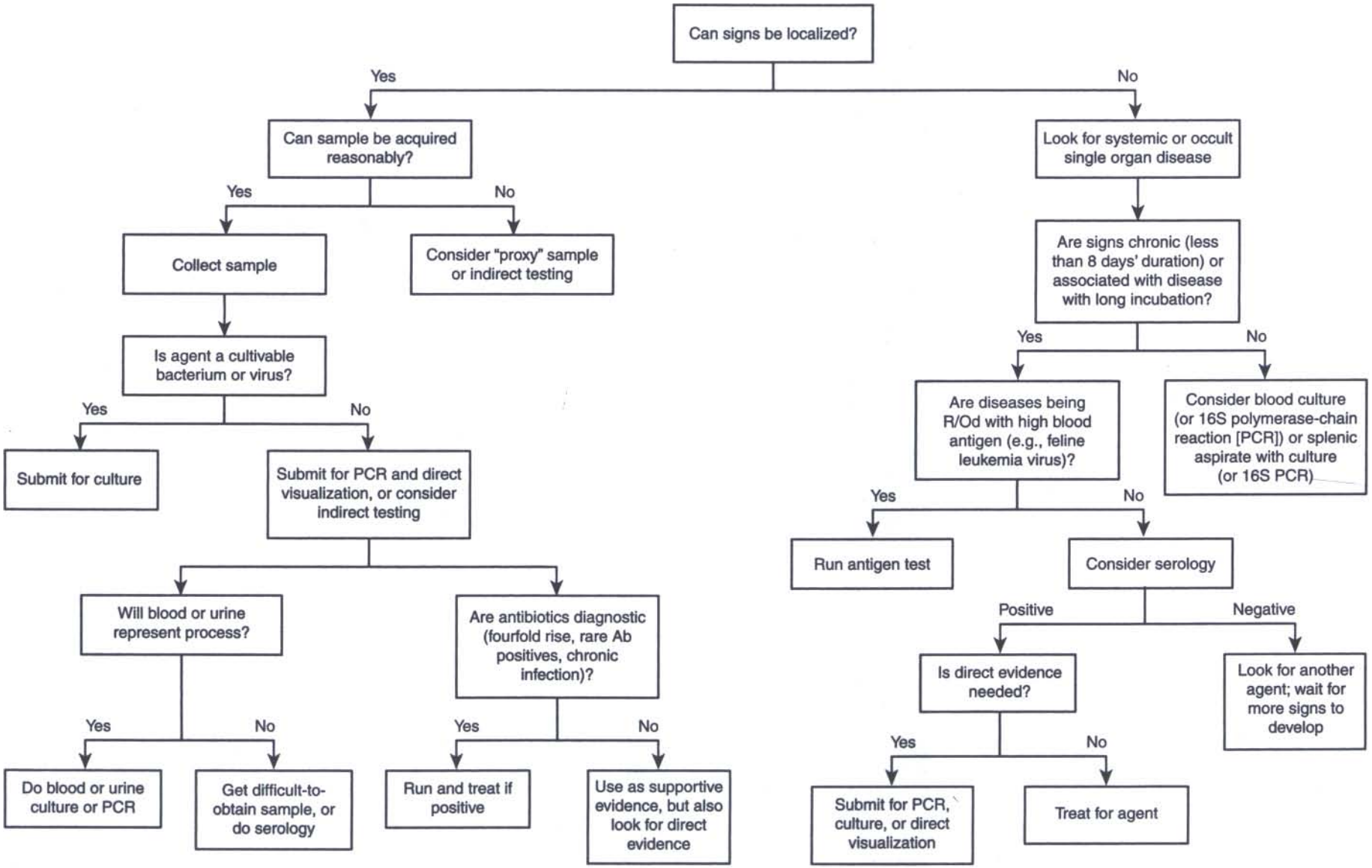


Figure 83-1 Algorithm for the diagnosis of bacterial, fungal, and viral diseases.

Antibody testing has several advantages. The sample typically is serum, which may be easier to obtain than, for example, tissue, and animals may remain seropositive for months after exposure, providing a larger window for testing. However, this large window may be a drawback as well, because the animal remains seropositive long after infection has resolved. In diseases that do not resolve (e.g., FIV), antibody testing documents infection; however, in other diseases, such as ehrlichiosis, serology only documents previous exposure. Serology has two other drawbacks: there is no detectable immunoglobulin G (IgG) early in infection (up to 10 to 14 days), and vaccines induce cross-reacting seropositivity in some diseases, such as feline herpesvirus, calicivirus, and canine parvovirus. Twofold or fourfold rises in titer over 2 to 4 weeks are helpful for documenting recent infection in some diseases (and are part of the human case definition for ehrlichiosis) but are not helpful in others (e.g., feline infectious peritonitis [FIP]). Negative titers in a disease process that has been ongoing for at least 2 weeks are extremely informative in terms of ruling out some infections.

SAMPLE COLLECTING, HANDLING, AND SUBMISSION

The packaging and transport of samples depend on the tests to be run. The requirements are:

- *Direct visualization, pathology, or immunohistochemistry:* Rapid transport, room temperature, and room air (unless formalin fixed)
- *Virus isolation, PCR, or antigen and antibody tests:* Frozen
- *Aerobic and fungal culture:* Cooled with room air
- *Anaerobic or microaerophilic bacteria:* Cooled with special atmospheres

Although each institution has a different configuration of laboratories, infectious disease diagnosis could involve clinical pathology, virology, immunology, microbiology, parasitology, biochemistry, and/or molecular biology. Clinicians should verify, through contact with the laboratory, how much sample and what paperwork are required to route the sample to all desired laboratories.

CHAPTER 84

Urogenital Diagnostic Procedures

S. Dru Forrester

CYSTOCENTESIS

Cystocentesis is indicated to collect urine for diagnostic evaluation and also to temporarily decompress the urinary bladder in animals with urethral obstruction. Obtaining urine from the urinary bladder bypasses contamination from the lower urogenital tract and is the preferred technique when samples are to be submitted for bacterial culture. When performed correctly, cystocentesis is a safe procedure. In most dogs and cats, a 22-gauge, 1.5-inch needle attached to a 12-mL syringe is used. For large or obese dogs, a 22-gauge, 3-inch spinal needle may be needed. If the urinary bladder cannot be palpated, ultrasound guidance is helpful for localizing it.

Cystocentesis can be done with the dog or cat standing or in dorsal or lateral recumbency. The bladder is palpated to determine the site for puncture. Usually the needle is inserted into the ventral or ventrolateral aspect of the urinary bladder. Hair can be clipped over the site and the skin prepared aseptically. However, in almost all situations this is unnecessary, and alcohol can simply be used to wipe the skin over the puncture site. The urinary bladder is immobilized with one hand, and the other hand is used to insert the needle through the abdominal wall (Figure 84-1). If the urinary bladder contains a small amount of urine or if cystocentesis is done therapeutically, the needle should be inserted near the urinary bladder neck, rather than at the apex, so that urine can be removed continually as the urinary bladder becomes smaller. Urine is aspirated by pulling back on the plunger to create negative pressure. If urine is not obtained, the needle is not redirected; rather, the needle is removed from the abdomen and the procedure is begun again. Excessive pressure on the urinary bladder during and immediately after aspiration

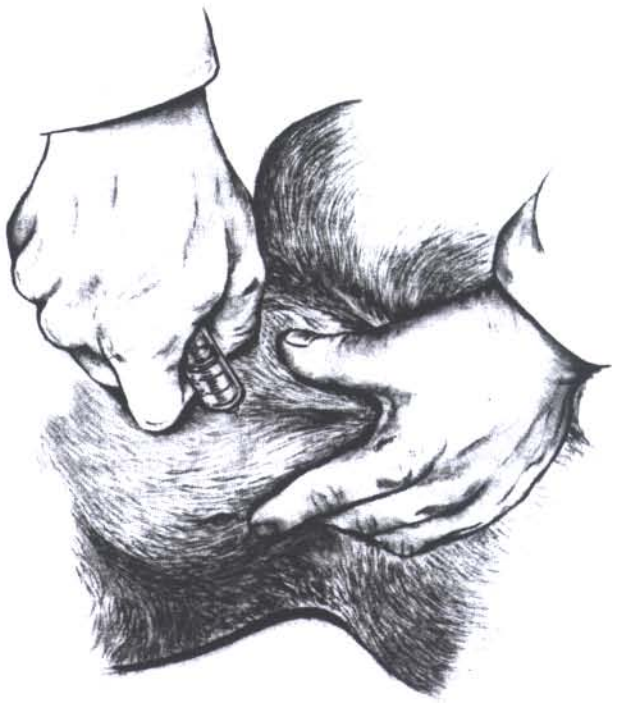


Figure 84-1 During cystocentesis the urinary bladder is immobilized with one hand while the other hand is used to insert the needle into the urinary bladder and aspirate urine.

should be avoided to prevent leakage of urine into the abdominal cavity.

If the urinary bladder cannot be palpated and ultrasound is not available, cystocentesis can be done "blindly." Although this technique may not be as effective, it can be attempted if a dog or cat cannot be hospitalized during the day or is likely to void frequently due to pollakiuria. The pet is positioned in dorsal recumbency, and a puncture site is selected on the midline, halfway between the umbilicus and pelvic brim (this is often the point where alcohol pools when dripped onto the area in female dogs). In male dogs, the penis and prepuce should be retracted laterally so that the needle can be inserted into the abdomen on the midline. Urine is aspirated as described above. If a sample is not obtained, the needle is removed and aspiration is attempted at a site just cranial or caudal to the original puncture. If urine is not obtained after a total of three attempts, cystocentesis should be delayed until the urinary bladder can be palpated.

URETHRAL CATHETERIZATION

Transurethral catheterization is indicated to collect urine for analysis or bacterial culture (primarily in male dogs), to measure urine output, to inject radiographic contrast material, and to relieve urinary retention secondary to functional or anatomic urethral obstruction. Potential complications include iatrogenic urinary tract infection (more likely in females) and urethral or urinary bladder trauma. Catheterization should always be performed aseptically using a sterile catheter. Flexible catheters (e.g., rubber) are appropriate for the collection of urine for diagnostic purposes and are less traumatic than polypropylene catheters. Urethral catheters with an inflatable balloon near the tip (e.g., Foley catheters) are useful for indwelling catheterization in female dogs. Catheters are available in a variety of sizes and lengths. Catheter diameter is most often expressed in French (F) units (3F = 1 mm). For male dogs, depending on the animal's size, catheter diameters of 3.5 to 5F (<10 kg), 8 to 10F (10 to 25 kg), and 10 to 12F (>35 kg) are appropriate. Catheters ranging from 5 to 14F are adequate for most female dogs.

Male dogs should be restrained in lateral recumbency, and an assistant should retract the prepuce to expose the penis. The tip of the penis should be cleansed with a mild antiseptic solution. The length of catheter needed to reach from the distal end of the penis to the neck of the urinary bladder should be estimated; this helps avoid overinsertion of the catheter, which could damage the urinary bladder mucosa. The tip of the catheter should be lubricated with a sterile, water-soluble lubricant from a single-use packet. The urinary catheter should be maintained in sterile condition during catheterization; this may be accomplished by using a sterile hemostat, wearing sterile gloves, or using a cut portion at the end of the catheter package to advance the catheter (Figure 84-2). The tip of the catheter is inserted into the external urethral opening and gently advanced. Some resistance may occur as the catheter is advanced through the area of the os penis and again at the ischial arch. If the catheter has been inserted to the appropriate level and urine is not observed, a syringe is attached to the catheter to aspirate urine. After urine collection, the catheter is gently removed from the urethra.

Urethral catheterization is more technically difficult in female dogs, and sedation may occasionally be helpful in some cases (e.g., with small or fractious dogs). Catheterization may be performed using a speculum (e.g., human nasal speculum, otoscope cone) to visualize the urethral orifice or blindly, with or without digital palpation. Selection of technique depends on the preference and experience of the clinician and the temperament of the dog or the size of the vagina. It is helpful to insert a lubricated, sterile, metal stylet or 3.5F polypropylene catheter through the lumen of the Foley catheter to increase its rigidity and facilitate its passage. The stylet should be advanced to the tip of the Foley catheter to prevent it from exiting the eye of the catheter and causing urethral damage during placement.

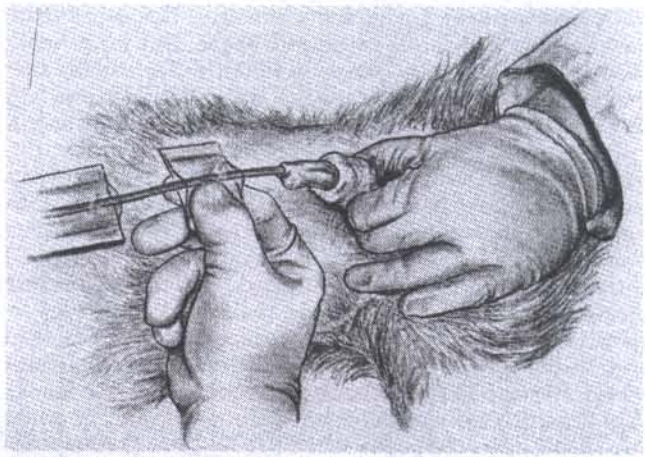


Figure 84-2 Urethral catheterization of a male dog. A portion of the catheter's package is used to aseptically advance the catheter through the urethra.

Female dogs are most easily catheterized while standing or in sternal recumbency with the rear legs hanging over the end of a table; an assistant should hold the tail to one side. Excessive hair around the vulva should be clipped, if necessary, and the area should be cleansed with antiseptic soap. A lubricated tuberculin syringe is inserted into the vagina, and 0.25 to 0.5 mL of local anesthetic (e.g., 0.5% lidocaine or topical ophthalmic anesthetic) is instilled in the area of the urethral orifice (approximately 3 to 5 cm cranial to the vulvar opening). While sterile conditions are maintained, the tip of the catheter is lubricated with water-soluble lubricant.

For the visual technique, the vaginal speculum is lubricated and the tip is gently inserted dorsally through the vulva and then directed cranially to avoid the clitoral fossa. The blades of the speculum are opened gently so that the urethral orifice can be visualized. The handles of the speculum should be directed dorsally so that they do not interfere with visualization. A sterile glove is worn to pick up the catheter; the tip is inserted through the urethral orifice, and the catheter then is gently advanced into the urinary bladder. If the catheter is to remain in place, air or saline is injected to inflate the balloon at the catheter tip.

For the digital technique, the person passing the catheter should wear sterile gloves. A lubricated index finger is inserted into the vagina, and the urethral orifice is palpated. The other hand is used to insert the catheter ventral to the finger in the vagina; the catheter is guided ventrally on the midline so that it enters the urethral orifice (Figure 84-3). If a finger cannot be inserted into the vagina, the catheter can be passed blindly. After the catheter has been inserted through the vulva, it is directed ventrally along the midline of the vestibular floor and advanced cranially. If resistance is encountered, the catheter has most likely advanced past the urethral orifice to the cervix. If this occurs, the catheter is withdrawn and the procedure is repeated. If urine is not noted from the

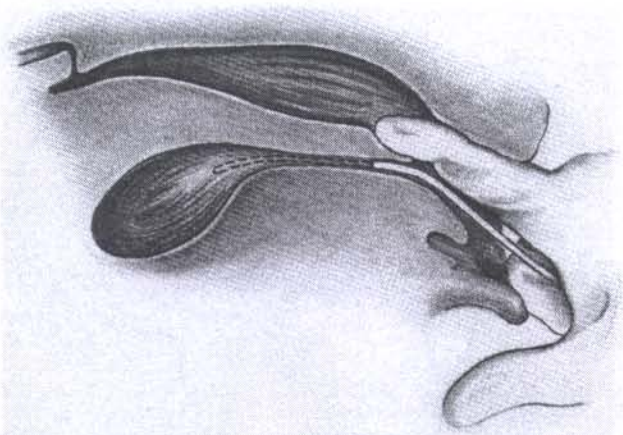


Figure 84-3 Urethral catheterization of a female dog. An index finger is placed over the urethral orifice to guide the catheter ventrally into the urethra.

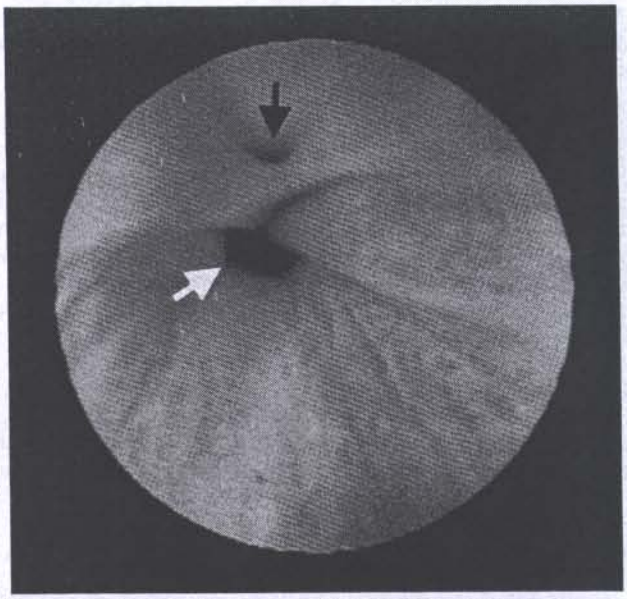


Figure 84-5 Urethroscopy of female Labrador retriever with incontinence since birth. Note the urethral lumen *(white arrow)* and the ectopic ureter entering the urethra *(black arrow)*. (Courtesy Dr. Patti Sura, Virginia Tech.)

catheter, a syringe is attached and urine is obtained through aspiration.

ASPIRATION/BIOPSY OF UROGENITAL MASSES

Tissue specimens may be obtained from urogenital masses (i.e., vagina, prostate gland, urethra, and urinary bladder) for cytologic and histologic evaluation by a variety of methods, including endoscopy, ultrasound-guided aspiration, and catheter-assisted biopsy. Catheter-assisted biopsy can be performed without the need of special diagnostic equipment.

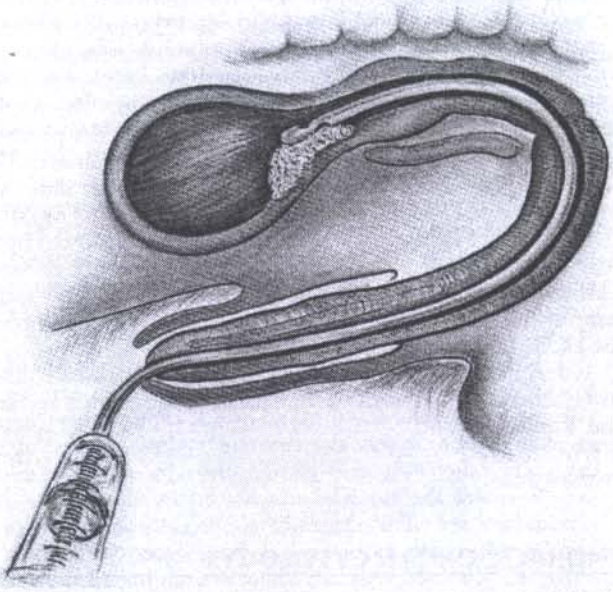


Figure 84-4 Passage of a flexible rubber catheter through the urethra of a male dog to aspirate tissue samples from a mass at the trigone of the urinary bladder.

Sedation may be helpful in fractious dogs. The location of the mass should be confirmed by physical examination or diagnostic imaging studies (e.g., ultrasound, contrast urethrography). As described above, a flexible urinary catheter with side openings (eyes) on the distal end should be passed into the urinary bladder and all urine removed. The tip of the catheter should then be withdrawn to the level of the mass (Figure 84-4). The location of the catheter tip can be confirmed by digital palpation per rectum or by radiographs if a radiopaque catheter is used. A 12-mL syringe containing sterile saline is attached, and all but 1 mL is injected through the catheter. The plunger is pulled back to create negative pressure, and mucosal pieces are aspirated into the side openings of the catheter. If the mass is located in the prostate gland, vigorous palpation of the prostate per rectum during aspiration may facilitate collection of prostatic tissue.

After the sample has been collected, negative pressure is released and the catheter is removed from the urethra. The tip of the catheter is placed in a vial, and additional saline is injected through the catheter to remove tissue samples. Any solid pieces of tissue should be placed in formalin and submitted for histologic evaluation. The remaining saline, containing small fragments of tissue, should be evaluated cytologically.

CYSTOSCOPY

Cystoscopy may be indicated for the evaluation of dogs or cats with hematuria, signs of lower urinary tract inflammation, recurrent urinary tract infections, urinary bladder or urethral masses, urolithiasis, and urinary incontinence. Procedures that can be performed include visualization of the urethral and urinary bladder mucosa, collection of tissue samples from masses or other lesions, removal of uroliths, collection of urine from individual ureters for diagnosis of renal hematuria or

pyelonephritis, and identification and location of ectopic ureters (Figure 84-5). Rigid or flexible cystoscopes can be inserted through the urethra of female dogs and cats; however, only flexible endoscopes can be used in males.

Cystoscopy is performed under general anesthesia with the dog or cat in lateral or dorsal recumbency. Hair should be clipped around the vulva, and the area should be gently scrubbed with antiseptic solution. Sterile gloves should be worn to assemble the cystoscope. The tip of the cystoscope is lubricated and then gently inserted into the vestibule. Sterile saline is infused through the fluid port of the cystoscope to distend the mucosa and allow visualization of the urethral orifice (Figure 84-6). The scope then is inserted through the urethral orifice and advanced slowly, allowing the urethra to be distended so that it can be examined thoroughly. After the cystoscope has been advanced into the urinary bladder, urine is drained completely and the bladder is distended with sterile saline. The entire urinary bladder mucosa should be examined. It may be helpful to examine the urinary bladder when it is distended at low pressure and also at high pressure. After cystoscopy an antimicrobial (e.g., ampicillin) should be given for 5 days to prevent urinary tract infection secondary to bacterial contamination.

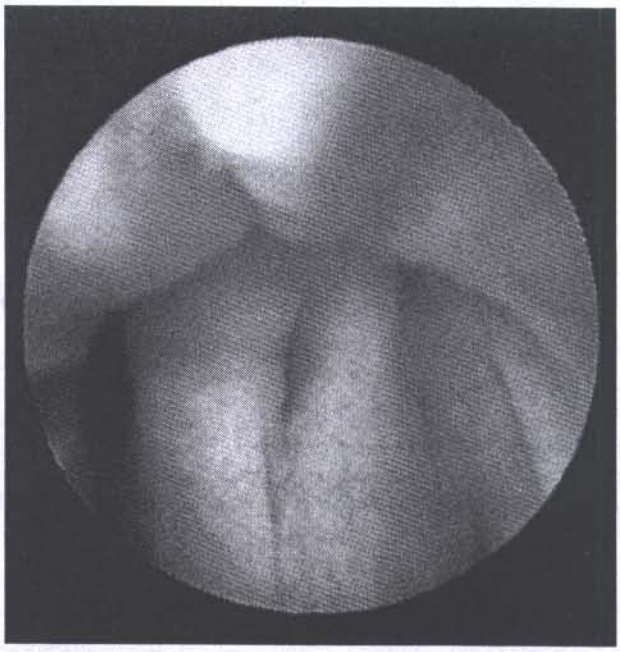


Figure 84-6 Urethral orifice on the ventral floor of the vagina in a female dog undergoing cystoscopy.

CHAPTER • 85

Cytology of Internal Organs

Amy L. MacNeill
A. Rick Alleman

Cytologic evaluation of internal organs is a powerful diagnostic technique. It is imperative that samples be collected and processed properly and that a well-maintained microscope is used. This chapter briefly describes proper sample handling and some diseases of internal organs that can be diagnosed cytologically.

ASPIRATE COLLECTION AND PREPARATION

Ultrasonography is recommended to guide sample collection and to monitor the dog or cat for bleeding. It is possible to obtain some samples without sedation. Aspiration of internal organs must be considered a sterile procedure. The center of large masses should be avoided, because this area is often necrotic. Multiple samples should be taken so that different areas of the lesion are represented. If fluid is collected, some should be smeared directly onto a slide, and the rest should be saved for determination of cell counts and protein content and concentration. If the fluid is bloody, it should be placed in an ethylenediamine tetra-acetic acid (EDTA) tube. Also, cytologic examination of touch preparations from nonfixed biopsy samples can be informative.

If generalized splenomegaly or hepatomegaly is detected, blinded aspiration can be performed but is not recommended. The animal should be placed in dorsal recumbency. A 6- to 12-cc syringe is attached to a 20- to 22-gauge, 1.5-inch needle. The needle is introduced into the caudodorsal aspect of the spleen or liver to avoid piercing the diaphragm. The plunger is pulled back to create 1 cc of vacuum. The needle position is carefully redirected within the organ. The pressure on the plunger is released, and the needle is withdrawn. The sample is placed near the frosted edge of a clean slide and smeared by placing a second slide flat onto the sample slide and pulling the second slide from the frosted edge to the open edge of the sample slide in one continuous, smooth motion. The weight of the second slide is sufficient to smear the sample. It is important not to pull the sample off the end of the slide.

Once a sample has been collected, it should be air dried and stained for cytologic examination. New methylene blue and Romanowsky-type stains are commonly used. If a slide is sent to a laboratory, it should be shipped separately from histology samples.

THORACIC ORGAN CYTOLOGY

Pulmonary Aspirates

Aspirates from normal pulmonary tissue tend to be hemodilute and contain low numbers of respiratory epithelial cells and macrophages. Inflammation caused by most bacterial agents is

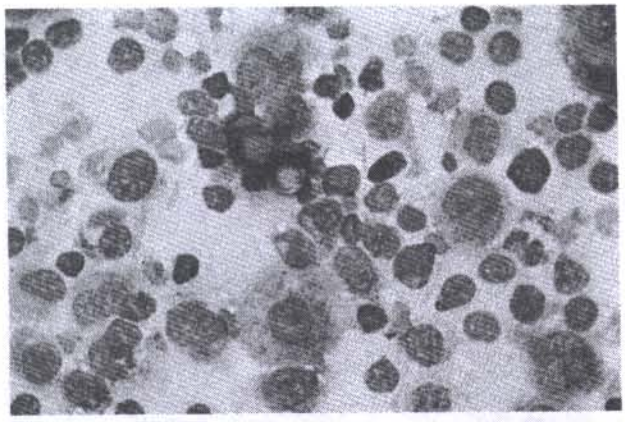


Figure 85-1 Blastomycosis. Several round organisms, approximately 15 µm in diameter and having a nonstaining capsule, are characteristic of *Blastomyces* infection. Infiltrating macrophages and lymphocytes are also noted. (Wright-Giemsa stain, ×250.)

purulent, whereas fungal infections cause pyogranulomatous disease. Culture is recommended with most inflammatory samples. Several specific fungal diseases can be diagnosed cytologically, including blastomycosis (Figure 85-1). Carcinomas tend to exfoliate as sheets of epithelial cells with visible cell junctions, basophilic cytoplasm, and round nuclei. Acinar structures or punctuate cytoplasmic vacuoles may be observed with adenocarcinomas (Figure 85-2). Metastatic carcinomas can rarely be distinguished from primary lung tumors. As with most malignant lesions, features such as anisocytosis, anisokaryosis, prominent nucleoli, an increased nuclear to cytoplasmic ratio (N:C), mitotic figures, coarse chromatin, and multinucleation must be observed for diagnosis. Also, inflammation can cause epithelial cells to have characteristics of malignancy; neoplasia, therefore, often cannot be reliably diagnosed if inflammation is observed.

Heart-Based Tumors

Echocardiography and anesthesia are necessary to obtain aspirates of heart-based masses. Hemangiosarcomas exfoliate poorly and are hemorrhagic with low numbers of basophilic, spindle-shaped cells with large pleomorphic nuclei, multiple prominent nucleoli, and other features of malignancy. Erythrophagia may be noted within neoplastic cells and macrophages. Neuroendocrine tumors, including chemodectomas and aortic body tumors, contain aggregates of pale blue cytoplasm with

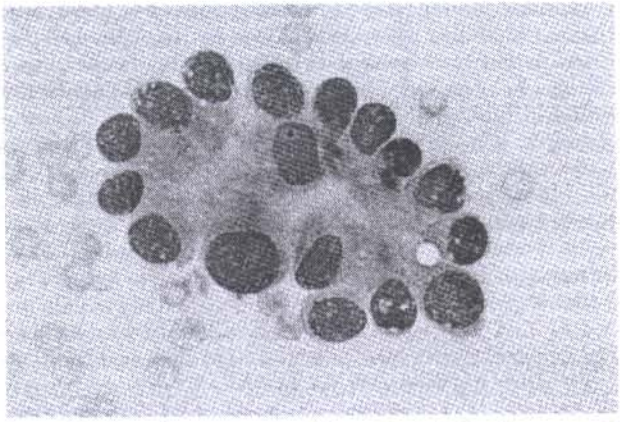


Figure 85-2 Adenocarcinoma, lung. Epithelial cells arranged in an acinar structure are pictured. Note the marked anisokaryosis and prominent nucleoli. (Wright-Giemsa stain, ×250.)

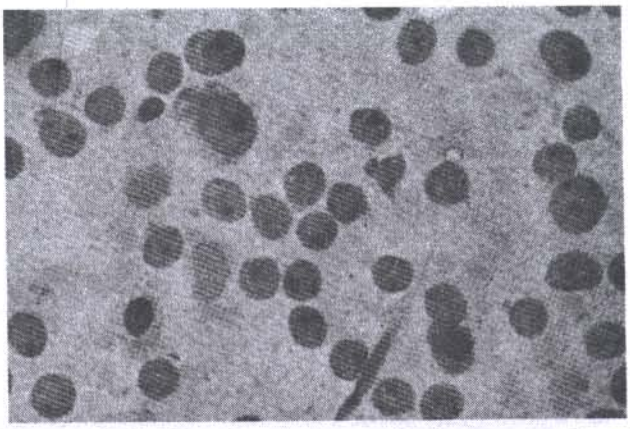


Figure 85-3 Heart-based neuroendocrine tumor. Round "naked" nuclei with single prominent nucleoli can be seen. (Wright-Giemsa stain, ×250.)

indistinct cell borders that are associated with round "naked" nuclei (Figure 85-3). Minimal characteristics of malignancy are seen with large heart-based masses because these tumors tend to be benign.

Thymus

Thymic enlargement can be caused by a thymoma or thymic lymphoma. Thymomas contain large clusters of thymic epithelial cells, large numbers of small lymphocytes, low numbers of intermediate to large lymphocytes, and mast cells (Figure 85-4). Thymic epithelial cells have a moderate amount of blue-grey cytoplasm and single round nuclei. Eosinophilic material may be associated with the cells. Thymic lymphomas have a predominant population of intermediate or large lymphocytes with scant, deeply basophilic cytoplasm, round to pleomorphic nuclei, and prominent nucleoli.

ABDOMINAL ORGAN CYTOLOGY

Liver

Normal hepatocytes are large cells that occur in clumps with distinct cytoplasmic borders and abundant, basophilic cytoplasm (Figure 85-5). The nuclei are round and contain a distinctive, large, single nucleolus. Vacuolar degeneration is a common cytologic finding and is classified as either glycogen or lipid

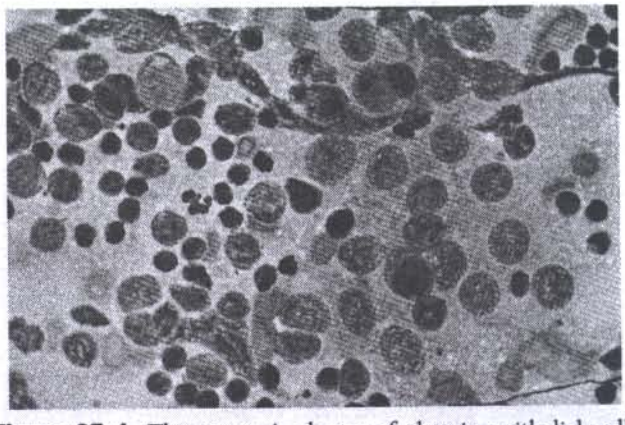


Figure 85-4 Thymoma. A cluster of thymic epithelial cells with a moderate amount of cytoplasm and large round nuclei are shown. Several small lymphocytes, low numbers of large lymphocytes, a neutrophil, and a mast cell are also present. (Wright-Giemsa stain, ×250.)

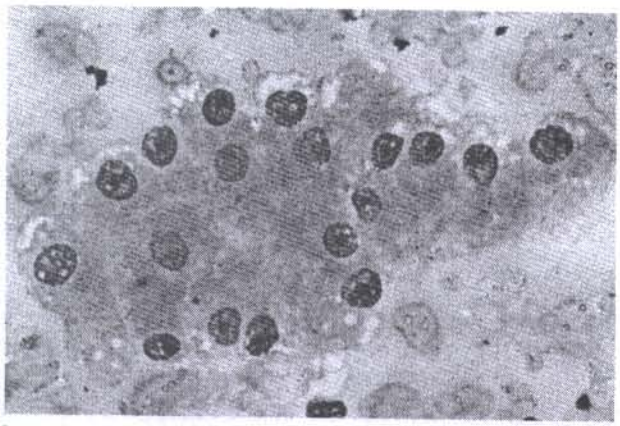


Figure 85-5 Normal liver. Hepatocytes have abundant cytoplasm, round nuclei, and single prominent nucleoli. (Wright-Giemsa stain, ×250.)

accumulation. Glycogen accumulation appears as a diffuse cytoplasmic clearing that is most prominent in the periphery of the cytoplasm (Figure 85-6). Glycogen accumulation is seen in dogs with steroid hepatopathy, nodular hyperplasia, or idiopathic vacuolar degeneration. Hepatocytes with lipid accumulation contain discrete, clear cytoplasmic vacuoles (Figure 85-7). Severe lipid degeneration is almost exclusively seen in cats with hepatic lipidosis syndrome. However, mild to moderate lipid degeneration can be seen as a secondary response to diseases such as diabetes mellitus, pancreatitis, cholangiohepatitis, or hepatic lymphoma. Hepatic cholestasis is characterized by the presence of dark blue bile pigment within the cytoplasm of hepatocytes or in casts between adjacent hepatocytes. This is a common finding in hepatobiliary disorders and precedes the onset of icterus.

Due to the focal nature of many inflammatory lesions, cytologic identification of inflammatory liver disease may be difficult. Tumors commonly found in the liver include hepatocellular carcinoma (HCC), bile duct carcinoma, lymphoma, and hemangiosarcoma. The diagnosis of HCC is made when anaplastic cells with differentiation toward mature hepatocytes are aspirated from a hepatic mass. These cells have a cytoplasm similar to that of hepatocytes with nuclear features of malignancy, particularly a high N:C, anisokaryosis, and extremely prominent nucleoli. Bile duct carcinomas contain dense clusters of epithelial cells that are smaller than hepatocytes and have a very high N:C and scant, basophilic cytoplasm.

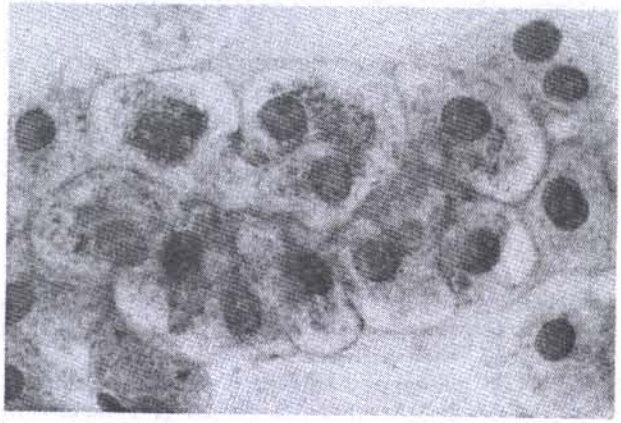


Figure 85-6 Steroid hepatopathy. Indistinct cytoplasmic vacuoles concentrated at the borders of hepatocytes indicate excess glycogen storage in the liver. (Wright-Giemsa stain, ×250.)

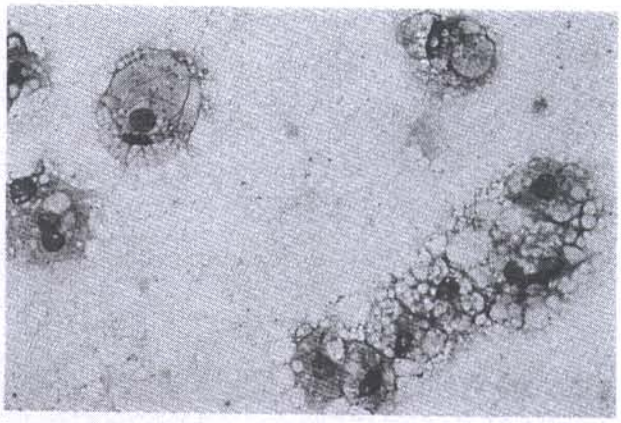


Figure 85-7 Hepatic lipidosis. The cytoplasmic vacuoles observed with lipid accumulation in the liver are large and distinct. (Wright-Giemsa stain, ×125.)

Nuclear features of malignancy are usually present with the exception of nucleoli.

Spleen

Aspirates from normal spleen are hemodilute with clusters of splenic reticular elements, large numbers of small lymphocytes, moderate numbers of intermediate to large lymphocytes, and low numbers of plasma cells and mast cells. Common cytologic diagnoses associated with generalized splenomegaly are extramedullary hematopoiesis (EMH) and lymphoma. EMH may be observed when the peripheral demand for erythroid or myeloid cells exceeds production in the bone marrow. All stages of erythroid and myeloid precursors, as well as megakaryocytes, can be present. Splenic lymphoma is difficult to diagnose due to the mixed population of lymphocytes in a normal spleen. If a monomorphic population of either intermediate or large lymphocytes makes up greater than 70% of the cells, splenic lymphoma can be suspected. The most common cause of splenic nodules is nodular hyperplasia, which is indistinguishable from normal spleen when aspirated. Hemangiosarcomas, hemangiomas, or hematomas cause large hemorrhagic splenic nodules that can be difficult to differentiate cytologically.

Intestinal Tract

Intestinal aspirates tend to be poorly cellular with low numbers of epithelial cells. Lymphocytes may be seen due to lymphoid tissue associated with the intestine. Inflammatory bowel disease and lymphoma also have lymphocytes. In all of these cases, small lymphocytes can predominate, which prevents a definitive cytologic diagnosis. However, large granular lymphoma is easily diagnosed cytologically. Infectious diseases may also be observed. Figure 85-8 is an example of intestinal pythiosis. Intestinal carcinomas contain dense clusters of epithelial cells with deeply basophilic cytoplasm, round to pleomorphic nuclei, prominent nucleoli, an increased N:C, and other features of malignancy. Acinar formation is observed with adenocarcinomas (Figure 85-9).

Kidney

Aspirates of enlarged kidneys require anesthesia and ultrasonography. Renal aspirates are hemodilute with rare clusters of renal tubular epithelial cells that have abundant blue cytoplasm, distinct cell borders, and round nuclei. Clear cytoplasmic vacuoles may be seen. A diagnosis of lymphoma is made if increased numbers of lymphocytes are observed. Inflammatory lesions may be purulent or pyogranulomatous and should be cultured. Renal carcinomas are rare.

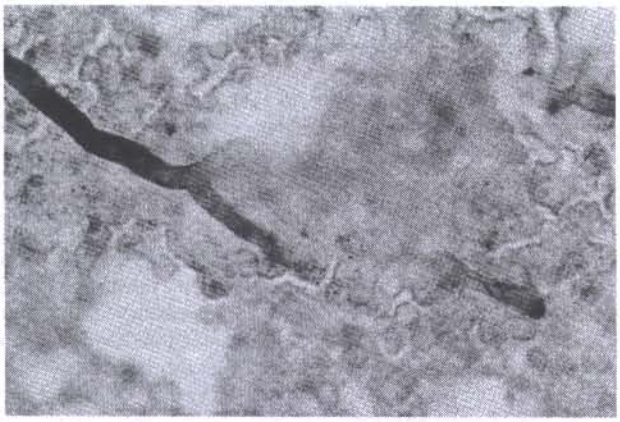


Figure 85-8 Pythiosis, intestine. *Pythium* organisms cause severe pyogranulomatous inflammation with increased numbers of eosinophils. Septate branching hyphal structures stain black with silver stain. (Grocott's methenamine silver [GMS] stain, ×250.)

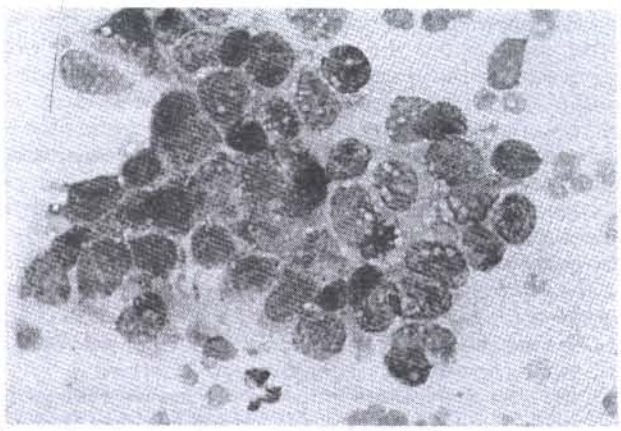


Figure 85-9 Adenocarcinoma, intestine. A cluster of intestinal epithelial cells with distinct cell borders, variably sized nuclei, an increased N:C, and multiple nucleoli are shown. Acinar formation is observed. (Wright-Giemsa stain, ×250.)

CHAPTER • 86

Cytology of the Skin and Subcutaneous Tissues

Deborah C. Bernreuter

Cytology should be regarded as a *rapid screening test* to determine if a biopsy, culture, or surgical excision is necessary. Quite often cytologic examination is the only test needed to arrive at a diagnosis, prognosis, and treatment plan. A representative cytologic sample at least can yield a short list of possible diagnoses. If the cytologic evaluation is not completely diagnostic, a biopsy is required to rule out or to confirm various differential diagnoses. When the cytologic results are considered in conjunction with the patient's history; the location, description, and duration of the lesion; the physical examination results; diagnostic imaging findings; and other laboratory determinations, the list of differential diagnoses becomes quite short.

REQUIRED EQUIPMENT

The following equipment is required for obtaining an adequate representative sample for cytologic evaluation:

- 22-gauge needle (21- to 23-gauge needles also can be used)
- 12-cc syringe
- Unused glass slides, preferably with frosted ends for ease of labeling
- Lavender-top tube (for fluid)
- Sterile swab (for fistulous tracts and mucous membranes) and saline
- Paper towel (for impression smears)

If the cytologic evaluation is to be done in-hospital, a good quality, well-maintained binocular microscope, a "quick" type of Romanowsky stain, and distilled water are also required.

PROCEDURE FOR SAMPLE COLLECTION

Samples from Solid Masses or Fluid-Filled Lesions

For solid masses and fluid-filled lesions, a 22-gauge needle on a 12-cc syringe is usually used to collect and transfer cells or fluid (or both) to several glass slides. Sedation or anesthesia can be used if required to reduce risk and unnecessary pain. Local anesthesia is not used on superficial lesions, because the pain associated with aspiration of a sample is no greater than the pain felt during injection of the local anesthesia. Skin preparation is the same as that required for a venipuncture or an injection. If the lesion will also be sampled for microbiologic culture, surgical preparation should be done on the collection site.

Before the sample is collected, four glass slides should be made ready to receive it. This minimizes clotting of the sample in the needle, which can occur while slides are located to receive the sample. It is not necessary to submit more than four smears; even a single smear can be adequate if it is representative.

The needle is attached to the syringe while the plunger is depressed. One hand is used to grasp the lesion firmly to stabilize it, and the other hand is used to insert the tip of the needle deep into the mass. Inserting the needle deeply into the mass yields a larger sample than inserting the needle only superficially. When the tip of the needle is in a representative location, the plunger of the syringe is pulled back as far as possible and *held* for a few seconds. *The plunger is never pumped!* The pumping action that is useful in the collection of bone marrow samples is harmful for cells in all other anatomic sites. It causes excessive tissue damage, and encourages bleeding

and clotting (release of tissue thromboplastin). The direction of the needle within the mass should be changed only when the needle has been almost completely withdrawn so as to avoid excessive tissue destruction and subsequent lysis of cells, which would occur with an attempt to change the direction of the needle while it is still embedded in the mass. Aspiration can be done in two or three different orientations in the mass to collect the most representative sample. The hub of the needle where it is attached to the syringe must be watched; *blood must not be allowed to flow into the syringe*. Blood dilutes a previously representative sample and causes clotting. If blood appears while the plunger is withdrawn, the plunger (and thus the vacuum pressure) is released immediately. A needleful of cells is sufficient to make a dozen smears if necessary.

Only after the vacuum in the syringe has been released is the needle removed, first from the lesion and then from the syringe. A small amount of air is then drawn into the syringe, the needle is reattached, and the plunger is rapidly advanced *while the needle's tip is close to a glass slide* (i.e., not from a great height). In this way, the sample is expelled onto the slide intended, and it does not inadvertently shed a few cells onto the adjacent slide. On several occasions this author has identified misdiagnoses made because a few tumor cells or organisms were inadvertently sprayed onto adjacent slides, which, because they grossly appeared to be unused slides, were then used to prepare smears from a different patient. When slides are prepared to receive cytology samples, they should not be placed close to each other, to avoid overspray.

Liquid Samples

If the sample is liquid, only one drop of sample should be placed on each slide so that when the sample is smeared *rapidly* to make a feathered edge (and thus a monolayer of cells), *the entire smear will be one half to three fourths the length of the slide*. If too large a drop is accidentally expelled onto a slide, the excess is immediately reaspirated into the syringe. It is helpful if an assistant who can make a feathered edge is available to smear out the drop of sample as soon as one is placed on a slide, while additional drops are being placed on additional slides. If the sample consists of a large amount of fluid, a couple of feathered edge smears are made, and the remaining fluid is expelled into a lavender-top tube. *Watery fluid* is smeared correctly by raising the angle between the sample slide and the spreader slide to 50 to 60 degrees and smearing very quickly. *Thick fluid* is smeared to a monolayer by lowering the angle to 25 to 30 degrees and smearing slightly more slowly. Normal blood is smeared with a 45-degree angle. Any remaining fluid should be expelled into a lavender-top tube and mixed well to avoid clotting so that accurate cell counts can be attained and smears of concentrated cells can be prepared. The ethylenediamine tetraacetic acid (EDTA) in the lavender-top tube is the preservative of choice for accurate cell morphology. Heparin can distort cells. Both the fresh smears and the fluid are submitted to the laboratory. At the laboratory, some of the fluid can be placed in a cytocentrifuge for production of concentrated smears. Cytocentrifuges concentrate the cells directly onto a small area of a glass slide, which is especially useful with fluids of low cellularity. In addition, some of the fluid can be centrifuged and a drop of sediment (or buffy coat smear, if the sample is very hemorrhagic) can be prepared, stained, and examined.

Semisolid Samples

If the sample is semisolid, another slide should be placed flat on top of the sample and the two slides should be gently pulled apart to make monolayers on both slides. With either the direct smear or the "pull" technique, *all smears should be thin enough to air dry within 1 minute*. The smears should be double-checked to ensure that they are completely dry before they are encased in a slide holder for transportation to a laboratory.

An *impression smear* can be useful with a biopsy sample. Before the biopsy sample is placed in formalin, its cut surface can be blotted with a paper towel to remove surface blood and tissue fluid and then touched to a glass slide several times to make an impression smear.

Samples from Mucous Membranes of the Vagina, Conjunctiva, and Mouth and from Fistulous Tracts

For sampling the mucous membranes of the vagina, conjunctiva, or mouth or for sampling fistulous tracts, a sterile swab moistened with saline can be used to swab the lesion. If the lesion is already moist, the saline is not needed. The tissue is swabbed, and the swab then is *rolled* onto a glass slide. *Never rub the swab on the slide;* it causes disruption of the cells.

COMMON MISTAKES TO AVOID IN COLLECTION AND PREPARATION OF CYTOLOGY/FLUID SAMPLES

The following common mistakes should be avoided in sample collection and preparation:

1. *Pumping the syringe plunger during collection.* This causes tissue destruction and lysis of cells and also increases the risk of clotting due to release of tissue thromboplastin.
2. *Using a syringe with a capacity of less than 10 cc.* If the syringe is too small, the vacuum pressure it creates is too weak, and the sample is often too small for adequate evaluation.
3. *Placing too large a sample on one slide.* If the drop of sample is too large, the consequences are (1) the largest cells are pushed off the end of the smear, resulting in a nonrepresentative sample; (2) a monolayer is not formed, and the smear will be too thick for evaluation; and (3) thick smears dry slowly, causing cell lysis and distortion.
4. *Failing to smear out the sample.* A drop of sample left in one place on the slide dries slowly, causing lysis, and forms a thick jumble of cells, which cannot be evaluated. If two cells are on top of each other, neither can be evaluated. If excessive cell fragility is present (as in some lymphomas and other tumors), the cells might not be able to survive smearing, and a biopsy would be necessary for evaluation.
5. *Refrigerating the smears.* When smears are placed in slide holders and then refrigerated, the ambient humidity from the room air in the holder condenses, causing droplets of water to fall onto the smears. Water is hypotonic and causes cell lysis; only a homogeneous, proteinaceous background is observed on cytology.
6. *Placing the slides in the slide holder before they are completely dry.* Slow drying causes lysis of cells. If cells are lysed and then placed near an ice pack while liquid, the cells crystallize into shapes of long spears, preventing evaluation.
7. *Submitting samples for cytology or fluid analysis without including the signalment, patient history, and other physical findings, as well as the anatomic location, a description, and the duration of the lesion.* Without these other parameters, only a description, not an interpretation, is possible.
8. *Submitting fluid without EDTA.* Fluid is always submitted for analysis in an EDTA tube, and a fresh smear is submitted as well for accurate cell counts (without clots).

DETERMINING THE CHOICE OF CYTOLOGY OR BIOPSY

The choice of cytology or biopsy depends on the type and location of the lesion. For discrete masses in the intradermal and subcutaneous tissues, a fine needle aspiration biopsy is

often diagnostic. It is useful for identifying the mass as a site of inflammation, a cyst, or a solid tumor. In addition, if the lesion is a site of inflammation, the etiology (e.g., bacteria, fungal elements, yeast, parasites, or keratin debris from a ruptured epithelial cyst) can often be observed. Bacteria can be identified as cocci, rod shaped, spirochetes, possible anaerobes, mycobacteria, or a mixed population, which can be helpful in choosing an appropriate class of antibiotic while awaiting results of a culture and sensitivity test. If Gram stain is also available, additional samples can be used to determine Gram positivity or negativity. If the lesion is a solid tissue tumor, an experienced cytologist can further classify it as epithelial or mesenchymal in origin and list any criteria of malignancy observed. If it is a round cell tumor, cytology is often sufficient for diagnosis.

If the lesions are vesicular, however, such as pemphigus lesions, cytology is not useful. Instead, an intact vesicle (or at least the edge of a vesicle if none is intact) is gently excised, and the tissue is placed in formalin for biopsy. For other superficial lesions (e.g., ulcers) that are not associated with a mass, a biopsy of the edge of the lesion is usually more helpful than cytology. If a dermal mass has an ulcerated surface, impression smears of the lesion will contain only the secondary inflammatory cells and organisms; they will not be representative of the primary lesion underneath. For this reason, an aspirate of the deeper layers of the mass would probably be more representative.

CHAPTER 87

Ear Flushing

Kinga Gortel

Most cases of acute otitis externa in cats and dogs can be managed by treatment with topical medications and ear cleaning administered by owners. There are, however, many instances in which in-clinic ear flushing is essential for the successful resolution of otitis. The most common indication for ear flushing is failure of owner-administered therapy to clear an infection within a reasonable period (2 to 4 weeks). Ears containing exudate that cannot be removed by simple cleaning respond poorly to topical medications, which are unable to reach the target tissue and pathogens. Another common indication is the presence of purulent exudate associated with Gram-negative bacteria, such as *Pseudomonas*. Ear flushing is also recommended when there is a suspicion of otitis media, a foreign body, or otic neoplasia.

Ear flushing allows evaluation of the ear canal and tympanic membrane, and myringotomy if necessary. It permits cleaning of the tympanic bulla and its sampling for culture and cytology. It also facilitates removal of foreign bodies and visualization and sampling of masses.

Complications from ear flushing are infrequent in dogs but more common, although usually transient, in cats. These include vestibular symptoms, deafness, Horner's syndrome, and facial nerve paralysis. The possible need for myringotomy to fully evaluate and treat a diseased ear should be explained to the owner. Owners are often unaware that the tympanic membrane usually heals after myringotomy. Ear flushing, however gentle, during another anesthetic procedure should be avoided unless the owner has been forewarned of possible side effects. It is important to understand the anatomy of the external and middle ear, because it may be severely altered by chronic inflammation.

If ear canal stenosis, glandular hyperplasia, or edema prevent passage of an otoscope tip, ear flushing should be postponed until the canal can be rendered more accessible by a 1- to 2-week course of topical and systemic corticosteroids (e.g., prednisone, 1 mg/kg given orally daily for dogs). If severe stenosis persists, surgical intervention is more likely to result in a favorable outcome than ear flushing and medical therapy.

Sedation suffices for ear cleaning only when minimal exudate is present; general anesthesia is required for full cleaning or myringotomy. An endotracheal tube with an inflated cuff is used to prevent lower respiratory tract contamination via the auditory tubes.

Bulla radiographs or computed tomography is recommended prior to the ear flush when otitis media is suspected. These procedures allow evaluation of otic structures, including the bulla.

Various ear flushing techniques utilizing hand-held and video-otoscopes have been described. The procedure should allow removal and sampling of exudate in the outer ear canal, a myringotomy if needed, and sampling and cleaning of the bulla.

Ear flushing in dogs utilizing a hand-held otoscope may be performed as follows. While the patient is prepared for anesthesia, swabs for culture and cytology are collected from each ear. The ear canals are then filled with a mild ceruminolytic ear cleaner. Once the dog has been anesthetized and intubated, an ear bulb syringe and warmed irrigation saline solution are used to gently remove the exudate and ear cleaner. All the ceruminolytic agent must be removed from the ear canal to prevent irritation. The ear canal must not form a tight seal with the bulb syringe in order to avoid tympanic rupture. A new bulb syringe should be used for each patient. Once the flushing yields clear fluid, the canal can be suctioned with an 8 French polypropylene catheter (cut to the desired length) on a 12-cc syringe introduced through the otoscope. The tip of the catheter may be heated over a flame to smooth sharp edges. The ear should then be examined, and flushing should continue via the catheter until the canal appears clean. Repeated flushing, suctioning, and re-evaluation may be needed. An ear curette can be used to remove tenacious exudate, and grasping tools, such as alligator forceps, can be used to remove hair, wax balls, or foreign bodies. Finally, the ear canal should be thoroughly suctioned.

Ear flushing in cats is performed similarly. Pretreatment with a ceruminolytic agent is not recommended due to the higher incidence of complications from ear flushing in this species.

Video-otoscopy facilitates ear flushing procedures and permits documentation. Video-otoscopes provide greater magnification and resolution than hand-held units. Working channels allow simultaneous flushing and visualization. In contrast, when a hand-held otoscope is used, the visual field may be obscured by instruments and fluids.

Also, the stream of saline from the flushing catheter can be directed more effectively at adherent material using a video otoscope. A relatively simple technique uses a 5 French polypropylene catheter attached to a 20-cc syringe. An assistant flushes warmed saline solution in pulses while the tip of the catheter is moved within the ear canal by the operator. Pretreatment with a ceruminolytic agent and cleansing with an ear bulb syringe are still helpful but less necessary. Alternatively, a three-way stopcock may be attached by intravenous tubing to a 1 L bag of saline solution for flushing and to a syringe or suction apparatus for removing saline from the ear. A dual-port attachment may also be used for simultaneous infusion and suction.

After thorough cleaning, the area of the tympanic membrane can be evaluated. Obliteration of the tympanum in cases of chronic otitis is common but may be confusing unless one has extensive experience in observing the normal location of this structure. If the otoscope tip has been advanced as far as possible and the tympanum is not seen, it is likely absent. The intense light source in video-otoscopy may make the lining of the tympanic cavity appear reflective and white, confusing the operator by its similarity to the tympanum. If the tympanum is absent or partially ruptured, material from the middle ear is obtained by passing two sterile swabs into this area, preferably through a sterile otoscope cone. The first swab is cultured, and the second is used for cytologic evaluation. The middle ear cavity should be gently flushed to remove exudate or ceruminolytic agent.

Diagnostic and therapeutic myringotomy should be performed if otitis media is suspected, because the tympanum is frequently intact despite a middle ear infection. Otitis media should be suspected in cases of chronic, relapsing, or unremitting otitis, when the tympanum appears abnormal, when neurologic signs are present, or when radiographic evidence is present. Myringotomy allows collection of samples from, and thorough flushing of, the middle ear. After the ear canal has been cleansed and dried, the myringotomy incision may be made using a 5 French polypropylene catheter, an open-ended tomcat catheter, or a calcium alginate swab or with a short CO_2 laser pulse. The incision should be made in the caudoventral quadrant of the tympanic membrane to minimize the damage to the tympanic germinal epithelium and middle ear structures. The middle ear should be sampled and flushed as described above, using a catheter passed through the myringotomy incision.

Essential to the successful outcome of the ear flush is the ability to keep the ear clean, therefore topical and oral antimicrobial agents should immediately be initiated based on cytology. Once or twice daily ear cleaning by owners is prescribed, and a 1 week follow-up is scheduled. Saline solution may be used in an ulcerated ear or immediately after myringotomy. Oral corticosteroids are recommended to facilitate at-home treatment and to reduce the production of inflammatory exudate in painful or ulcerated ears. At the 1 week follow-up, topical and oral antimicrobial agents may be changed, based on the culture results, and a more effective ear cleaner prescribed.

CHAPTER • 88

Ear Vein Blood Glucose Monitoring

Melanie D. Thompson

In dog and cats with diabetes mellitus, owner observation of clinical signs and in-hospital evaluation of serial blood glucose curves are common methods both of assessing glycemic control and of determining the dosage and type of insulin to be used and the frequency of administration. For these blood glucose curves, affected dogs and cats are typically hospitalized and blood samples are collected at 1- or 2-hour intervals by means of direct venipuncture of a peripheral vein. Hospitalization, restraint for blood sample collection, and venipuncture have all been associated with stress hyperglycemia (especially in cats), and some hospitalized pets may not eat. This can complicate interpretation of the resulting blood glucose curve.

Most human diabetics perform self-monitoring of blood glucose concentrations using a portable blood glucose meter (PBGM) and capillary blood, which is collected by pricking a fingertip with a lancet device. Portable blood glucose meters are being used more frequently to generate serial blood glucose curves in diabetic dogs and cats. These meters are inexpensive, require only a single drop of blood for analysis, and provide results rapidly. In addition, the results obtained with these meters have been shown to correlate with those obtained by reference laboratories. When only a small amount of blood is required for analysis, use of an ear vein for blood sampling can minimize patient discomfort, preserve the integrity of peripheral veins, and decrease the need for physical restraint during sample collection. Recent studies have shown that the marginal ear vein nick technique is a reasonable alternative to venous blood collection for serial measurement of blood glucose concentrations. Studies have also shown good correlation between the glucose concentration of capillary and venous blood. Two methods of capillary blood sampling from the ear of dogs and cats are described here. Both methods are fast and easy to perform.

The first technique utilizes conventional lancet devices designed for pricking the fingertips of human beings. A device with a variable needle depth should be chosen. This allows the appropriate depth to be selected in order to provide an adequate amount of blood for the test (dogs usually require greater depth compared to cats). Although any portion of the inner pinna can be sampled, the marginal ear vein (MEV) usually results in the best sample. First the MEV is identified, then a warm, damp gauze sponge (or warm washcloth) is applied to it to increase perfusion as needed (Figure 88-1, *A*). A thin film of Vaseline can be placed over the sampling site in longhaired pets to allow the drop of blood to form without dissipating into the fur. The automatic lancing device should then be placed over the vein (Figure 88-1, *B*); the ejected needle will nick the ear, causing a drop of blood to form (Figure 88-1, *C*).

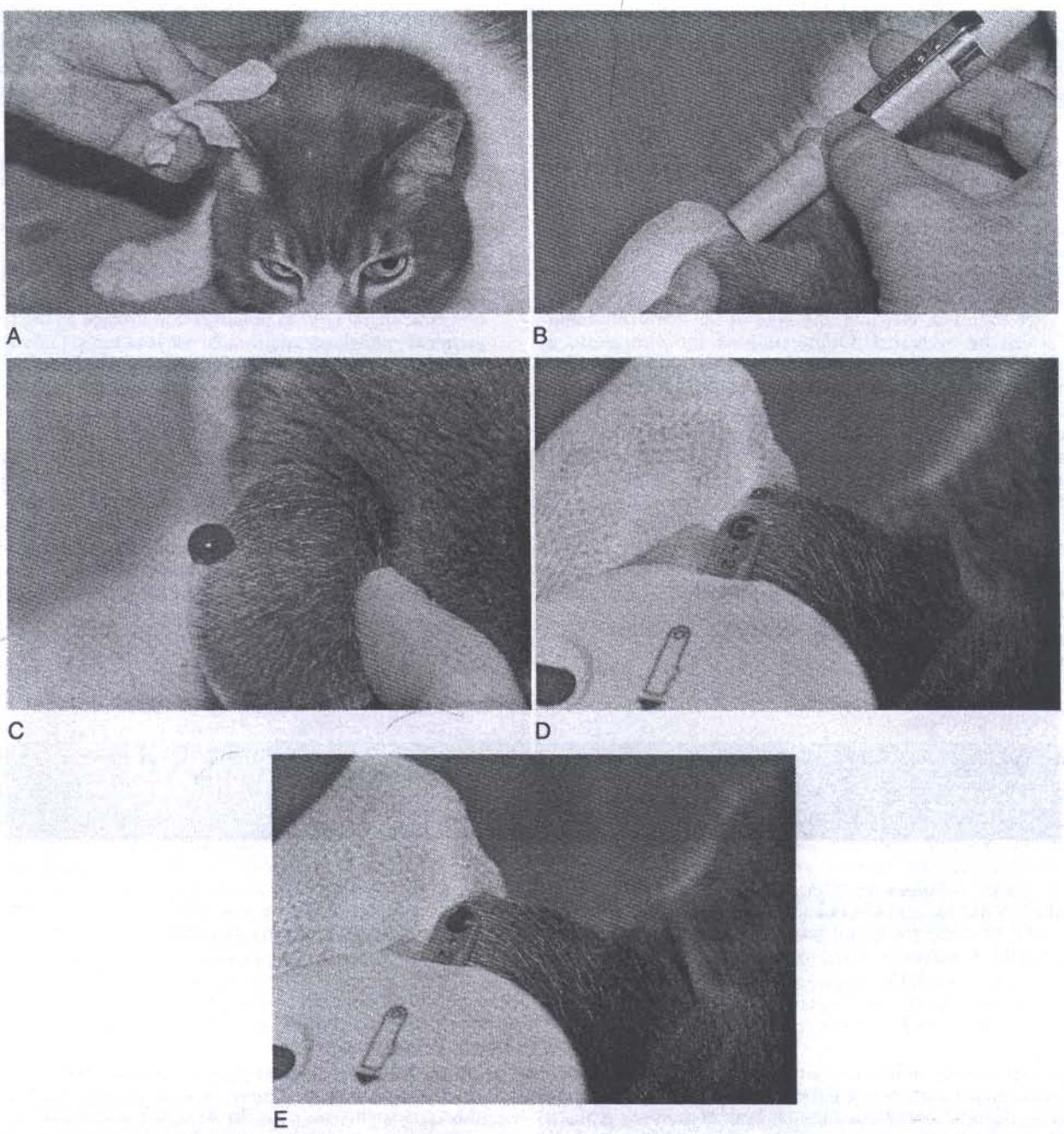


Figure 88-1 A, A warm, damp gauze sponge is applied to the ear vein to increase perfusion. B, The automatic lancing device is placed over the ear vein. Note that the gauze is folded so that the individual performing the test does not inadvertently get nicked. C, After the ejected needle nicks the ear, a drop of blood will form. D, The PBGM with the test strip already inserted is applied to the drop of blood. E, The drop of blood is aspirated by capillary action into the reaction chamber after contact with the test strip.

The person performing the test should place a folded gauze sponge between the ear and the individual's finger to avoid an inadvertent nick. The PBGM with the test strip already inserted is then applied to the drop of blood to measure the blood glucose concentration (Figure 88-1, *D* and *E*).

The second technique utilizes a vacuum lancing device, the Microlet Vaculance (Bayer Diagnostics, Tarrytown, New York), to facilitate collection of an adequate drop of blood (Figure 88-2, *A*). The device was designed to allow blood collection from body sites other than the fingertips in human beings. It also has variable needle depth. This technique allows sampling of the inner pinna in dogs and cats. The tip of the ear is held between the thumb and index finger, and the surface of the pinna is held flat by the rest of the fingers (Figure 88-2, *B*). The lancet device then is set on a nonhaired area of the ear. An airtight seal between the device and the ear is obtained by pushing the outer ear against the device with the tip of one finger. The entire edge of the endcap must be in contact with the skin (Figure 88-2, C). The site is lanced by pressing the plunger cap down until it comes to a complete stop. While pressure is maintained between the endcap and the skin, the plunger is slowly released. This creates a negative pressure,

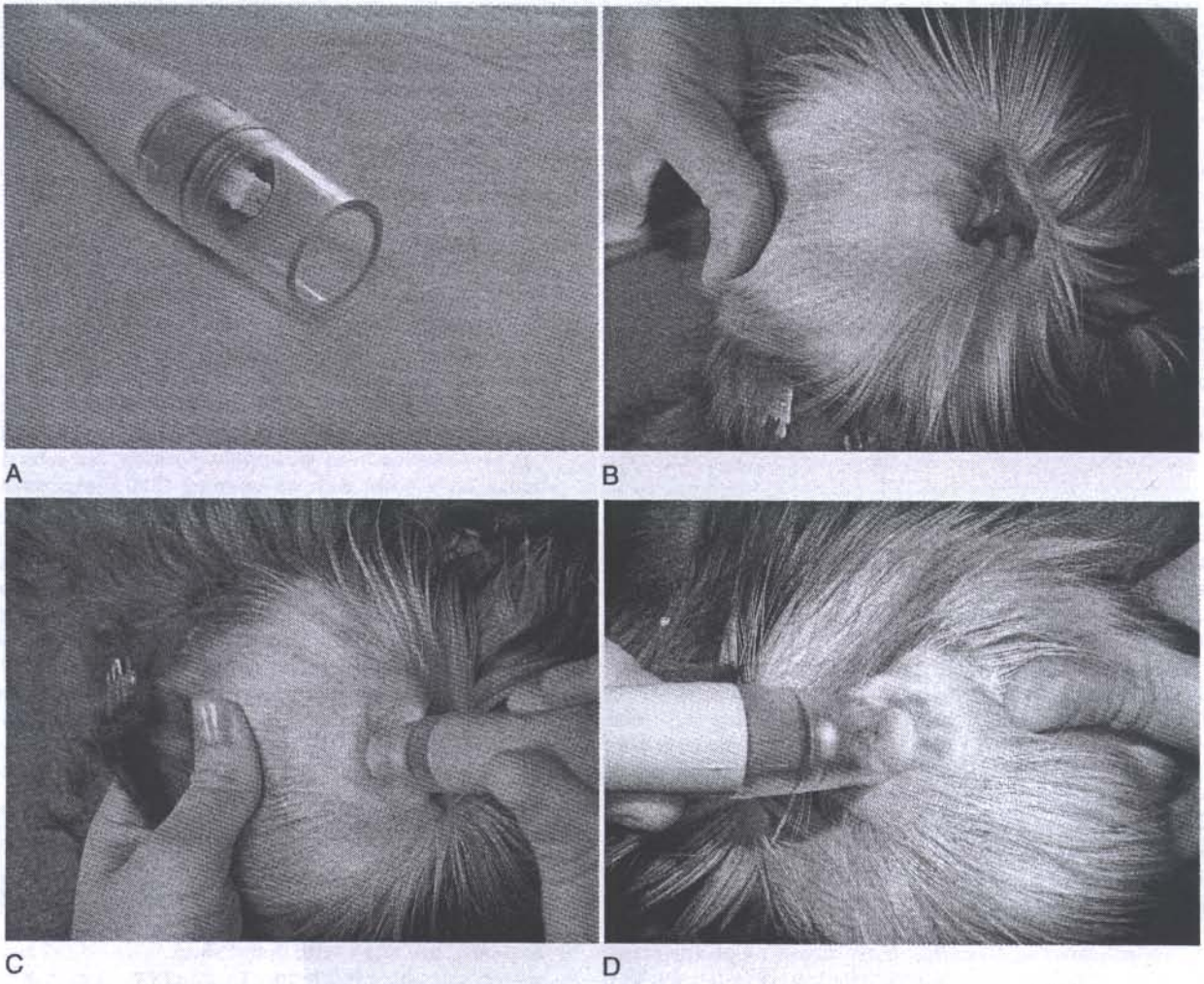


Figure 88-2 A, The Microlet vaculance (vacuum lancing device). B, The tip of the ear is held between the thumb and index finger. The surface of the pinna is held flat by the rest of the fingers. C, The lancet device is set on a nonhaired area of the ear. The outer ear is pushed against the device to form an airtight seal. D, After lancing the ear, pressure is maintained and the plunger is slowly released. Negative pressure causes the skin to bulge up into the endcap.

and the skin slightly bulges up into the endcap. The negative pressure is maintained until there is an adequate drop of blood (Figure 88-2, *D*). When an adequate drop of blood has formed, the plunger is pressed three fourths of the way down to release the vacuum and remove the device. The PBGM with the test strip already inserted is then applied to the drop of blood to measure the blood glucose concentration.

Clinicians should be aware that there are some important limitations to the use of a PBGM. In particular, several factors can affect the accuracy of the blood glucose concentrations obtained with these meters, including the level of training of the user, whether the meter is properly maintained, whether appropriate quality control checks are performed, whether the animal has any concurrent diseases, and the hematocrit of the animal. All PBGMs overestimate the blood glucose concentration of anemic animals. Dehydration results in falsely lower blood glucose concentrations. Other factors may also affect results, such as altitude, environmental temperature and humidity, hypotension, hypoxia, and the triglyceride concentration.

The Bayer Glucometer Elite (Bayer Diagnostics) is one of the easiest PBGMs to operate. It has no buttons to press. The meter automatically turns on when the test strip is inserted and turns off when the test strip is removed. It requires only 2 μL of blood, which is automatically aspirated by capillary action into the reaction chamber after contact with the test strip. The result is displayed in 30 seconds. It is important that the operator make sure the test strip is filled to the mark, because this meter starts the measuring process even if the test strip chamber is only partially filled with blood; this can result in an erroneously low blood glucose value.

A PBGM that is simple to operate should be chosen. Portable blood glucose meters are constantly being improved, and the result is greater precision, faster measurement, decreased blood volume, and decreased operator dependence. It is important to become familiar with the PBGM and perform routine maintenance. With practice, veterinarians, veterinary technicians, and veterinary students can become proficient in the techniques outlined here, and errors can be minimized. Ear vein sampling can become the routine method of generating serial blood glucose curves in the hospital. These techniques can also be taught to clients for home monitoring of blood glucose concentrations.

Owners also can be directed to web sites dedicated to diabetic pets, which contain information on home monitoring of glucose. In the search field, type "home monitoring of diabetic pets."

CHAPTER • 89

Echocardiography

Marie-Claude Bélanger

Cardiac ultrasonography has become a powerful diagnostic tool in the noninvasive evaluation of the size, structure, function, and blood flow dynamics of the canine and feline heart. This chapter is designed to guide the practitioner through veterinary transthoracic echocardiography.

BASICS OF CARDIAC ULTRASONOGRAPHY

Propagation of sound waves is favored by fluids and soft tissue and inhibited by bone, metal, and air. The operator must therefore obtain a suitable air-free window between the ribs of the animal and ventral to the lungs. A *window* is described as a transducer location or region where the heart contacts the intercostal muscles, allowing adequate imaging of cardiac structures.

The basic idea of any ultrasound technique is that the probe emits a pulse of sound that penetrates the target tissue. A portion of that emitted ultrasound goes through the organ and is lost; another portion is reflected back to the probe. If considerable sound is reflected back (as occurs with the myocardium, for example), the structure is said to be *hyperechoic;* a hyperechoic structure appears on the screen as a whiter image. When very little of the sound is reflected back (as with blood or blood vessels), the structure is *hypoechoic* and appears dark on the screen.

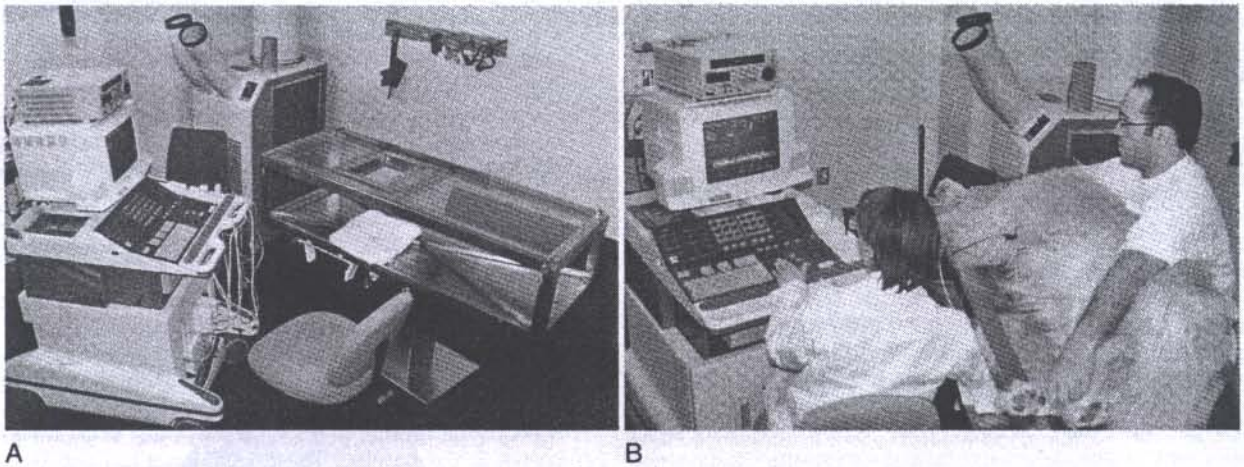
Echocardiographic transducers are made of piezoelectric crystals that generate sound waves, which travel in cycles. The frequency of a probe is determined by the number of cycles sent out per minute. High-frequency transducers emit more cycles per time unit and thus have shorter wavelengths. These transducers reflect sound from smaller structures and therefore produce better image definition and resolution, but less tissue penetration, than low-frequency transducers.

Equipment

The quality of images obtained from echocardiographic studies depends on the sophistication and technology of the ultrasound machine, the skill and experience of the operator, and the individual patient's characteristics. Echocardiograms can be obtained from an upright position, but lateral recumbency on a table with an opening that allows examination from beneath the animal is optimal, because this arrangement creates a larger echo window. Sector scanning transducers are recommended for cardiac studies in veterinary medicine, because the small intercostal space of our patients limits the size of the available acoustic windows. The choice of transducer is directed by the size of the patient, because tissue penetration is inversely proportional to the frequency of the probe. In other words, the higher the frequency of the probe, the less the tissue penetration. Cats and small dogs usually require a 7.0 MHz transducer. A 5.0 MHz probe is appropriate for most dogs. For very large dogs, a 3.5 MHz transducer may be required to obtain optimal tissue penetration.

Technique

In animals, the hair is usually clipped to improve skin contact and image quality, and coupling gel is applied over the right or left precordial impulses. However, shaving may not be required for dogs with very short hair. Also, one should always warn breeders before shaving a show dog! Application of alcohol or water can sometimes replace the coupling gel; either of these provides good but briefer contact. The animal is restrained in lateral recumbency on a special table with an imaging opening (Figure 89-1). The patient's forelimbs should be gently pulled cranially by a technician to keep the elbows out of the acoustic window. The probe is placed on



A B

Figure 89-1 A, Typical examination setting for echocardiographic studies in veterinary medicine. Rectangular or circular cutouts allow the transducer to be introduced from the bottom of the scanning table. B, The animal is held in lateral recumbency with the shaved thoracic window over the hole. The examiner is scanning from the right parasternal location.

the prepared area and twisted, tilted, or slid as needed to find a good window for optimizing the quality of images from the cardiac structures. A complete echocardiographic study includes two-dimensional (2-D), M-mode, and Doppler examinations.

An echocardiogram can usually be performed in animals with minimal or no chemical restraint. On the other hand, sedation has the advantage of minimizing stress and poor image quality in squirmy patients. Low doses of ketamine hydrochloride (2 to 5 mg/kg given intravenously [IV] or intramuscularly [IM]), alone or with midazolam (0.1 to 0.2 mg/kg given IV or intramuscularly [IM]), can be used on asymptomatic fractious cats. A combination of butorphanol (0.2 mg/kg IM) and midazolam (0.1 to 0.2 mg/kg IM) (0.05 mg/kg IM) is a good alternative when one wishes to avoid the positive chronotropic effect of ketamine or when sedation is necessary in a cat with congestive heart failure. An opiate (buprenorphine, 0.0075 to 0.01 mg/kg IV) with acepromazine (0.03 mg/kg IV) can be helpful in uncooperative dogs. Oxymorphone (0.05 mg/kg IM) with midazolam (0.2 mg/kg IM) is the protocol used by the author when sedation is needed in a cardiac dog, although other options are also utilized.

The potential influence of the sedation used must be considered in the interpretation of echocardiograms. For example, an increased heart rate, a decreased left ventricular (LV) internal diameter in diastole, an increased septal and left ventricular wall thickness, and a decreased fractional shortening are observed in most cats sedated with ketamine. Also, the potentially hazardous side effects of some sedatives must be considered in the decision on whether to chemically restrain a compromised cardiac patient.

NORMAL CARDIAC ULTRASONOGRAPHIC EXAMINATION

2-D Echocardiography

Two-dimensional echocardiography is used to evaluate the cardiac structural changes resulting from congenital defects or cardiac diseases. It produces a real-time anatomic evaluation of the heart throughout the cardiac cycle. A complete 2-D study involves imaging of all valves and great vessels, as well as the relative size and wall thickness, of the cardiac chambers.

Common 2-D Echocardiographic Positions

The animal is first imaged from its right side. The transducer is placed on the right side of the chest wall just dorsal to the sternum at the fourth or fifth intercostal space. This typical position is called the right parasternal location. The views routinely performed from the right parasternal location are the long axis four-chamber view, the long axis left ventricular outflow view, and the different short axis views described in Figures 89-2 and 89-3. Conventionally, echocardiographic

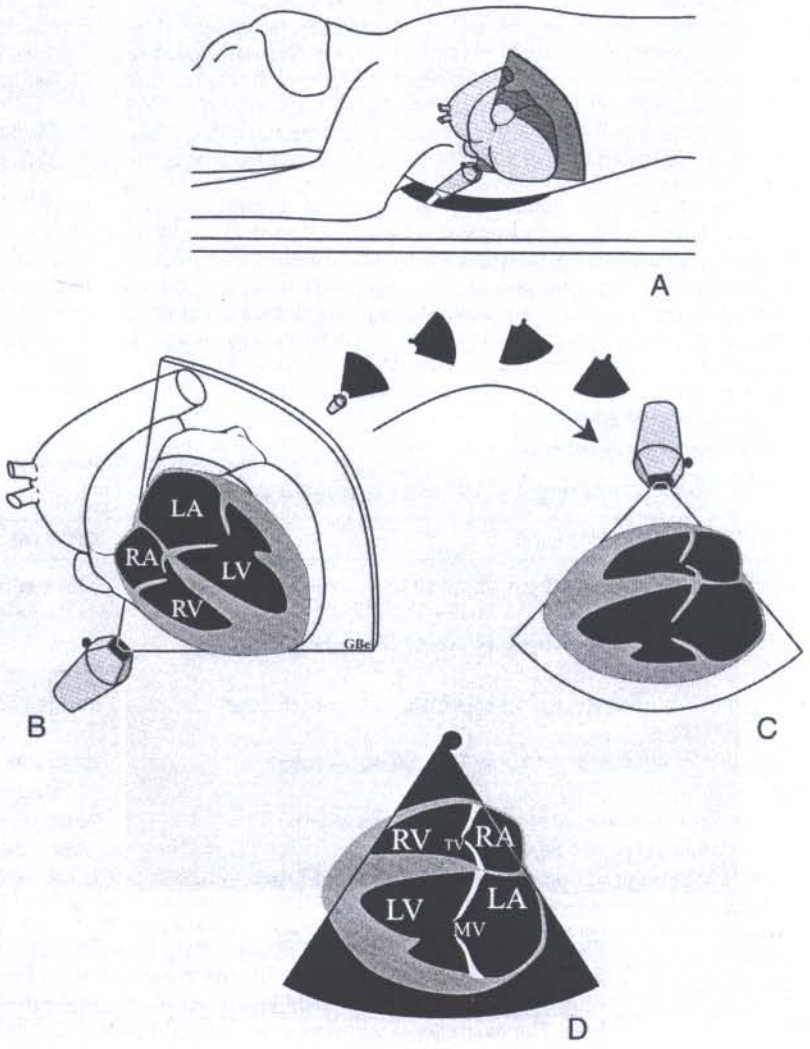


Figure 89-2 A, Typical positioning of the animal for visualization of the right parasternal long axis view. In the dog, the long axis of the heart is parallel to an imaginary line connecting the shoulder to the xiphoid. B, Spatial orientation of the right parasternal location, long axis four-chamber view. C, Spatial orientation of the right parasternal location, long axis four-chamber view as observed on the ultrasound monitor. D, Illustration of the different cardiac structures observed with this window. *Continued*

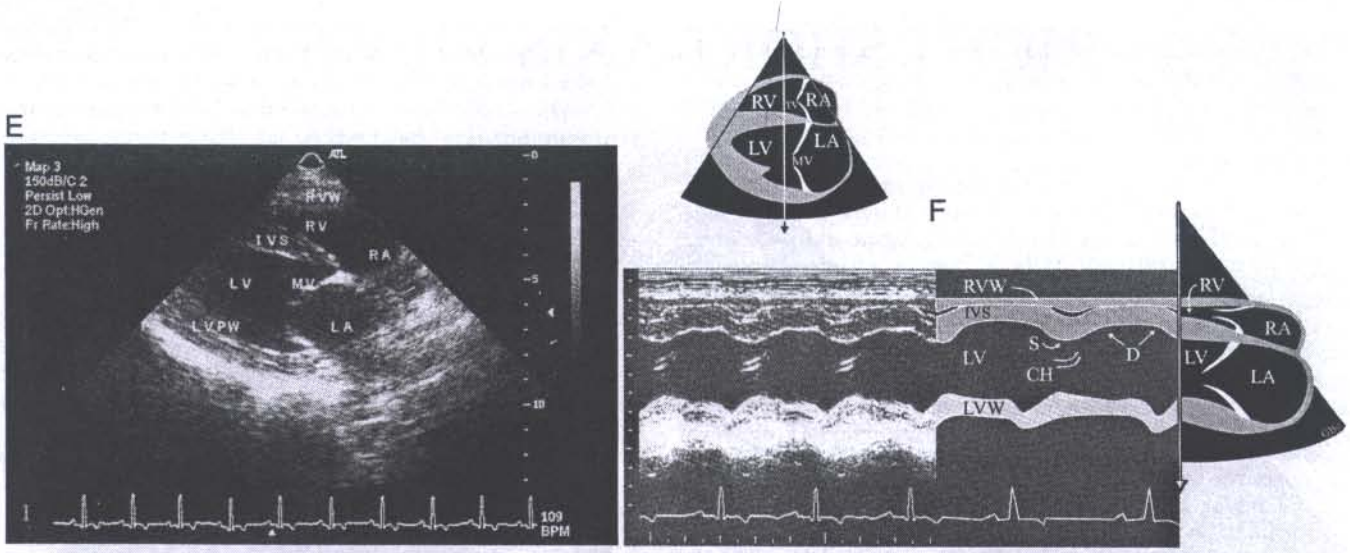


Figure 89-2 Cont'd E, Real-time 2-D image of the right parasternal location, long axis four-chamber view. F, Corresponding M-mode image obtained from this window. The heart is seen as it fills and empties (diastole and systole). *D*, diastole; *IVS*, interventricular septum; *LA*, left atrium; *LV*, left ventricle; *LVPW*, left ventricular posterior wall; *MV*, mitral valve; *RA*, right atrium; *RV*, right ventricle; *RVW*, right ventricular wall; *S*, systole; *TV*, tricuspid valve.

views are named from the positioning of the transducer and the structures that are examined (e.g., right parasternal long axis view). The right and left parasternal positions are used most often, but a multitude of planes can be obtained to better visualize a distinct part of the heart. The subcostal or subxiphoid position is an example of another window used to specifically evaluate the left ventricular outflow tract (LVOT) in the dog. The long axis view is obtained by an imaging plane that transects the heart parallel to its long axis from apex to base; a perpendicular imaging plane is performed to obtain the short axis view (see Figures 89-2 to 89-4). Technically, this means that the short axis views can be obtained from the long axis views by a 90-degree rotation of the probe.

The second half of the echocardiographic study consists of the left-sided views. As opposed to the right parasternal location, there are two acoustic windows on the left side. The left cranial parasternal views are obtained at the level of the fourth intercostal space, and the left caudal (apical) parasternal views are best visualized from the fifth to sixth intercostal spaces (see Figure 89-4). Table 89-1 presents useful tips for optimizing the imaging of the canine and feline heart in some situations.

M-Mode Echocardiography

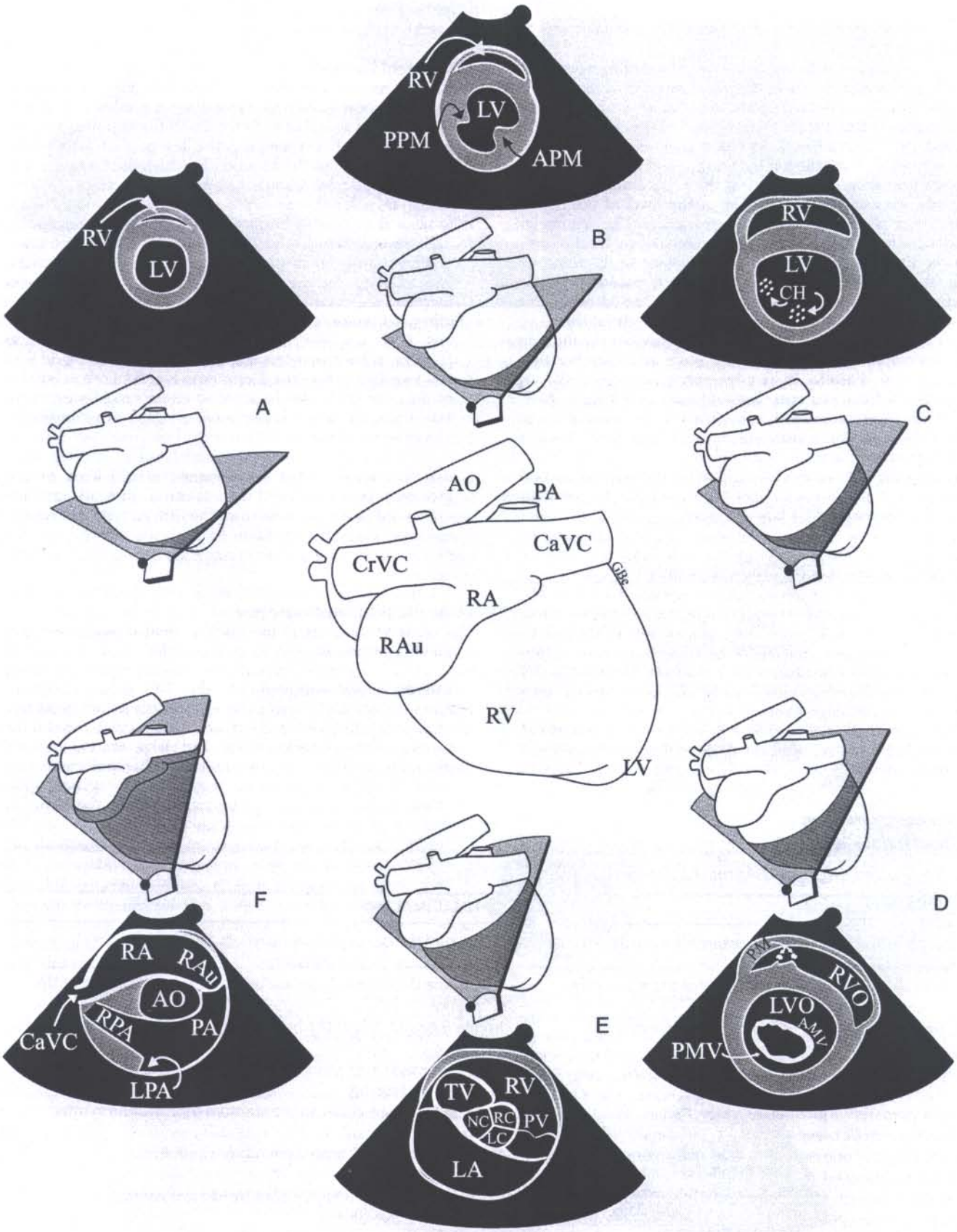
The term *M-mode* refers to real-time *motion-mode*. M-mode echocardiography is used to evaluate the phasic motion of the cardiac structures during the cardiac cycle. M-mode echocardiography complements the 2-D echocardiogram, because it has a higher sampling rate, which allows good resolution of rapidly moving structures. It is especially useful for recording subtle changes in wall and valve motion and for performing accurate measurements of chamber diameters

Table • 89-1

Tips for Optimizing Small Animal Echocardiography

REQUIREMENT/PROBLEM	OPTIMAL IMAGING
The view required is the right parasternal long axis view.	Make sure the dot on the probe points toward the shoulder of the animal.
The view required is the right parasternal short axis view.	Make sure the dot on the probe points toward the elbow of the animal.
Structures from the right side of the heart are difficult to image.	Image the right side of the heart from the left parasternal location.
A specific cardiac structure is difficult to visualize.	Remember the three ways the probe can be moved: twisting, tilting, and sliding.
The right parasternal location must be used in a brachycephalic breed.	Position the probe closer to the sternum than is done in other breeds.
Optimal image of one extremity of the heart (apex or base) cannot be obtained.	Slide one intercostal space cranially or caudally.
Horizontal lines with a hazy image are observed.	Add coupling gel to improve poor transducer contact.
Resolution of the structures in the lateral field is decreased.	Decrease the overall gain.
Near-field resolution is poor in very small patients.	Change to a higher frequency probe.

RIGHT SHORT-AXIS VIEWS



and wall thicknesses. The M-mode image is viewed on a video screen, on which the depth of the structures is plotted on the *Y* axis and time is shown on the *X* axis. Only the structures transected by the cursor are seen on the M-mode images. The steerable cursor scrolls across the heart, and the associated changes in thickness or position of the structures are recorded on the screen as the heart fills and contracts (see Figure 89-3, *F*).

In veterinary medicine, M-mode echocardiography is generally performed only from the right parasternal location. The usual M-mode echocardiogram includes an evaluation of the left ventricle (see Figure 89-2, *F*) and of the mitral valve and aortic root (Figure 89-5). As recommended by the American Society of Echocardiography (ASE), end-diastolic measurements are taken at the onset of the QRS complex, and end-systolic measurements are taken at the level of the maximal excursion of the interventricular septum. The *leading edge method* is used; that is, the measurements of each echo line are made beginning at the edge that is closest to the transducer. The sonographer should be aware that a tremendous potential exists for artifactual measurements when the M-mode image is obtained in a suboptimal plane (e.g., tangential slices).

The left ventricular M-mode study provides absolute measurements of the left ventricular walls and chamber during systole and diastole. It can be performed using the right parasternal long axis four-chamber view (see Figure 89-2, *F*) or the right parasternal short axis view at the level of the papillary muscles (see Figure 89-3, *B*). Tables 89-3, 89-4, and 89-5 describe these M-mode measurements are also used to evaluate the left ventricular systolic function by calculation of the ejection phase indices (as described later in the chapter under Evaluation of Cardiac Function).

DOPPLER ECHOCARDIOGRAPHY

Spectral and color flow Doppler imaging techniques are used to evaluate blood flow velocity and direction in the heart and great vessels. The transducer generates ultrasound waves, which are reflected off the red blood cells. The change in frequency between the sound transmitted by the transducer and the sound received by it is called the *Doppler shift* (Δf). Because velocity = frequency × wavelength, the magnitude of the Doppler shift is directly proportional to red blood cell (RBC) velocity:

$$\Delta f = \frac{2f_0 \times V \times \cos\Theta}{C}$$

Where f_0 is the frequency transmitted by the transducer; V is the flow velocity of RBC in meters per second (m/sec); Θ is the intercept angle; and C is the speed of sound in blood (1540 m/sec).

Doppler echocardiography assesses the direction and velocity of blood flow. Blood moving toward the transducer creates a positive frequency shift encoded in red on color Doppler and is displayed above the baseline of spectral Doppler. Blood flow moving away from the transducer is blue and is inversely displayed as a negative flow profile under the baseline (Figure 89-6).

Spectral Doppler

Cardiac spectral Doppler study uses imaging planes that align the sound beam along the blood flow. A marker is represented on the cursor line that corresponds to the sampling volume or *gate* where the flow is interrogated. The parallel beam positioning is in contrast to the M-mode, in which the beam is oriented in a perpendicular manner to visualize the cardiac structures. When Doppler studies are performed, care must be taken to align the Doppler beam with the jet flow (intercept angle <20 degrees) to minimize underestimation of the flow velocity.

Flow signals are displayed with time on the horizontal axis and velocity on the vertical axis. Two types of spectral Doppler are used clinically, *pulsed wave (PW) Doppler* and *continuous wave (CW) Doppler.* An intermediate between PW and CW Doppler, called *high pulse-repetition frequency (HPRF)*, is another type of spectral Doppler, one that is used less frequently. Spectral Doppler is helpful in the assessment of pressure gradients, intracardiac chamber pressure, regurgitant fractions, shunt ratios, valve area, effective orifice area, and cardiac output.

In veterinary medicine, spectral Doppler is often used to calculate *instantaneous pressure gradients* (ΔP) across a stenotic area or regurgitant valve. The maximal pressure gradient is calculated from the maximal flow jet velocity *(v)* using the modified Bernoulli equation:

$$(\Delta P) = 4v^2$$

The peak pressure gradient, along with the determination of the effective orifice area and other 2-D and M-mode echocardiographic findings, is used in the clinical assessment of the severity of stenosis.

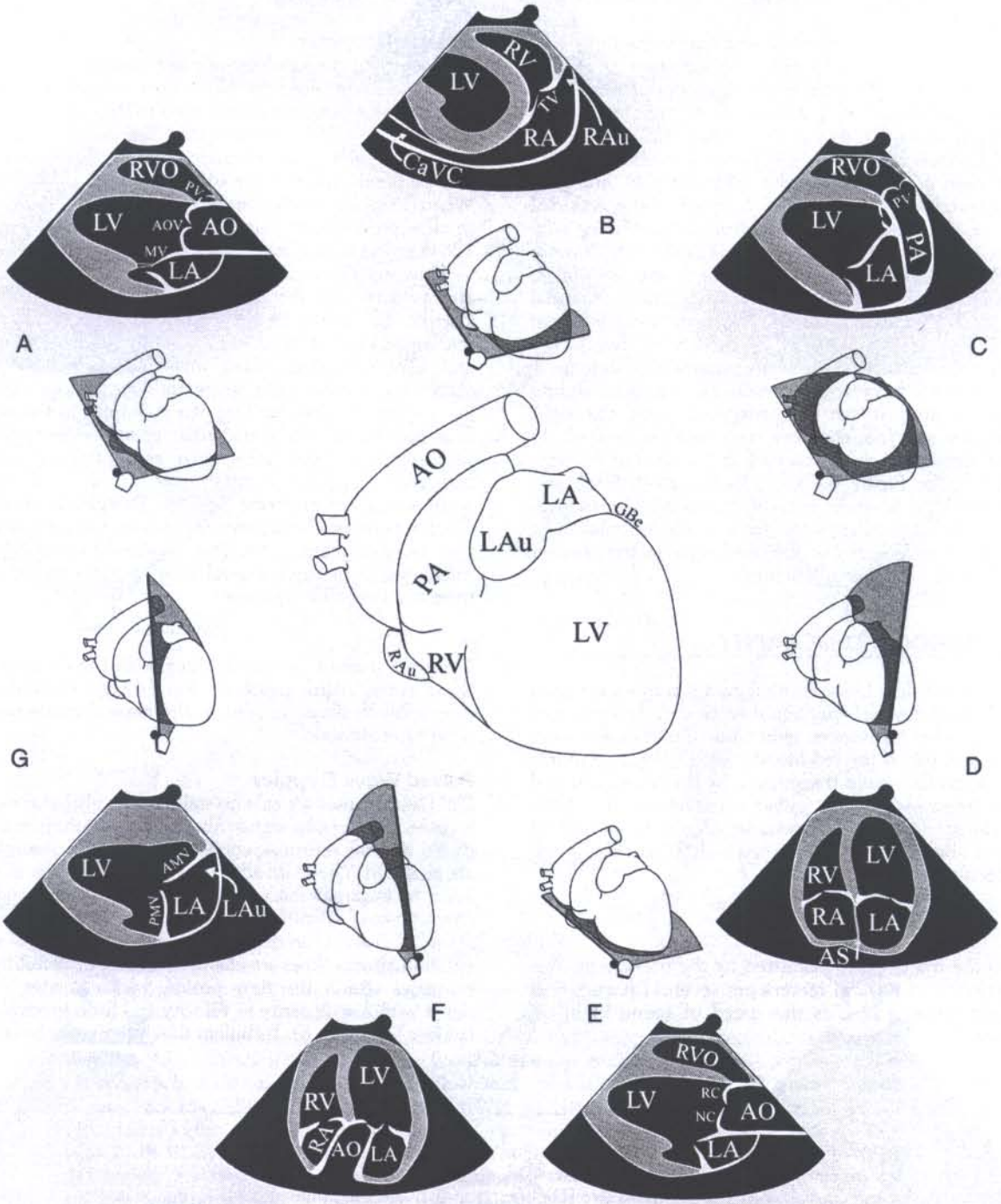
Pulsed Wave Doppler

PW Doppler uses a single crystal transducer that transmits and receives the Doppler signal. Short pulses of ultrasound are produced, and the returning echoes from a specific sample volume are analyzed. The main advantage of PW Doppler is the possibility of interrogation of the direction, velocity, and spectral characteristics (laminar versus turbulent) of the blood flow from a distinct anatomic region of the heart or blood vessels. Laminar flows are characterized by the similitude of the velocities within the flow profile, which creates a Doppler signal with less disparity in velocity and little spectral broadening (see Figure 89-6). Turbulent flow profiles are broad, and the

Figure 89-3 Standard 2-D echocardiographic study obtained from the right parasternal transducer location; short axis views are at the level of the apex **(A)**, the papillary muscles **(B)**, the chordae tendineae **(C)**, the mitral valve **(D)**, the aorta **(E)**, and the pulmonary arteries **(F)**. *AMV,* anterior mitral valve cusp; *APM,* anterior papillary muscle; *CaVC,* caudal vena cava; *CH,* chorda tendineae; *CrVC,* cranial vena cava; *LA,* left atrium; *LC,* left coronary aortic cusp; *LPA,* left pulmonary artery; *LV,* left ventricle; *LVO,* left ventricular outflow; *NC,* noncoronary aortic cusp; *PA,* pulmonary artery; *PM,* papillary muscle; *PMV,* posterior mitral valve cusp; *PPM,* posterior papillary muscle; *PV,* pulmonary valve; *RA,* right atrium; *Rau,* right auricle; *RC,* right coronary aortic cusp; *RPA,* right pulmonary artery; *RV,* right ventricle; *RVO,* right ventricular outflow; *TV,* tricuspid valve. (Modified from Thomas WP, Gaber CE, Jacobs GJ: Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat, Echocardiography Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine, *J Vet Intern Med* 7:247-252, 1993.)

LONG-AXIS VIEWS

LEFT CRANIAL PARASTERNAL LOCATION



LEFT CAUDAL (APICAL) PARASTERNAL LOCATION

Figure 89-4 Standard 2-D long axis views. A, Left cranial parasternal view optimized for the aortic root. B, Left cranial parasternal view optimized for the right atrium and auricle. C, Left cranial parasternal view optimized for the right ventricular outflow tract and main pulmonary artery. D, Four-chamber inflow view from the left caudal (apical) parasternal position. E, Left caudal (apical) parasternal view optimized for visualization of the left ventricular outflow tract. F, Five-chamber left ventricular outflow view from the left caudal (apical) parasternal position. G, Left caudal (apical) parasternal location, two-chamber view optimized for visualization of the left ventricular inflow and left auricle.

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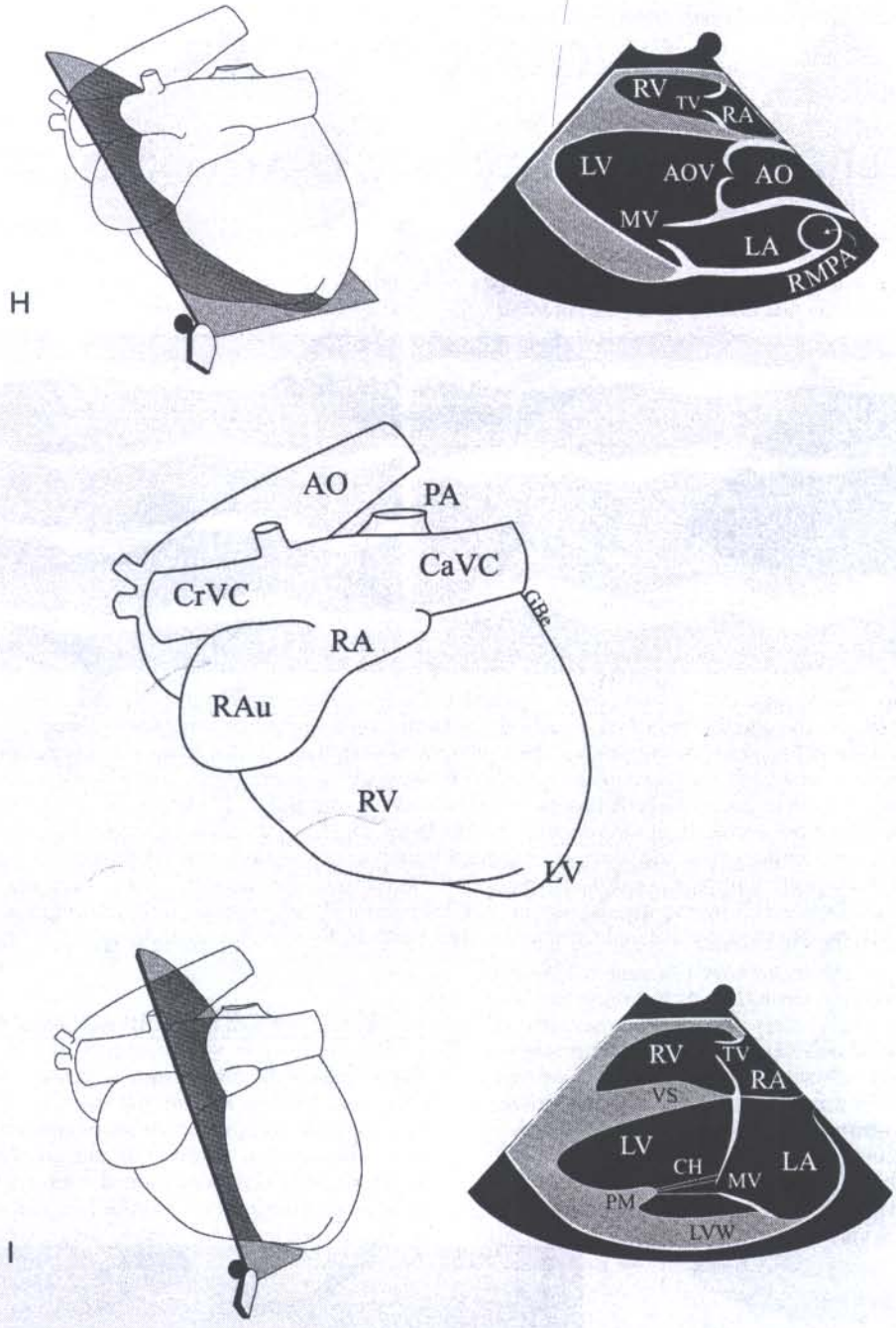


Figure 89-4 **Cont'd H,** Left ventricular outflow view from the right parasternal position. **I,** Four-chamber right parasternal long axis view. *AO,* aorta; *AOV,* aortic valve; *AMV,* anterior mitral valve cusp; *AS,* atrial septum; *CaVC,* caudal vena cava; *CH,* chorda tendineae; *CrVC,* cranial vena cava; *IVS,* interventricular septum; *LA,* left atrium; *LAu,* left auricle; *LPA,* left pulmonary artery; *LV,* left ventricle; *LVO,* left ventricular outflow; *LVW,* left ventricular wall; *MV,* mitral valve; *NC,* noncoronary aortic cusp; *PA,* pulmonary artery; *PM,* papillary muscle; *PMV,* posterior mitral valve cusp; *PV,* pulmonary valve; *RA,* right atrium; *Rau,* right auricle; *RC,* right coronary aortic cusp; *RMPA,* right main pulmonary artery; *RV,* right ventricle; *RVO,* right ventricular outflow; *TV,* tricuspid valve. (Modified from Thomas WP, Gaber CE, Jacobs GJ: Recommendations for standards in transthoracic two-dimensional echocardiography in the dog and cat, Echocardiography Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine, *J Vet Intern Med* 7:247-252, 1993.)

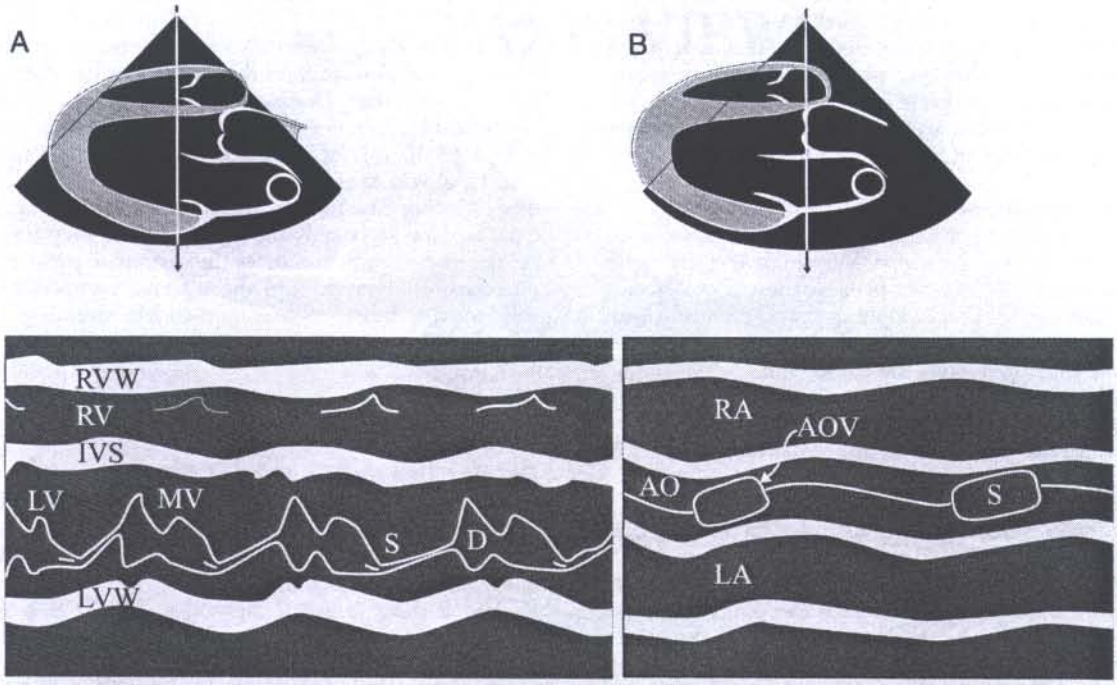


Figure 89-5 Standard M-mode views obtained at the level of the mitral valve *(A)* and the aortic valve *(B)*. **A,** The mitral valve is seen as an M shape. During rapid ventricular filling (early diastole), the mitral valve is forced to open up toward the interventricular septum. As ventricular filling progresses, the pressure in the left atrium equalizes with the left ventricular pressure and the mitral leaflets move toward each other. The mitral leaflets open again during atrial contraction. Closure of the mitral valve occurs after atrial systole. **B,** During diastole, the line in the middle of the aorta represents the closed aortic cusps. During systole, the aortic valve opens toward the walls of the aorta, remains open during the systolic ejection of blood, and then rapidly closes at the end of systole. *AO,* Aorta; *AOV,* aortic valve; *D,* diastole; *IVS,* interventricular septum; *LA,* left atrium; *LV,* left ventricle; *LVW,* left ventricular wall; *MV,* mitral valve cusp; *RA,* right atrium; *RV,* right ventricle; *RVW,* right ventricular wall; *S,* systole.

area under the curve is filled in because the transducer is receiving many frequency shifts associated with variable velocities. The disadvantage of PW Doppler lies in a maximal measurable velocity, called the *Nyquist limit*, that cannot be exceeded because of a limited pulse-repetition frequency. In other words, PW Doppler is only accurate when measuring low velocities.

PW Doppler is very useful in the evaluation of valvular blood flow patterns. Diastolic flows across the atrioventricular valves have similar patterns, which are characterized by an initial high-velocity signal associated with the rapid ventricular filling known as the *E wave*, followed by a lower velocity signal produced by the atrial contraction, or

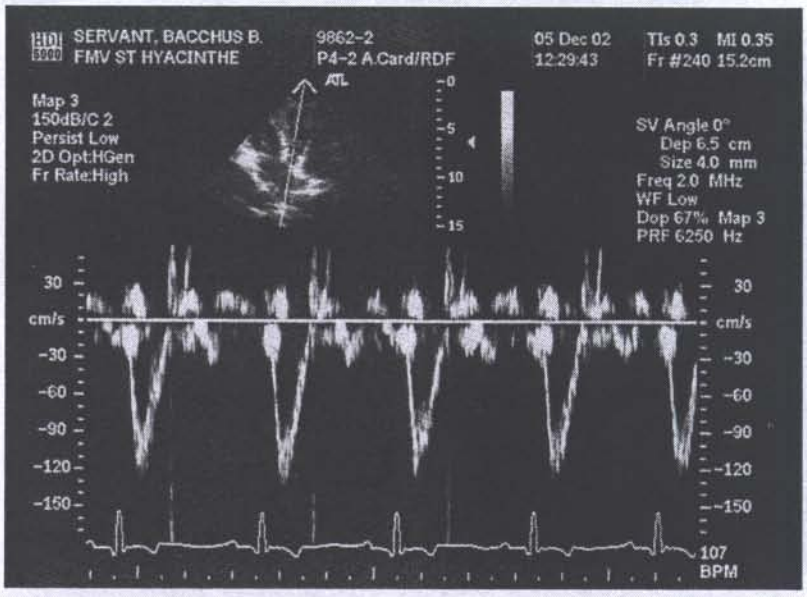


Figure 89-6 Normal left ventricular systolic outflow signal measured from the apical five-chamber view with PW Doppler.

A wave (Figure 89-7). The flow patterns across the semilunar valves are characterized by a rapid acceleration during ejection followed by a more gradual deceleration. The variance of these valvular flow patterns is studied to identify different valvular diseases as described elsewhere. Table 89-6 describes the normal values for valvular spectral doppler echocardiographic velocities in dogs and cats.

Continuous Wave Doppler

CW Doppler uses dual crystals for simultaneous transmission and reception of the Doppler signal. Very high velocity flows can be recorded with CW Doppler, because there is no Nyquist limit. The disadvantage of CW Doppler is that the specific location and characteristic of flow cannot be documented, because all velocities are measured along the cursor line.

PW and CW Doppler, therefore, are complementary, and both techniques are used to accurately describe the location, quality, and maximal velocity of an abnormal flow jet.

Color Flow Doppler

Color flow Doppler is a form of PW Doppler. Its primary clinical use is the detection of flow disturbances. The Doppler shift is encoded with a color map, which usually uses red, blue, and green to produce other color shades such as cyan, yellow, and white. Conventionally, blood moving away from the probe is blue, whereas blood moving toward the probe is red. This color map configuration is called the BART display (Blue/Away and Red/Toward). Color Doppler is very helpful for appropriately aligning with flow jets, searching for modest insufficient jets, describing the size and shape of regurgitant jets, identifying areas of turbulent flow, and confirming some cardiac shunts seen on 2-D echocardiograms. Turbulent flow is characterized by disparate velocities within the sampled area, which appears as a disorganized flow with a mosaic pattern. Several transducer positions and planes are used to find the optimal color flow imaging of a specific cardiac structure.

SPECIAL ECHOCARDIOGRAPHIC TECHNIQUES

Other echocardiographic techniques can provide useful information in the imaging of the canine and feline heart. These techniques include transesophageal and three-dimensional (3-D) echocardiography. Although useful in the clinical setting, these imaging methods have limited application in veterinary medicine, because they require expensive equipment. Transesophageal echocardiography requires general anesthesia, which increases the time and cost of the procedure.

Contrast echocardiography is another useful imaging method in the clinical evaluation of the cardiovascular system. It now is mostly used when Doppler echocardiography is unavailable. Microbubbles (obtained from the agitation of a syringe filled with 3 to 10 mL of physiologic saline) can be injected in a peripheral vein to assist in the diagnosis of right-to-left intracardiac shunting. The microbubbles reflect ultrasound and do not cross pulmonary or systemic capillaries, and they are reabsorbed by the pulmonary capillaries. In a normal patient, therefore, microbubbles injected into the cephalic vein stay on the right side of the heart. When right-to-left shunting is present, microbubbles are also observed in the left side of the heart.

EVALUATION OF CARDIAC FUNCTION

Cardiac Size and Chamber Dilatation

Cardiac chamber dimensions are determined by M-mode echocardiography and sometimes by 2-D echocardiography. Table 89-2 summarizes the most common etiologies for anomalies in chamber size.

The *E point to septal separation (EPSS)* is a very useful parameter in the assessment of left ventricular dilatation and systolic dysfunction. EPSS measures the distance from the maximal opening of the mitral valve (E point) to the endocardial aspect of the interventricular septum (Figure 89-8). In the normal heart, the mitral valve opens in diastole, and its anterior leaflet almost contacts the interventricular septum. In dilated hearts with decreased contractility (e.g., dilated cardiomyopathy), the mitral valve does not reach the septum. Reports in human medicine have shown that the size of the left ventricle alone does not alter the EPSS unless systolic dysfunction is present.

The *left atrial to aortic ratio (LA:Ao ratio)* is used to estimate the degree of left atrial enlargement. It compares the M-mode diameter of the left atrium in systole to the diameter of the aorta in diastole. This ratio is best obtained from the right parasternal short axis view but may also be evaluated from the right parasternal long axis view. The M-mode LA:Ao method has often been criticized because of the subjectivity of the cursor placement. This method underestimates left atrial size if the cursor does not reach the body of the left atrium. Conversely, it overestimates the relative left atrial size if a tangential plane of the aorta is performed. The reported LA:Ao ratio in normal dogs and cats is less than 1.3.

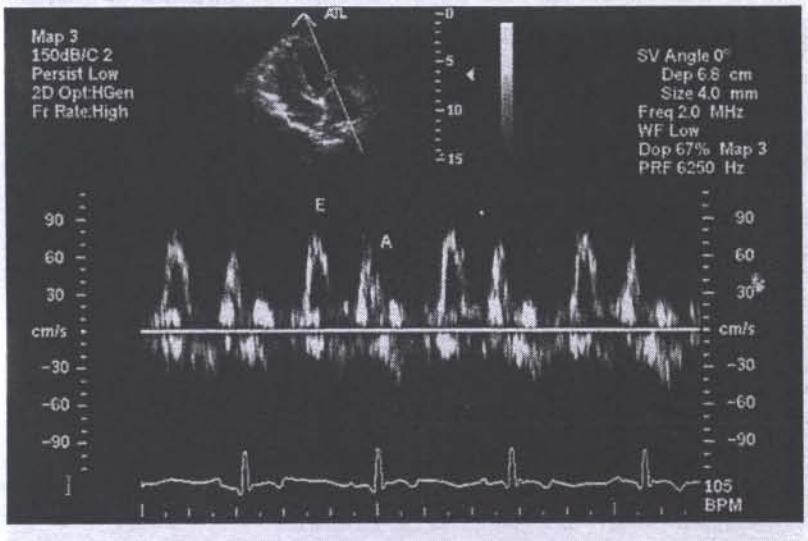


Figure 89-7 Spectral Doppler recording of a normal mitral flow obtained from the left apical position with the PW Doppler gate located in the left ventricular inflow tract. The E point represents the rapid ventricular filling. The A wave corresponds to the atrial contraction.

Table • 89-2

Common Etiologies for Anomalies in Cardiac Chamber Size

ANOMALY	ETIOLOGY
Left ventricular dilatation	Volume overload
	Mitral regurgitation
	Right-to-left shunting
	Aortic insufficiency
	Dilated cardiomyopathy
	High output stage
	Hyperthyroidism
	Anemia
Left ventricular reduction	Volume depletion
	Severe dehydration
	Hypoadrenocorticism
	Hypovolemic shock
	Inadequate blood return to the left heart
	Dirofilariasis
	Tetralogy of Fallot
Left ventricular hypertrophy	Pressure overload
	Aortic stenosis
	Hypertension
	Hypertrophic cardiomyopathy
	Infiltrative myocardial disease
Right ventricular dilatation	Volume overload
	Tricuspid regurgitation
	Atrial septal defect
	Dilated cardiomyopathy
Right ventricular reduction	Cardiac tamponade
	Volume depletion
Right ventricular hypertrophy	Pressure overload
	Pulmonic stenosis
	Tetralogy of Fallot
	Cor pulmonale
	Pulmonary hypertension
	Dirofilariasis
	Feline hypertrophic cardiomyopathy
	Feline restrictive cardiomyopathy
Left atrial enlargement	Chronic degenerative mitral valve disease
	Dilated cardiomyopathy
	Left-to-right shunting
	Mitral stenosis
	Mitral dysplasia
Right atrial enlargement	Tricuspid regurgitation/ dysplasia
	Dilated cardiomyopathy
	Dirofilariasis
	Right-to-left shunting
	Tricuspid stenosis
	Cor pulmonale
	Pulmonary hypertension

Rishniw reported a more accurate 2-D echocardiographic method for estimating left atrial size in adult dogs. This method measures the LA:Ao ratio from the right parasternal short axis view of the aorta and left atrium when the aortic valve is closed. The internal diameter of the aorta is measured along the commissure between the noncoronary and right coronary aortic valve cusps after aortic valve closure (Figure 89-9). The left atrial internal diameter is measured from a line parallel to the commissure between the noncoronary and left coronary aortic valve cusps to the distant margin of the left atrium. A LA:Ao ratio greater than 1.6 suggests left atrial dilation.

Left Ventricular Volumes

Many experimental models and formulas have been described in the canine patient to assess left ventricular volumes (LVV) by use of M-mode and 2-D echocardiography. Left ventricular end-diastolic and end-systolic volumes can be estimated by the Teichholz method; the bullet method; or the disk summation method (i.e., Simpson's rule). The disk summation method is considered the more accurate echocardiographic method in veterinary medicine. The Teichholz method is considered the more accurate M-mode method in the assessment of LVV, but one must realize that much of the volumetric estimates calculated from only one-dimensional measurements are less accurate, especially with an abnormal heart. The Teichholz method calculates the volume as follows:

$$LVV_{ES} = \frac{7(ESD^3)}{2.4 + ESD} \qquad LVV_{ED} = \frac{7(EDD^3)}{2.4 + EDD}$$

Where *ESD* is the left ventricular internal dimension at the end of systole, and *EDD* is the left ventricular internal dimension at the end of diastole, LVV_{ES} is the left ventricular volume at the end of the systole. This formula takes into consideration that the short axis of the left ventricle widens more than the long axis when the heart dilates.

Because of the inaccuracy of M-mode calculations for ventricular volumes in the diseased heart, the American Society of Echocardiography recommends the use of 2-D methods involving fewer geometric assumptions, such as the disk summation method (Figure 89-10). This method is especially more accurate when the heart has an irregular, enlarged, or asymmetric shape, as is the case in many of the canine and feline cardiomyopathies.

Ejection Phase Indices

Ejection phase indices are used to evaluate cardiac performance, especially the left ventricular systolic function. These indices, which are calculated from linear M-mode measurements, include the fractional shortening, the velocity of circumferential fiber shortening, the stroke volume, and the ejection fraction. The *end-systolic diameter*, by itself, is also a good indicator of left ventricular performance and is a more specific index of myocardial contractility than the fractional shortening. Although M-mode methods of volume determination have a poorer correlation with more invasive methods, these indices are still useful in the clinical setting, especially in the normal heart. It should be remembered that these indices are significantly influenced by ventricular loading conditions (preload and afterload).

Fractional shortening (FS) is the percent change in diameter of the ventricular cavity from diastole to systole. It provides a rough index of cardiac function. In veterinary medicine, the FS is the clinical index used more commonly in the evaluation of global inotropism and systolic function. Normal values in dogs range from 27% to 48%. FS is calculated as follows:

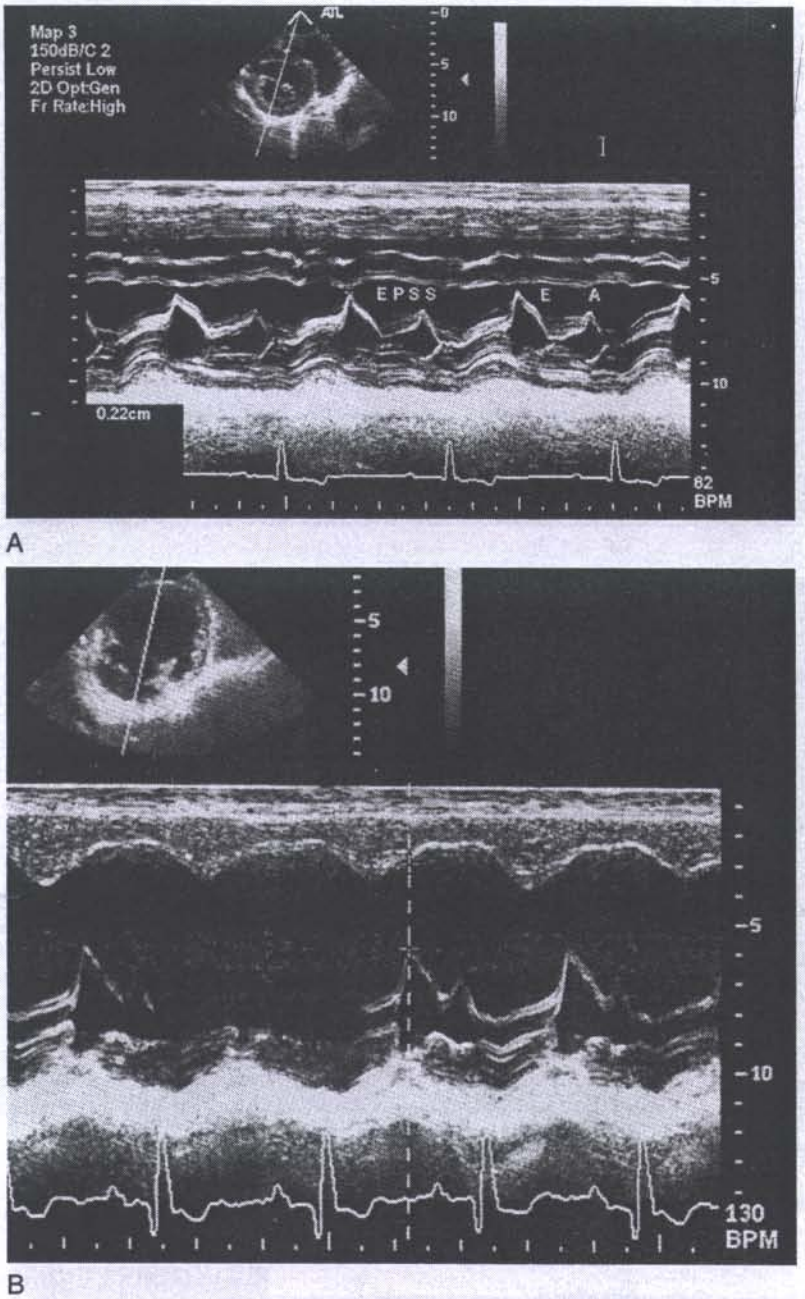


Figure 89-8 A, EPSS measurement in a normal dog. A line is drawn between the interventricular septum and the maximal initial opening of the mitral valve (E point). B, Increased EPSS (2.9 cm) in a dog with dilated cardiomyopathy.

$$FS\ (\%) = \frac{EDD - ESD}{EDD} \times 100$$

where, as noted previously, *EDD* is the left ventricular internal dimension at the end of diastole, and *ESD* is the left ventricular internal dimension at the end of systole. The *velocity of circumferential fiber shortening* (V_{cf}) measures the rate of change in the circumference *(circ)* of the left ventricle during systole. It is calculated as follows:

$$V_{cf}(circ/sec) = \frac{EDD - ESD}{EDD \times LVET}$$

where *LVET* is the left ventricular ejection time (see Systolic Time Intervals, below). Normal values for V_{cf} are 1.6 to 2.8 circ/sec in dogs and 1.3 to 4.5 circ/sec in cats.

The *stroke volume (SV)* and ultimately cardiac output can be calculated from M-mode measurements or more accurately by Doppler echocardiography (see Hemodynamic Parameters, below). M-mode SV is computed as follows:

$$SV\ (mL) = LVV_{ED} - LVV_{ES}$$

where, as noted previously, LVV_{ED} is the left ventricular volume at the end of the diastole, and LVV_{ES} is the left ventricular volume at the end of the systole.

The *ejection fraction (EF)* is a rough index of LV cardiomyocyte shortening, because it is the percentage of the LVV_{ED} ejected with each heartbeat. It also corresponds to the 3-D volumetric equivalent of the FS. The EF is the ratio of the left ventricular SV to the LVV_{ED} as calculated here:

$$EF\ (\%) = \frac{LVV_{ED} - LVV_{ES}}{LVV_{ED}} \times 100$$

Systolic Time Intervals

Systolic time intervals (STI) are other indices used in the assessment of global LV function. They are obtained by simultaneous

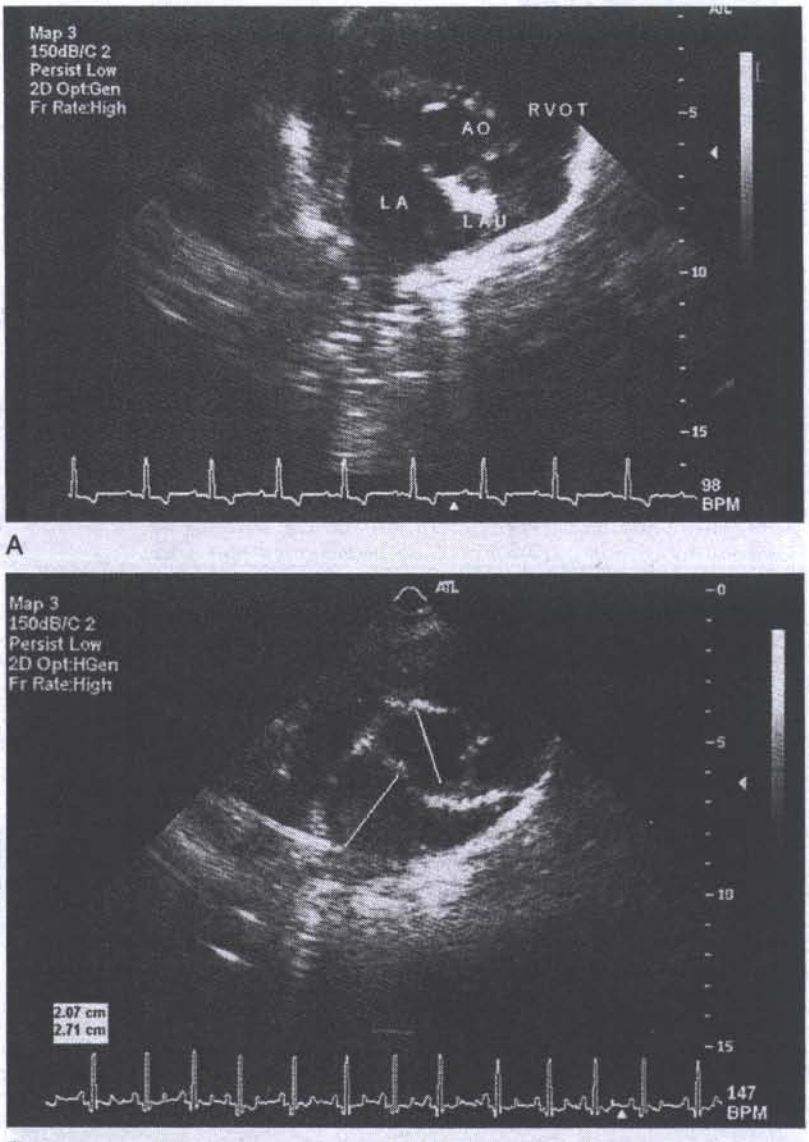


Figure 89-9 Two-dimensional measurement of the left atrium to aortic root ratio. **A,** Right parasternal short axis view of the aorta and left atrium. **B,** Measurement of the internal diameter of the aorta and left atrium. (See text for details.) *AO,* aortic; *LA,* left atrium; *LAU,* left auricule; *RVOT,* right ventricular outflow tract.

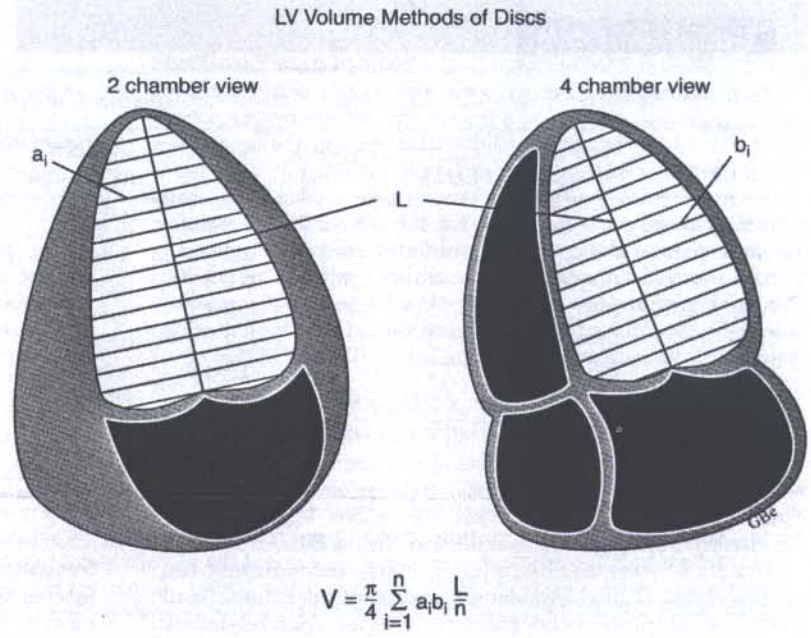


Figure 89-10 Disk summation method for estimating left ventricular volumes.

Table • 89-3

Normal Mean M-mode Echocardiographic Values in Dogs

BODY WEIGHT (kg)	$LVID_{ED}$ (cm)	$LVID_{ES}$ (cm)	IVS_{ED} (cm)	LVW_{ED} (cm)	EPSS (cm)	Ao_D (cm)	LA_S (cm)
3	2.0	1.1	0.5	0.6	0.1	1.1	1.3
5	2.4	1.3	0.6	0.7	0.1	1.3	1.5
10	3.0	1.8	0.7	0.8	0.2	1.6	1.8
15	3.4	2.1	0.8	0.8	0.2	1.9	2.0
20	3.8	2.4	0.9	0.9	0.3	2.1	2.2
25	4.0	2.6	0.9	0.9	0.3	2.2	2.4
30	4.3	2.8	1.0	1.0	0.4	2.4	2.5
35	4.5	3.0	1.0	1.0	0.4	2.5	2.6
40	4.7	3.1	1.0	1.0	0.5	2.6	2.7
45	4.9	3.3	1.1	1.1	0.5	2.7	2.8
50	5.0	3.4	1.1	1.1	0.6	2.8	2.9
55	5.2	3.6	1.2	1.1	0.6	2.9	3.0
60	5.3	3.7	1.2	1.1	0.7	3.0	3.1
65	5.5	3.8	1.2	1.2	0.7	3.1	3.1
Formula	1.44 BW	0.69 BW	0.36 BW	0.46 BW	0.03 BW	0.72 BW	0.90 BW
R value	0.97	0.95	0.89	0.81	0.94	0.96	0.98
Number of dogs	350	328	309	309	175	204	204

Ao_D, Aortic root diameter in diastole; *BW*, body weight; *EPSS*, E point to septal separation; *IVS_{ED}*, interventricular septal thickness at the end of diastole; *LA_S*, left atrial diameter in systole; *$LVID_{ED}$*, left ventricular internal diameter at the end of diastole; *$LVID_{ES}$*, left ventricular internal diameter at the end of systole; *LVW_{ED}*, left ventricular posterior wall thickness at the end of diastole.

recording of the electrocardiogram (ECG) and M-mode echocardiogram of the aortic valve (Figure 89-11). The following three intervals are routinely measured during systole:

- The *pre-ejection period (PEP)*, which is the time between ventricular depolarization (initial deflection of the QRS) and the onset of LV ejection, which corresponds to the opening of the aortic valve. PEP represents the isovolumetric contraction time.
- The *left ventricular ejection time (LVET)*, which is the time required for aortic valve opening, which is measured from the opening of the aortic valve to its closure. The LVET is determined by the SV and the rate of flow. Generally, improvement of LV systolic performance is characterized by a shortening of the PEP or a decreased isovolumetric contraction time and a prolongation of the LVET, which corresponds to an improved SV.
- The *total electromechanical systole (QAVC)*, which is the interval between the beginning of the Q wave and aortic valve closure. In other words, QAVC is the summation of PEP + LVET.

It should be remembered that STI are affected by heart rate and preload or afterload variations. The PEP/LVET index is therefore recommended because it is less influenced by these loading parameters. Normal values for STI are shown in Table 89-7.

Table • 89-4

M-Mode Echocardiographic Reference Values for Certain Canine Breeds

VALUE	MINIATURE POODLE	BEAGLE	COCKER SPANIEL	AFGHAN HOUND	GOLDEN RETRIEVER	DOBERMAN	NEW-FOUNDLAND	GREAT DANE	IRISH WOLFHOUND
$LVID_{ED}$ (cm)	1.6-2.8	1.8-3.3	3.1-3.7	3.3-5.2	3.7-5.1	3.5-4.6	4.4-6.0	4.4-5.9	4.9-5.9
$LVID_{ES}$ (cm)	0.8-1.6	0.8-2.7	1.9-2.5	2.0-3.7	1.8-3.5	2.6-3.7	2.9-4.4	3.4-4.5	3.0-4.0
IVS_{ED} (cm)	0.4-0.6	0.5-1.1	0.7-1.0	0.8-1.2	0.8-1.3	0.8-1.1	0.7-1.5	1.2-1.6	0.6-1.0
IVS_{ES} (cm)	0.6-1.0	0.6-1.2	—	0.8-1.8	1.0-1.7	1.3-1.6	1.1-2.0	1.4-1.9	1.0-1.7
LVW_{ED} (cm)	0.4-0.6	0.6-1.3	0.7-0.9	0.7-1.1	0.8-1.2	0.6-1.0	0.8-1.3	1.0-1.6	0.7-1.2
LVW_{ES} (cm)	0.6-1.0	0.7-1.7	—	0.9-1.8	1.0-1.9	0.8-1.4	1.1-1.6	1.1-1.9	1.2-1.8
EPSS (cm)	0-0.2	—	—	0-1.0	0.1-1.0	0-0.8	0.3-1.4	0.5-1.2	0-1.0
FS (%)	35-57	20-70	30-39	24-48	27-55	21-38	22-37	18-36	30-40
LA_S (cm)	0.8-1.8	—	—	1.8-3.5	1.6-3.2	2.4-3.0	2.4-3.3	2.8-4.6	2.8-4.0
Ao_D (cm)	0.8-1.3	—	—	2.0-3.4	1.4-2.7	2.5-3.5	2.6-3.3	2.8-3.4	2.7-3.5

Ao_D, Aortic root diameter in diastole; *EPSS*, E point to septal separation; *FS*, fractional shortening; *IVS_{ED}*, interventricular septal thickness at the end of diastole; *IVS_{ES}*, interventricular septal thickness at the end of systole; *LA_S*, left atrial diameter in systole; *$LVID_{ED}$*, left ventricular internal diameter at the end of diastole; *$LVID_{ES}$*, left ventricular internal diameter at the end of systole; *LVW_{ED}*, left ventricular posterior wall thickness at the end of diastole; *LVW_{ES}*, left ventricular posterior wall thickness at the end of systole.

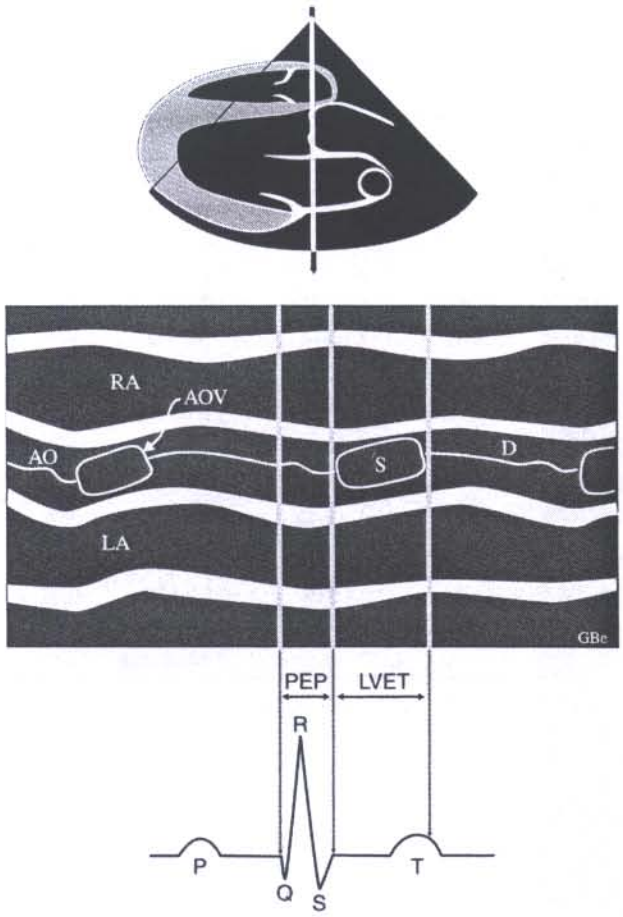


Figure 89-11 Illustration of the method used to evaluate the systolic time intervals. *AO*, aorta; *AOV*, aortic valve; *D*, diastole; *LA*, left atrium; *LVET*, left ventricle ejection time; *PEP*, Pre-ejection period; *RA*, right atrium; *S*, systole.

Hemodynamic Parameters

Doppler echocardiography is used to calculate the cardiac output (CO). The cardiac index is the CO indexed for body surface area (BSA), which takes into account body size variation among animals. The BSA is calculated from body weight using the following formula:

$$BSA = (10.1 \times w^{2/3}) \times 10^{-4}$$

where w is the body weight in grams. Cardiac output is calculated from the product of the heart rate (HR) and stroke volume:

$$CO = HR \times SV$$

The continuity equation is used to evaluate the CO. This equation is based on the theory of conservation of mass that is applied to fluids, which specifies that flow through a given area of a conduit must equal flow through an adjacent area over a given time. Accordingly, SV ejected through a valvular orifice during systole is equal to the flow that passes through the valve, as expressed by the following equation:

$$SV = A \times VTI$$

where A is the cross-sectional area of the orifice calculated from the diameter of that oriface (O) measured by 2-D echocardiography, and *VTI* is the velocity-time integral of the PW Doppler signal across the valvular orifice.

$$A = D^2 \times (\pi/4)$$

$$CO = HR \times D^2(\pi/4) \times VTI$$

Virtually any valve or area in the heart can be used to estimate the CO, but the left ventricular outflow tract and the aortic valve are used most often.

Diastolic Function

Historically, the assessment of diastolic function has received little attention in veterinary medicine. The diastolic function should be evaluated when abnormal ventricular compliance or abnormal diastolic filling patterns are suspected. Doppler echocardiographic study of the transmitral flow profiles (E and A waves) is useful in the characterization of diastolic function. In general, with a decrease in ventricular compliance, the passive filling velocity (E wave) is decreased, and the active atrial contraction velocity (A wave) is increased; thus the E/A ratio is less than 1, representing a delayed relaxation pattern in diastole. This finding has been recognized inconsistently in dogs suspected of having depressed diastolic function. The E/A ratio is even more difficult to evaluate in the cat, owing to its high heart rate, which often causes a fusion of the E and A waves. A *restrictive pattern* has also been described in some cardiomyopathies; in this pattern, the peak E wave velocity is increased and the A wave velocity is decreased. A number of other diastolic indices have been described elsewhere, including the isovolumetric relaxation period, relaxation time index, duration of rapid filling phase, time to peak filling rate, rate of change in LV dimension, and peak rate of ventricular wall thinning in diastole.

NORMAL VALUES

M-mode measurements vary with body size, body surface area, breed, and sedative drugs used. They are also modified by factors such as fear and stress, which significantly affect heart rate and contractility in patients. Therefore reported normal values should always be regarded as approximate. Kienle collected values from the literature to establish mean normal M-mode values for dogs ranging from 3 to 68 kg (Table 89-3). Normal dogs generally have values within a range of 10% of either side of the mean. Figure 89-12 shows the typical echocardiography report used in veterinary medicine.

Table • 89-5

Normal M-Mode Echocardiographic Values in Cats*

$LVID_{ED}$ (mm)	$LVID_{ES}$ (mm)	LVW_{ED} (mm)	LVW_{ES} (mm)	IVS_{ED} (mm)	IVS_{ES} (mm)	LA_S (mm)	Ao_D (mm)	FS (%)	EPSS (mm)
12-18	5-10	3-5	4-9	3-5	5-9	8-13	8-11	30-55	≤4

*These measurement guidelines are based on the author's experience and published data.
Ao_D, Aortic root diameter in diastole; *EPSS*, E point to septal separation; *FS*, fractional shortening; IVS_{ED}, interventricular septal thickness at the end of diastole; IVS_{ES}, interventricular septal thickness at the end of systole; LA_S, left atrial diameter in systole; $LVID_{ED}$, left ventricular internal diameter at the end of diastole; $LVID_{ES}$, left ventricular internal diameter at the end of systole; LVW_{ED}, left ventricular posterior wall thickness at the end of diastole; LVW_{ES}, left ventricular posterior wall thickness at the end of systole.

ECHOCARDIOGRAPHY REPORT

Date _____

File # _____

Patient _____ **Owner** _____

Diagnosis: _____

M-MODE MEASUREMENTS (mm)

	Feline	Min. Poodle	Cocker	Afghan	Golden	Wolfhound
IVS_{ED} _____	3-5	4-6	6.9-9.5	8-12	8-13	6.1-9.9
IVS_{ES} _____	5-9	6-10	-	8-18	10-17	10.3-17.1
$LIVD_{ED}$ _____	12-18	16-20	30.5-37.1	33-52	37-51	48.7-59.1
$LIVD_{ES}$ _____	5-10	8-16	19.4-25	20-37	18-35	30.4-40
LVW_{ED} _____	3-5	4-6	6.8-9	7-11	8-12	7.4-11.6
LVW_{ES} _____	4-9	6-10	—	9-18	10-19	11.7-18.3
FS (%) _____	30-55	35-57	34-39	24-48	27-55	30-40
EPSS _____	<4	<6	—	<10	<10	<10
Ao_D _____	8-11	8-13	—	20-34	14-27	26.5-34.5
LA_S _____	8-13	8-18	—	18-35	16-32	27.8-39.8
LA:Ao _____	<1.3	<1.6	—	<1.6	<1.6	<1.6

LVEF _____

CI _____

2D-STUDY

Pericardial effusion none mild moderate severe

Cardiac masses none observed Location: _____ Size: _____

Blood clots/smoke effect none observed Location: _____ Size: _____

Intraluminal anomalies none observed Location: _____

Valvular anomalies _____

Myocardial anomalies _____

COLOR DOPPLER STUDY

Normal Other: _____

Spectral DOPPLER STUDY

Normal Other: _____

Sedation

NO YES Protocol: _____

Comments _____

Veterinarian's signature: _____

Figure 89-12 Typical echocardiography report.

Table • 89-6

*Normal Values for Spectral Doppler Echocardiography Velocities in Dogs and Cats**

VALVE	CANINE (m/sec)	FELINE (m/sec)
Mitral Valve		
Peak E wave	0.8-1.0	0.55-0.77
Peak A wave	0.5-0.7	0.44-0.6
Tricuspid Valve		
Peak E wave	0.8-0.9	—
Peak A wave	0.5-0.6	—
Aortic Valve		
Peak systolic velocity	≤2.0	≤1.2
Pulmonic Valve		
Peak systolic velocity	≤1.5	≤1.2

*These guidelines are based on the author's experience and published data.

Table • 89-7

Normal Values for Left Ventricular Systolic Time Intervals in Dogs and Cats†*

SYSTOLIC TIME INTERVALS (ms)	CANINE	FELINE
PEP	54 ± 7	46 ± 5
LVET	159 ± 15	116 ± 19
PEP/LVET	0.34 ± 0.05	0.40 ± 0.05
QAVC	214 ± 18	162 ± 24

Atkins IE, Snyder PS: Systolic time interval and their derivatives for the evaluation of cardiac function. *J Vet Intern Med* 1992; 6:55-63.
PEP, Pre-ejection period; *LVET*, left ventricular ejection time; *QAVC*, total electromechanical systole.

CHAPTER • 90

Electrocardiographic (ECG) Techniques

Kelly Anderson-Wessberg

The heart is an electrical field created by the flow of current through individual cardiac muscle cells. These cells are connected by intercalated discs, which allows for rapid spread of electrical activity throughout the heart. The arms and legs are linear extensions of this electrical field. When electrodes are connected to the extremities, an electrocardiograph machine can record electrical activity within the heart.

A *dipole* generates an electrical force by having a positive pole and a negative pole, which are separated by a small distance. The sum of multiple dipoles in the heart is measured at the body surface by the electrocardiograph. The *equivalent dipole theory* assumes that all cardiac cells summate to one dipole on the body's surface.

LEAD SYSTEMS

Each lead evaluates the heart at a specific angle and in a certain plane. The augmented unipolar leads and the standard bipolar leads relate to the frontal plane. They provide information about current flowing right, left, inferior, and superior (head and tail). Chest leads are in the horizontal plane and provide information about current flowing right, left, anterior, and posterior (ventral and dorsal). Bipolar leads use a positive and a negative electrode on that lead. Unipolar leads use a single electrode and a neutral reference point. The letter V indicates a unipolar lead.

Bipolar Leads

Leads I, II, and III are standard bipolar limb leads (Table 90-1). They were devised by Willem Einthoven in 1902 and were the first fixed lead system to be used. The position of these leads forms an approximate equilateral triangle, called *Einthoven's triangle.*

Augmented Unipolar Leads

Leads aVR, aVL, and aVF are augmented unipolar leads ("a" stands for augmented) (Table 90-2). These leads record only half the voltage of the other leads, and the electrocardiograph must amplify, or augment, the deflections to make the size of the complexes comparable to those of the other leads. Because these leads are unipolar, they have a positive electrode and

Table • 90-1

Electrode Placement for Standard Limb Leads

LEAD	POSITIVE	NEGATIVE
I	Left front limb	Right front limb
II	Left hind limb	Right front limb
III	Left hind limb	Left front limb

Table • 90-2

Electrode Placement for Augmented Unipolar Leads

LEAD	POSITIVE ELECTRODE	NEUTRAL REFERENCE POINT
aVL	Left front limb	Right front limb, left hind limb
aVR	Right front limb	Left front limb, left hind limb
AVR	Left hind limb	Right front limb, left front limb

a neutral reference point. The neutral reference point is the average of the other two limb electrodes.

Precordial Chest Leads

In humans, chest leads are used most often for their ability to identify myocardial infarctions. In animals, chest leads are most helpful for identifying P waves not easily seen in other leads; bundle branch blocks; and heart enlargement patterns. Right heart enlargement, in particular, may be identified only through the use of chest leads. In animals, the leads are connected as indicated in Table 90-3. Chest leads are unipolar leads. The neutral reference point is the sum of electrical activity at the left arm (LA), left leg (LL), and right arm (RA). This neutral reference point is essentially the center of the heart.

Other Lead Systems

The orthogonal lead system was designed to measure the heart's electrical activity in three dimensions. This system uses three axes, X, V, and Z, and the three leads are perpendicular to each other. Lead I approximates the X axis; lead aVF approximates the Y axis; lead V_{10} approximates the X axis; lead aN/F approximates the Y axis; and lead V approximates the Z axis. The vectorcardiogram is derived from these leads. This system is not commonly used today because it is cumbersome and usually does not provide additional information.

RECORDING THE ELECTROCARDIOGRAM

The canine patient is placed in right lateral recumbency. This position is recommended because the majority of reference

Table • 90-3

Electrode Placement for Unipolar Chest Leads

CURRENT LEAD NAME	ELECTRODE LOCATION	OLDER LEAD NAMES	HUMAN EQUIVALENT
rV_2	Right side, 5th ICS, near sternum	CV_5 RL	V_1
V_2	Left side, 6th ICS, near sternum	CV_6 LL	V_2, V_3
V_4	Left side, 6th ICS, at costochondral junction	CV_6 LU	V_4, V_5
V_{10}	Over dorsal spine of 7th thoracic vertebra	CV_{10}	V_6

ICS, Intercostal space.

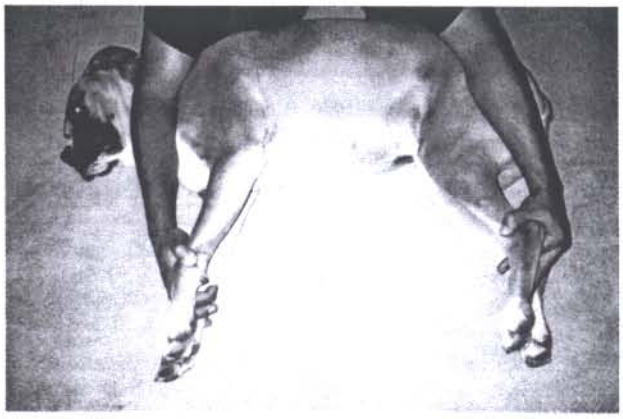


Figure 90-1 Proper patient positioning.

data were obtained from dogs in this position. Metal tables should not be used, nor should the animal be positioned directly on the ground. With the patient's head to the right, the handler may place the right arm over the patient's neck and the left arm over the hindquarters. The patient's legs are held perpendicular to the body and parallel to each other. It is essential that each pair of limbs remain parallel to each other and that enough space remains between the limbs to avoid contact between limbs or electrodes. Patient movement is restricted without discomfort. Figure 90-1 shows proper patient positioning.

The electrodes are attached directly to the skin. It is not necessary to clip the hair or prepare the skin. Electrodes may be alligator clips, adhesive patches, or wire. If alligator clips are used, patient discomfort can be minimized by filing or blunting the teeth and relaxing the spring. Alternatively, a gauze pad can be placed between the alligator clip and the skin. Limp electrodes are placed just proximal to the caudal surface of the elbow (LA, RA) and just proximal to the stifle on the cranial surface of the hind limbs (LL, RL). Chest leads are placed according to their respective locations (see Table 90-3). To maintain electrical contact, the electrodes are saturated with 70% isopropyl alcohol or covered with ECG electrode gel.

A 1-millivolt pulse should be recorded at the beginning of every ECG to ensure standardization. A minimum of three complexes of each lead, at 50 mm/sec, is recorded. A rhythm strip is obtained by recording lead II at 25 or 50 mm/sec. The ECG is labeled with the patient's name and medical record number, the date, and the paper speed.

Inaccurate ECG recordings may lead to misdiagnosis and inappropriate treatment. Improper patient positioning, electrical interference, and breathing artifacts are the most common causes of inaccurate ECG recordings. Small changes in limb or electrode placement can result in significant changes on the ECG. Lead aVL has been shown to be the lead most affected by forelimb malposition. Electrical interference may occur because of loose connections between the alligator clips and cable tips or because of nearby operation of electrical equipment.

In feline patients or dyspneic dogs, an ECG recorded in a sternal position is adequate. If restraining the animal at all presents a danger, a rhythm strip may be obtained in any position. An ECG recorded in a nontraditional position may yet provide vital information, particularly about the rhythm, while avoiding any harm to the patient.

CHAPTER 91

Electromyography and Nerve Conduction Velocity Studies

David Lipsitz

Diseases involving any part of the neuromuscular system (peripheral nerve, muscle, neuromuscular junction) may be clinically identical, and the neurologic examination may not always reveal which part of the neuromuscular system is affected. Electrodiagnostic testing may extend the examiner's capabilities in these disorders, by supplementing clinical findings and localizing lesions within the neuromuscular system. They may also aid in selecting and guiding nerve and muscle biopsies. To avoid movement, discomfort, and lack of cooperation, dogs and cats are usually placed under general anesthesia when examined.

ELECTROMYOGRAPHY

Electromyography (EMG) is a method for detection and display of insertional, spontaneous, and voluntary electrical activity of skeletal muscles. EMG deals primarily with the electrical activity of a single muscle fiber or groups of muscle fibers. EMG is based upon the inherent excitability of normal skeletal muscle and on changes in this excitability during disease. Normal muscle is electrically and mechanically silent except during voluntary contraction. Denervated muscle fibers and muscle fibers damaged due to primary disease will spontaneously depolarize, causing readily detectable spontaneous activity.

EMG is most useful in defining mononeuropathies, polyneuropathies, and myopathies and for differentiating neurogenic from disuse atrophy. Disuse atrophy and diseases of neuromuscular transmission do not induce EMG abnormalities. EMG abnormalities are not specific for a particular neuromuscular disease, but a distinction can frequently be made based on neurologic examination, distribution of affected muscles, and results of nerve conduction studies. EMG can also be used to select a biopsy site in diseases where only specific muscles are involved, such as masticatory muscle myositis.

The most commonly used EMG electrodes are concentric (coaxial) needle electrodes, which measure the potential difference between a nichrome silver or platinum wire and the surrounding stainless steel shaft. Factors to consider when performing an EMG examination are the amount of electrical interference in the room from extraneous sources (heating pads, electrical outlets) and patient-monitoring equipment. The dog or cat must be properly grounded and the machine set to filter 60 Hz interference and radio interference to obtain proper recordings. The sensitivity of the EMG examination can be increased by performing multiple insertions into a specific muscle group and by examining multiple muscle groups. EMG abnormalities may be patchy in their distribution within a muscle or within muscle groups.

Normal muscle is electrically silent, but electrical activity may be detected in normal skeletal muscles. These are as follows:

- Insertional activity is caused by mechanical stimulation and disruption of both muscle fibers and membranes by the EMG needle; it should subside in a few hundred milliseconds.
- Miniature endplate potentials (MEPPs) are caused by spontaneous release of single quanta of acetylcholine causing partial depolarization of the postsynaptic membrane.
- Endplate spikes are associated with MEPPs when enough acetylcholine is released to completely depolarize a single muscle fiber. They should not be confused with fibrillation potentials.
- Motor unit action potentials (MUAPs) are large action potentials caused by summation of action potentials of one or several motor units. They are present during contraction. They are not routinely evaluated in veterinary electrophysiology.

The spontaneous activity of abnormal skeletal muscles are as follows:

- Increased and prolonged insertional activity is due to mechanical irritation of firing muscle fibers.
- Fibrillation potentials and positive sharp waves arise from depolarization of the T-tubular system or depolarization of the surface sarcolemma. They result from the same type of pathologic process but have a different morphology due to their orientation with respect to the EMG electrode.
- Giant MUAPs are large polyphasic potentials that suggest reinnervation of muscle fibers.
- Myotonic discharges result from delayed relaxation of single muscle fibers due to ion channel defects; the discharges have a distinct waxing and waning firing rate and produce the classic "dive bomber" sound.
- Complex repetitive discharges are the spontaneous firing of groups of muscle fibers; they do not wax and wane like myotonic discharges. They have previously been termed *pseudomyotonia* and *bizarre high-frequency discharges*.

MOTOR AND SENSORY NERVE CONDUCTION

Nerve conduction and nerve conduction velocities are affected by various neuropathies, and methods have been developed for testing nerve conduction of both motor and sensory nerves. Nerves commonly tested are the peroneal, tibial, radial, and ulnar. Clinicians can evaluate motor nerves by stimulating a peripheral nerve and recording the stimulated compound muscle action potential (CMAP). They can evaluate sensory nerves by stimulating cutaneous nerves (which have no motor axons) and recording the sensory nerve action potentials (SNAP) while the electrical potential conducts along the nerve.

Regardless of which nerves are stimulated, certain aspects of neurophysiology must be considered. Insulated stainless steel needle electrodes (except for the tip) are commonly used for stimulating and recording. Stimulating electrodes should be placed such that the negative pole (cathode) is more proximal to the recording site than the positive pole (anode) to avoid conduction block. The negative charges at the cathode depolarize the nerve, whereas the positive charge

at the anode hyperpolarizes the nerve. Supramaximal stimulus strength is necessary to ensure that all axons are activated. A ground electrode is imperative, usually placed between stimulating and recording electrodes. Motor nerve conduction velocities are calculated by measuring the latency difference between the CMAP responses from two sites along the nerve and by measuring the distance between these sites, using the following formula:

$$\text{MNCV (m/s)} = \text{Distance (mm)}/\text{Latency}_{\text{proximal}} - \text{Latency}_{\text{distal}}\text{(ms)}$$

Using only one stimulation site results in inaccuracies of MNCV because it takes into account neither the neuromuscular transmission time nor the muscle fiber depolarization time. Sensory nerve action potentials are recorded directly from the nerve itself, so only one stimulation site is necessary to calculate the conduction velocity. SNAPs are quite small compared with CMAPs (μV versus mV), so signal averaging is necessary to obtain recordings, thereby avoiding background noise and muscle artifact.

Abnormalities of both motor and sensory nerve conduction studies include the following:

- Slowing of conduction velocity without a significant decrease in CMAP amplitude is caused by demyelination with the axons remaining intact.
- Temporal dispersion and polyphasia of action potentials occur normally due to axons with different conduction velocities but may be prolonged with demyelination.
- The number of muscle fibers activated determines the amplitude of the CMAP. Decreased amplitude of CMAPs without temporal dispersion is caused by axonal degeneration, myopathies, or disorders of neuromuscular transmission.
- Many neuropathies cause both segmental demyelination and axonal degeneration; therefore all of the previously mentioned abnormalities may be seen together.

CHAPTER 92

Nasoesophageal, Esophagostomy, and Gastrostomy Tube Placement Techniques

Stanley L. Marks

The enteral route is the preferred method of nutritional support in animals with a functional gastrointestinal (GI) tract. Many techniques for obtaining enteral access are available, and the approach used depends on several issues, including anticipated duration of enteral support, aspiration risk, condition of the GI tract, the animal's temperament, and the level of local expertise. The reader is advised to review Chapter 161 in the Dietary Considerations of Systemic Problems section for a comprehensive overview of diet selection and feeding implementation for the anorectic or sick animal.

ENTERAL FEEDING ACCESS DEVICES

Most feeding tubes today are made of polyurethane or silicone. These materials have tended to replace the older polyvinyl chloride feeding tubes that stiffened when exposed to digestive juices and are more irritating, necessitating frequent tube replacement. Silicone is softer and more flexible than other tube materials with a greater tendency to stretch and collapse. Polyurethane is stronger than silicone, allowing for a tube of the same French size to have thinner walls and a larger internal diameter. The flexibility and decreased internal diameter of silicone tubes may lead to clogging or kinking of the tube. Both polyurethane and silicone do not rapidly disintegrate or embrittle in situ, providing a longer "wear." The French (F) unit measures the outer lumen diameter of a tube (each F unit is equal to 0.33 mm).

Nasoesophageal Tube Placement

Nasoesophageal tubes are a simple and efficient choice for the short-term (less than 10 days) nutritional support of most anorectic hospitalized animals that have a normal nasal cavity, pharynx, esophagus, and stomach. Nasoesophageal tube feeding is contraindicated in animals that are vomiting, comatose, or lack a gag reflex. Polyvinyl chloride (Infant Feeding Tube, Argyle Division of Sherwood Medical, St. Louis, Mo.) or red rubber tubes (Sovereign Feeding Tube, Monoject Division of Sherwood Medical) are the least expensive tubes for dogs and cats, although the polyvinyl chloride tubes may harden within 2 weeks of insertion and cause irritation or ulceration of the pharynx or esophagus. Tubes made of polyurethane (MILA International, Inc., Florence, Ky.) or silicone (Global Veterinary Products, Inc., New Buffalo, Mich.) are more expensive; however, they are less irritating and more resistant to gastric acid, allowing prolonged usage. An 8 to 10 F × 43-inch tube (preferably with a guide wire) is suitable for dogs weighing more than 15 kg. A 5 to 8 F × 22- to 43-inch tube is recommended for dogs weighing less than 15 kg and for cats.

The length of tube to be inserted into the distal esophagus is determined by measuring the distance from the tip of the pet's nose to the eighth or ninth rib. This will help verify the correct placement of the tube in the distal esophagus rather than the stomach and decrease the likelihood of reflux esophagitis. Desensitization of the nasal cavity with four or five drops of 0.5% proparacaine hydrochloride is recommended. The tube tip should be lubricated with a water-soluble lubricant or 5% lidocaine ointment to facilitate passage. The tube is passed by maintaining the animal's head in the normal angle of articulation and gently directing the tip of the tube in a ventromedial direction. The tube should move with minimal resistance through the ventral meatus and nasopharynx and into the esophagus. In dogs, the presence of a small ventral ridge at the proximal end of the nasal passage necessitates directing the tip of the tube dorsally initially to allow

passage over the ventral ridge and into the nasal vestibule (Figure 92-1). Nasoesophageal intubation is more difficult to perform in dogs because of their long, narrow nasal passages and extensive turbinate structures. In the dog, the tube is directed in a ventromedial direction while pushing the external nares dorsally. This maneuver opens the ventral meatus and guides the tube into the oropharynx.

If the tube is unable to be passed with minimal resistance into the oropharynx, it should be withdrawn and redirected because it could be positioned in the middle meatus with its tip encountering the ethmoid turbinate. Once the tube has been passed to the level of the attached "butterfly" tape, it should be secured as close to the nostril as possible, with either suture material or glue (Superglue, Loctite Corp., Cleveland, Ohio). A second tape tab should be secured to the skin on the dorsal midline between the eyes (Figure 92-2). An Elizabethan collar is usually required for dogs to prevent inadvertent tube removal; however, most cats do not require such a device. The clinician can remove the tube by clipping the hair that is attached to the glue.

After placement the tube position is checked by injecting 5 to 10 mL of air while auscultating the cranial abdomen for borborygmus, or it is done by infusing 3 to 5 mL of sterile saline or water through the tube and observing for a cough response. Correct tube placement can also be confirmed with a lateral survey thoracic radiograph and observing the position of the radiopaque tube in the esophagus. The most common complications associated with the use of nasoesophageal tubes include epistaxis, dacryocystitis, rhinitis, tracheal intubation and secondary pneumonia, and vomiting.

Pharyngostomy Tube Placement

The increasing availability of endoscopic equipment and the superior benefits of esophagostomy and percutaneous gastrostomy tube placement have resulted in pharyngostomy tubes becoming virtually obsolete. Nevertheless, the introduction of placement modifications has resulted in a dramatic reduction in complications associated with the interference of epiglottic movement and partial laryngeal obstruction. The indications for pharyngostomy tube placement are similar to those for

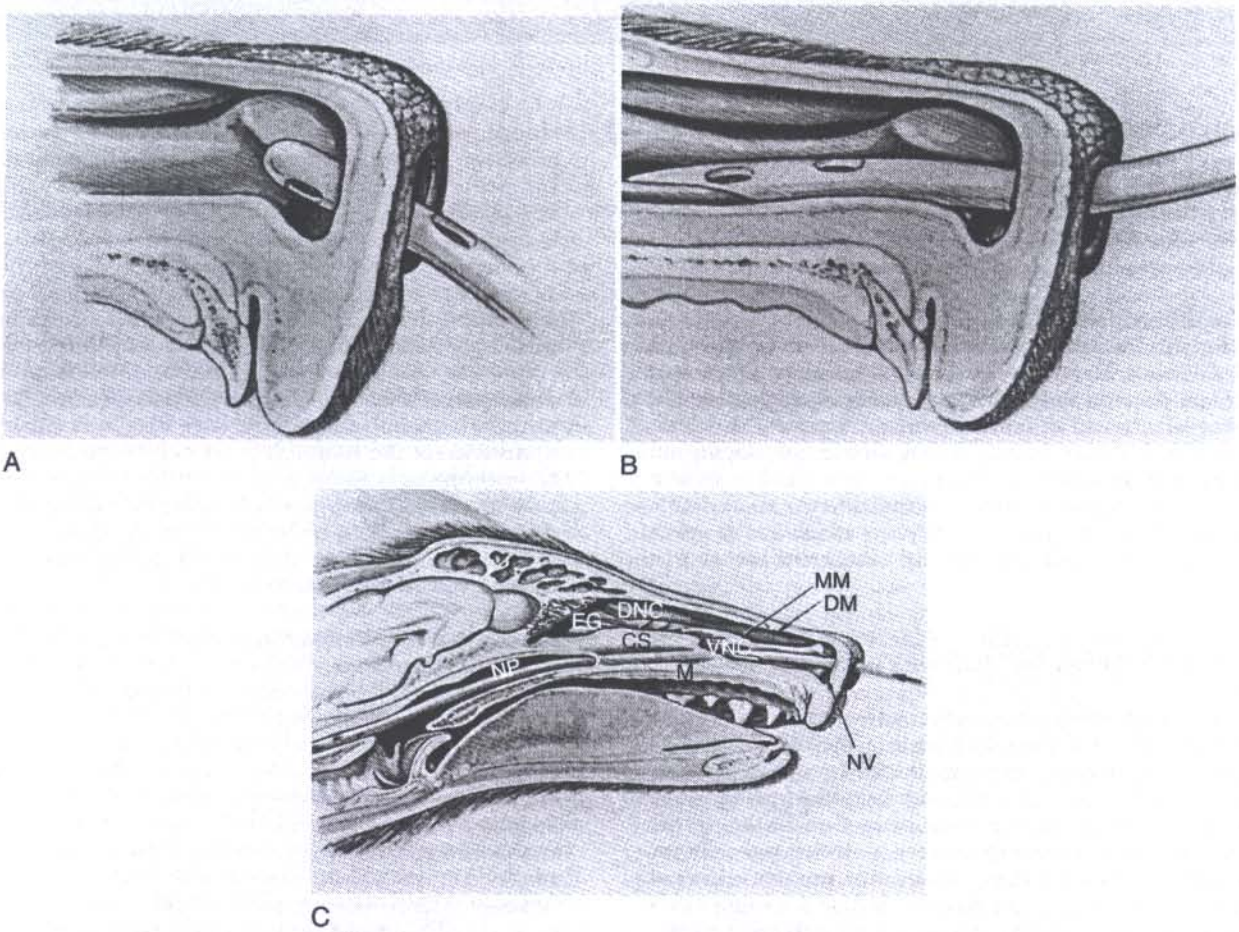
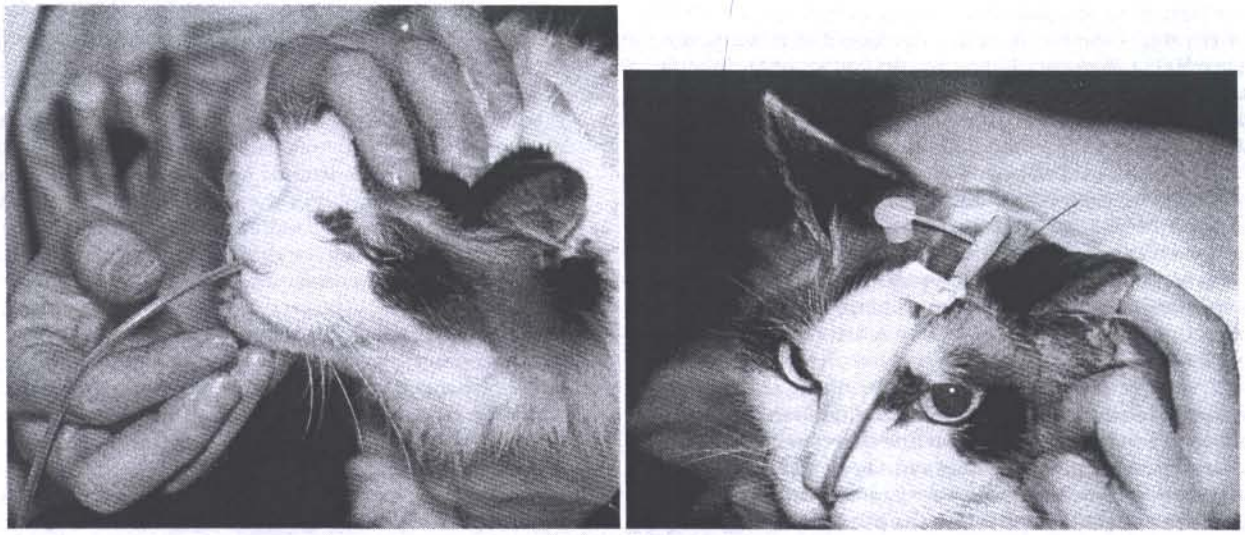


Figure 92-1 Parasagittal section showing step-wise insertion of a nasoesophageal tube through the ventral meatus of a dog. A, The presence of a small ventral ridge at the rostral end of the nasal passage necessitates directing the tip of the tube dorsally to clear the protuberance. B, Once past the protuberance, the tube is aimed medially and ventrally and advanced into the ventral meatus. C, Tube through ventral meatus and nasal pharynx *(NP)*. Structures identified: nasal vestibule *(NV)*, cartilaginous septum *(CS)*, maxilla *(M)*, dorsal meatus *(DM)*, middle meatus *(MM)*, ethmoidal conchae *(EC)*, ventral nasal conchae *(VNC)*, dorsal nasal conchae *(DNC)*, and alar fold *(AF)*. (Reprinted with permission from Crowe DT: Clinical use of an indwelling nasogastric tube for enteral nutrition and fluid therapy in the dog and cat, *J Am Anim Hosp Assoc* 22:675, 1986.)



A B

Figure 92-2 A, The tip of the nasoesophageal tube has been lubricated and passed into the ventral meatus by positioning the animal's head in a normal angle of articulation. B, The nasoesophageal tube can be secured to the skin on the dorsal midline between the eyes with tape "butterflies." A second tape tab should be secured as close to the nostril as possible, using either suture material or glue.

nasoesophageal tube placement; however, the procedure requires general anesthesia. Pharyngostomy tubes are specifically indicated for pets requiring long-term nutritional support with bypass of the oral cavity or oropharynx.

For tube placement, the animal is anesthetized with either a short-acting injectable or inhalant anesthetic, intubated, and placed in lateral recumbency. The tube can be placed on either the right or left side of the oral pharynx. An area of skin caudal to the mandible over the hyoid apparatus is aseptically prepared. A 14 to 20 F red rubber, latex, silicone, or polyurethane tube can be used and is premeasured as described for nasoesophageal intubation, to avoid entering the stomach. A mouth gag is placed and an index finger is used to palpate the hyoid apparatus from inside the patient's mouth. Caution should be exercised to palpate dorsally and caudal to the stylohyoid and epihyoid bones, as close to the cervical esophagus as possible. This will help avoid creating the stoma site rostral to the hyoid apparatus and causing obstruction or interference with epiglottic function. The pulsating carotid artery is palpated and avoided while a 1 cm skin incision is made over the finger that is pushing the pharyngeal wall outwards. The landmarks for the incision include the hyoid apparatus and the bifurcation of the external jugular vein into the maxillary and linguofacial veins. The incision is made caudal to the hyoid in a direction that bisects the angle created by the bifurcation of the external jugular vein. Curved Kelly forceps are used to bluntly dissect soft tissue to create a stoma from the skin incision to the inside of the pharynx in a caudal direction. Blunt dissection will help prevent damage to the external carotid artery, vagosympathetic trunk, and hypoglossal nerve in the dissection field. The flared end of the tube should be cut and grasped with the curved hemostats before inserting the tube into the esophagus by way of the oral cavity and tunneling the cut end of the tube out through the stoma. Alternatively, the tube can be advanced through the tunnel created by blunt dissection and passed down the esophagus. The tube should run straight into the esophagus without kinking to avoid interference with the epiglottis or glottis. The clinician secures the tube by placing adhesive tape in a butterfly configuration around it and suturing the tape to the skin or by placing friction (Chinese finger-tie) sutures. Antibiotic ointment should be applied to a cut gauze sponge that is placed around the tube at the stoma-skin edge. A protective circumferential bandage is used to keep the tube against the patient's neck.

Complications of pharyngostomy tube placement include airway obstruction, aspiration of food, vomiting or reflux, epiglottic entrapment, laryngeal obstruction, recurrent laryngeal nerve injury, tube displacement, chewing of the tube, esophagitis, and infection of the wound site. Large diameter tubes (larger than 24 F) are not recommended due to the increased risk of interference with epiglottic movement or obstruction of the glottis. Displacement of the tube secondary to vomiting or regurgitation necessitates replacement of the tube by opening the animal's mouth and redirecting the tube down the esophagus. If the tube is damaged due to chewing, a new tube may be passed through the old stoma, provided it has had at least 5 days to form.

Esophagostomy Tube Placement

Esophagostomy feeding tubes are easily inserted, and insertion only requires light general anesthesia with isoflurane, or heavy sedation and intubation with a cuffed endotracheal tube. The technique is minimally invasive, and no specialized endoscopic equipment is needed. The dog or cat should be placed in right lateral recumbency, and the left lateral cervical region clipped and aseptically prepared for tube placement. A 14 to 20 F red rubber catheter, (Sovereign Feeding Tube, Sherwood Medical) silicone catheter (Global Veterinary Products) or polyurethane catheter (MILA International) should be premeasured from the midcervical esophagus to the eighth rib and marked with a permanent marker to ensure the distal end of the catheter terminates in the distal esophagus.

Three basic techniques for placement of a midcervical esophagostomy tube have been described:

1. Technique using right-angled forceps (Carmalt, Mixter, Schnidt or Kantrowitz) forceps: The clinician should advance the right-angle forceps into the midcervical esophagus from the oral cavity and use the angle of the jaw and

the point of the shoulder for landmarks to help ensure that the tip of the forceps can be palpated externally in the midcervical region. Then the curved tips of the Carmalt forceps should be pushed laterally at the midcervical esophagus, so they can be palpated below the skin. A No. 11 scalpel blade should be used to make a stab incision through the skin only, exposing the subcutaneous tissue and muscle layers of the esophagus. The clinician should be careful to avoid the jugular and maxillofacial veins when selecting the stoma site. The tip of the forceps should be exteriorized from the esophageal lumen through the skin incision, and the advancing forceps should be guided through the esophageal muscle layers; then the clinician should carefully dissect the esophageal mucosa off the tip of the forceps with a scalpel blade. The tip of the forceps should be used to grasp the distal end of the feeding tube, and the tube should be drawn out of the oral cavity. Next, the clinician should secure the distal end of the feeding tube using the forceps to ensure that the tube remains exteriorized while the proximal end of the tube is pulled out of the animal's mouth. The proximal tip of the feeding tube should be retroflexed and advanced in an aboral direction across the pharynx and down the esophagus, while the external end of the tube is slowly retracted 2 to 4 cm. A wire guide can be used to facilitate pushing the proximal tip of the feeding tube into the esophagus. The exteriorized portion of the tube will be observed to rotate in a cranial direction while the tube moves down the esophagus, indicating correct placement of the tube in the esophagus. Retention sutures (Chinese finger-knot suture) using 3-0 polypropylene are used to secure the distal end of the tube to the skin. An additional method of securing the tube involves passing a heavy suture on a taper needle through the skin next to the tube and into the periosteum of the wing of the atlas.

Antibiotic ointment and gauze dressing is placed at the incision site, and the tube and entrance site is loosely bandaged with conforming gauze wrap. The correct placement of the tube in the mid- to distal esophagus should be confirmed radiographically. It is important to ensure that the tube does not traverse the lower esophageal sphincter, because the tube can cause irritation and predispose the pet to vomiting and gastroesophageal reflux. Feeding can be instituted once the animal has recovered from anesthesia. The tube esophagostomy and skin interphase should be examined at least daily during the first week for evidence of infection or leakage of food or saliva. The stoma site can be kept clean with a topical antiseptic solution (1:100 Betadine solution in 0.9% saline). Once nutritional support is no longer needed, the tube can be easily removed by cutting the Chinese finger-trap anchoring suture and pulling the tube. The wound should be allowed to heal by second intension.

2. Percutaneous feeding tube applicator technique: An alternative tube esophagostomy technique using an (ELD) percutaneous feeding tube applicator or similar device can be used. The applicator is inserted into the midcervical esophagus via the oral cavity. The distal tip is palpated, and an incision is made through the skin and subcutaneous tissue over the tip of the ELD. The trocar is advanced through the esophageal wall and directed through the incision. The distal end of the feeding tube is secured to the eyelet of the trocar with suture material. The ELD device and attached feeding tube are retracted into the esophagus and exteriorized out of the oral cavity. The feeding tube is redirected into the midcervical esophagus after inserting a wire stylet into the distal tip of the feeding tube. The tube is secured to the skin as previously mentioned.
3. Percutaneous needle catheter technique: This method incorporates the use of an esophagostomy introduction tube (Van Noort oesophagostomy tube set, Global Veterinary Products) (Figure 92-3) that is introduced into the midcervical esophageal area. The slot in the distal portion of the tube is palpated, and a peel-away® sheath needle (Global Veterinary Products) is introduced into the distal portion of the tube. The needle is removed from the sheath, and a 10 F catheter is introduced through the sheath to the distal third of the esophagus. The sheath is peeled away and the esophagostomy tube is carefully removed. The feeding tube is secured as described previously. This technique has limitations because the small diameter of the feeding tube (10 F) only allows for the administration of fluids and liquid enteral formulas.

Despite the potential for esophageal scarring and stricture formation, esophageal stricture or a persistent esophagocutaneous fistula has not developed. The most common minor complication is peristomal inflammation, with peristomal abscessation occurring infrequently. Most of the inflammatory reactions are mild and respond to thorough cleansing with topical antibiotics. Other less common complications include vomiting of the tube into the oral cavity.

Gastrostomy Tube Placement

Gastrostomy tube feeding is indicated for long-term (weeks to months) nutritional support of anorectic or dysphagic animals. Gastrostomy feeding tubes are relatively large in diameter (20 to 24 F), allowing administration of blended pet foods and medications. Gastrostomy tube feeding is contraindicated in animals with persistent vomiting, decreased consciousness, or GI obstruction. Caution should be exercised in conditions under which the stomach cannot be apposed to the body wall (severe ascites, adhesions, space-occupying lesions).

Gastrostomy tubes can be placed percutaneously or during laparotomy. Placement is usually accomplished with a percutaneous endoscopic gastrostomy (PEG) technique or a blind percutaneous gastrostomy (BPG) technique. There are a variety of feeding tubes that can be used for gastrostomy feeding including latex, polyurethane, and silicon tubes with French-Pezzer mushroom, balloon, bumper, or silicone dome tips (Figure 92-4).

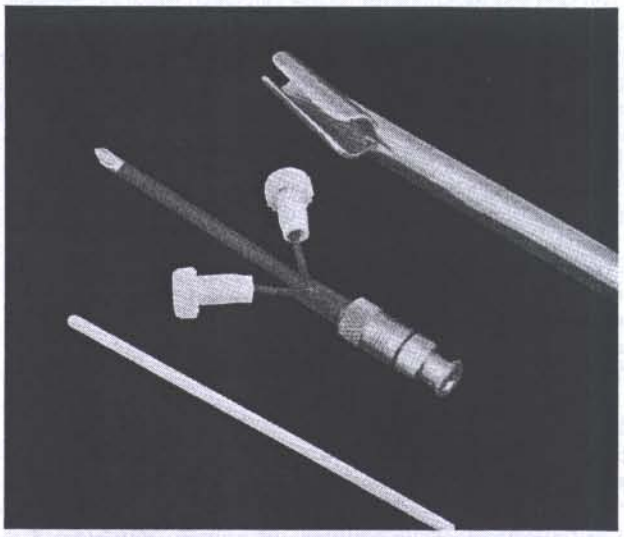


Figure 92-3 Photograph of the esophagostomy tube set, illustrating the esophagostomy introduction tube, 10 gauge, 5.0 cm long needle with Peel-away® sheath needle, and a 10 F silicone catheter.

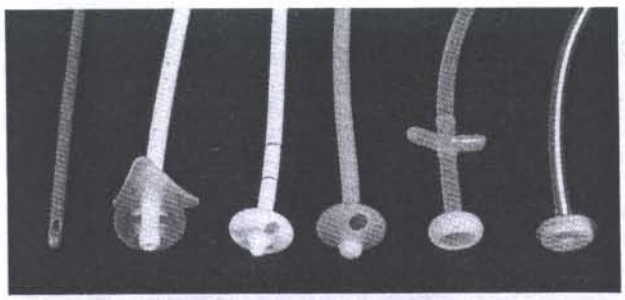


Figure 92-4 Gastrostomy tubes illustrating the various materials and catheter tips. *Left to right:* French red rubber catheter, silicone balloon catheter, silicone mushroom catheter, latex mushroom catheter, silicone catheter with dome, polyurethane catheter with bumper.

The silicone catheters can be purchased from Global Veterinary, Inc. (New Buffalo, KY) and US Endoscopy (Mentor, OH); polyurethane from MILA International, Inc. (Florence, KY); and latex catheters from BARD Urological Division (Murray Hill, NJ). One can modify the catheters by cutting off and discarding the flared, open end of the catheter and cutting off two 2 cm pieces of tubing (to be used as internal and external flanges) from the same end of the catheter. The end of the catheter opposite the mushroom tip is trimmed to facilitate its introduction into the larger opening of a disposable plastic micropipette. The clinician should make a small stab incision through the center of each flange, and fit one flange over the cut end of the catheter—sliding it down until it rests against the mushroom tip. The other 2 cm piece of tubing will be used as an external flange that lies against the abdominal wall. Cutting the small nipple on the mushroom tip to enhance the flow of food through the tube is *not* recommended. Removing the tip of the mushroom compromises the integrity of the mushroom and hinders percutaneous removal of the tube.

Percutaneous Endoscopic Gastrostomy Technique

Endoscopic and blind placement of gastrostomy tubes necessitates brief anesthesia. The animal should be placed in right lateral recumbency so that the stomach tube can be placed through the greater curvature of the stomach and the left body wall. Preparation for both percutaneous procedures is identical and involves a surgical prep of the skin caudal to the left costal arch. The endoscope is introduced into the stomach, and the stomach is carefully inflated until the abdomen is distended but not drum tight. The left body wall is transilluminated with the endoscope to ensure that the spleen is not positioned between the stomach and body wall. An appropriate site for insertion of the tube is determined by endoscopically monitoring digital palpation of the gastric wall. A small incision is made in the skin with a scalpel blade, and an intravenous catheter (16 to 18 G, 1.5 to 2 inches) is stabbed through the body wall into the lumen of the stomach (Figure 92-5, *A*). The stylet is removed and nylon or polyester suture is threaded through the catheter into the lumen of the stomach. The suture material is grasped with the endoscopic biopsy forceps (Figure 92-5, *B*), and the endoscope and forceps are carefully withdrawn through the esophagus and out of the mouth. The suture material is secured to the feeding tube, and gentle traction is applied to the suture material at its point of exit from the abdominal wall (Figure 92-5, C). The feeding tube is pulled out through the body wall, allowing the mushroom end to draw the stomach wall against the body wall (Figure 92-5, *D*). The feeding tube is anchored in this position by the external flange placed over the catheter at the skin surface (Figure 92-5, *E*). The endoscope is then reinserted into the stomach to verify the correct placement of the mushroom against the gastric mucosa. If blanching of the mucosa is observed, less tension should be applied to the tube, otherwise ischemic necrosis of the gastric wall may ensue. A plastic clamp is placed over the tube, and the tube is capped with a Y-port connector. A jacket made from stockinette (San Jose Surgical Supply, Inc., San Jose, CA) is fitted to protect the tube (Figure 92-5, *F*).

Complications related to PEG tubes include those associated with placement of the tube (splenic laceration, gastric hemorrhage, and pneumoperitoneum), and delayed complications such as vomiting, aspiration pneumonia, tube extraction, tube migration, and stoma infection. Clinicians can minimize splenic laceration by insufflating and transilluminating the stomach prior to placement of the needle or catheter into the abdominal wall. The authors have recognized a discordant number of large breed dogs that have had major complications secondary to the stomach "falling off" the silicone dome at the end of the gastrostomy tube. The stoma appeared normal in all dogs, with the unfortunate consequence that several dogs were fed through the gastrostomy tube. This complication occurred despite the placement of an internal flange between the dome and the gastric mucosa. For this reason, it is recommended that all dogs heavier than 30 kg do not have a PEG procedure and instead have a gastrostomy tube placed surgically. Minor complications include pressure necrosis at the stoma site and cellulitis.

Blind Percutaneous Gastrostomy Technique

An alternative technique for nonendoscopic and nonsurgical gastrostomy tube placement has been described. The gastrostomy tube placement device can be prepared with a length of vinyl or stainless steel tubing (diameter 1.2 to 2.5 cm) purchased from a hardware store, or an ELD gastrostomy tube applicator (Jorgensen Laboratories, Loveland, Colo.) or gastrostomy tube introduction set (Global Veterinary) can be used. The ELD gastrostomy tube applicator is the only device that uses an internal trocar, whereas the Cook gastrostomy tube introduction set contains a wire that is threaded through an introduction needle. The distal tip of a stainless steel tube can be flared and deflected 45 degrees to the long axis of the tube to help displace the lateral body wall. The lubricated tube is passed through the mouth and into the stomach. The tube is then advanced until the end of the tube displaces the stomach and lateral abdominal wall. Positioning the animal with its head over the edge of the table and lowering the proximal end of the tube will facilitate identifying the tube tip through the body wall. For the Cook gastrostomy introduction set or similarly prepared device, a percutaneous needle is introduced into the lumen of the tube while the assistant firmly holds the distal tip of the tube between two fingers. A skin nick is made over the end of the tube and a 14-gauge over-the-needle catheter advanced into the lumen of the tube. Proper positioning of the catheter is confirmed by moving the hub from side to side and feeling the catheter tip strike the inside of the tube. A guide wire prepared from a banjo string is attached to suture material that is 60 cm longer than the stomach tube. The guide wire is threaded through the catheter, into the tube, and out the mouth of the patient. The attached suture is pulled through the tube and cut from the wire at the mouth. The tube and catheter are removed, and the suture is attached to a gastrostomy tube that is secured in an identical fashion to the PEG tube procedure.

The reported complication rate for BPG is similar to that of PEG; however, the risk of penetrating the spleen, stomach, or omentum is greater when the stomach is not insufflated with air prior to positioning the tube against the lateral abdominal wall. Contraindications to using the "blind" technique include pets with esophageal disease and those that are

severely obese (which would preclude accurate palpation of the tube against the abdominal wall). Such animals should have gastrostomy tubes placed surgically.

Gastrostomy Tube Removal

For percutaneously placed tubes, it is recommended that the tube be left in place for a minimum of 14 days. Animal's receiving immune-suppressive therapy or those that are severely debilitated may require longer for a peritoneal seal to form. The tube should only be removed when oral food intake is sufficient to meet the pet's caloric requirement. One of two methods of Pezzer tube removal can be applied: The tube can be cut at the body wall and the mushroom tip pushed into the stomach to be passed in the feces. This method is safe in medium to large size dogs, because the mushroom and internal bumper should be easily passed in the stool. Alternatively, a stylet can be inserted into the tube to flatten the mushroom tip, while exerting firm traction on the tube. This method is recommended for cats and small dogs, because the mushroom can cause intestinal obstruction. Removal of the MILA catheter is accomplished by deflating the bumper, which occurs once the Y-port adapter is removed. Catheters with a dome (US Endoscopy) are removed by gentle, but firm traction on the tube. The gastrocutaneous tract should seal with minimal or no leakage within 24 hours.

Gastrostomy Tube Replacement

The PEG tube may malfunction or be prematurely removed by the dog or cat, requiring replacement. If the gastrostomy

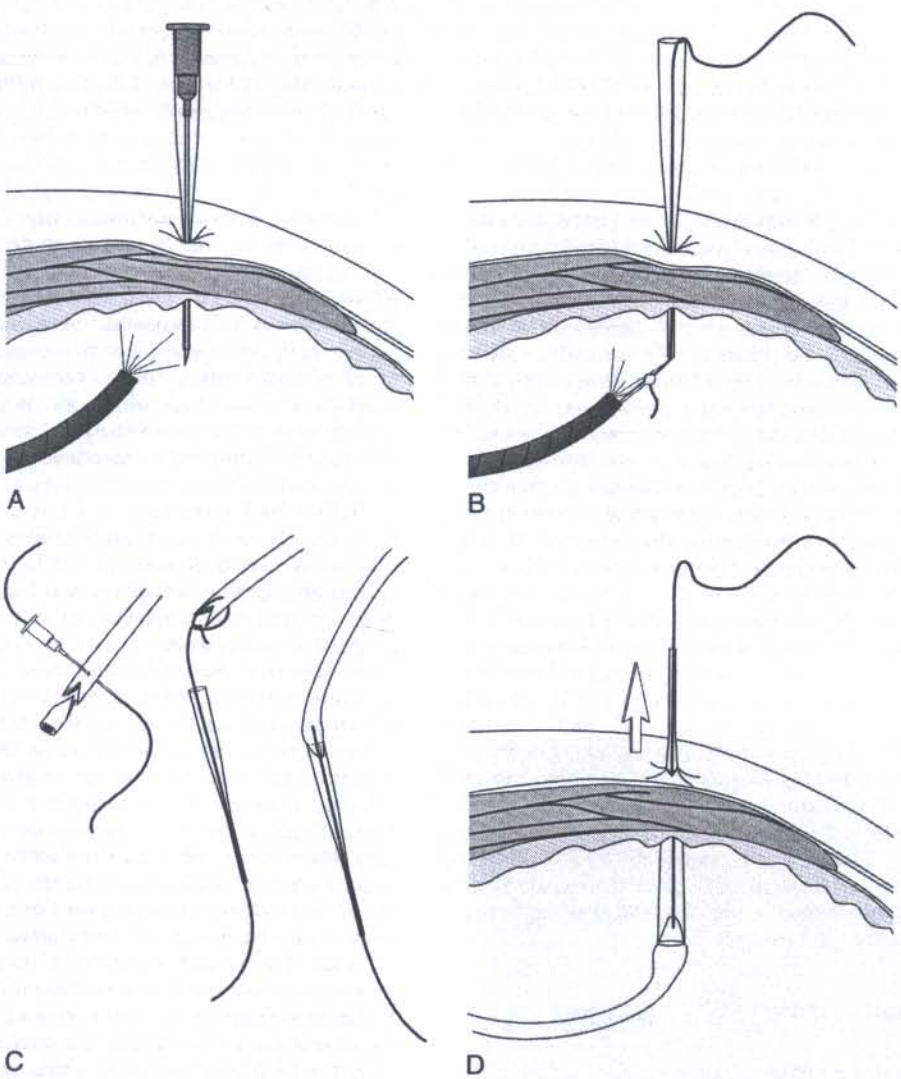


Figure 92-5 Percutaneous endoscopic gastrostomy (PEG) technique. **A,** With the dog in right lateral recumbency, the endoscope is introduced into the stomach, and the stomach is insufflated with air. The left body wall is transilluminated with the endoscope to ensure that the spleen is not between the stomach and the body wall. A 16 to 18 G sheathed catheter is pierced transabdominally into the insufflated stomach lumen. **B,** The catheter stylet is removed, and nylon suture is advanced through the catheter until it can be grasped with endoscopic retrieval forceps. The nylon suture is pulled out through the mouth while the endoscope is withdrawn. **C,** The suture material is secured to the feeding tube and water-soluble jelly is applied liberally to the catheter sheath and the mushroom tip catheter. **D,** The lubricated catheter is drawn down the esophagus and into the stomach while the assistant applies traction on the suture exiting the abdominal wall.

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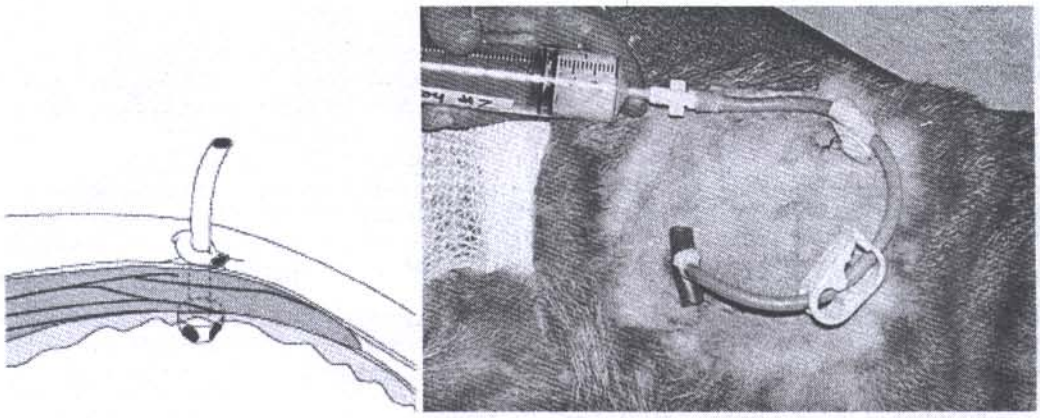


E F

Figure 92-5 Cont'd E, The catheter is advanced until the mushroom tip rests gently against the gastric mucosa. Endoscopy should be repeated to confirm the correct position of the mushroom tip. An external flange is fitted down the tube against the skin to prevent the tube from slipping into the stomach. F, Gastrostomy feeding tube in place with the clamp in the open position. The stockinette jacket is pulled over the gastrostomy tube once feeding is completed.

tube is removed within 14 days of placement (before establishment of the gastrocutaneous tract), a PEG procedure should be performed to evaluate the gastric mucosa and verify correct positioning of the replacement gastrostomy tube. If the tube is inadvertently removed once the gastrocutaneous tract is well healed, one can replace the original catheter with a balloon-type catheter (Flexiflo Gastrostomy tube, Ross Laboratories, Columbus, OH) or a low-profile gastrostomy device (LPGD, Bard Interventional Products Division) (Figure 92-6, *A*). Neither of these catheter types require an endoscopic procedure or anesthesia for placement. The gastrostomy "button" is a small, flexible silicone device that has a mushroomlike dome at one end and two small wings at the other end that lie flush with the outer abdominal wall (Figure 92-6, *B*). A one-way antireflux valve prevents reflux of gastric contents through the top of the tube. There are two types of LPGDs: (1) obturated and (2) nonobturated. The obturated device has an enlarged mushroom tip that must be stretched for placement in the stomach by using a special introducer (Figure 92-6, C). The nonobturated tube works like a Foley catheter and does not require forceful entry into the gastrostomy stoma. The length of the gastrocutaneous fistula must be precisely determined to guide correct selection of the appropriate "button" shaft length. This is accomplished with a special stoma-measuring device provided with the kit. The main advantages of the LPGD include their durability due to their silicon material, decreased likelihood of inadvertent removal by the pet, and their aesthetically pleasing appearance to the owners.

COMPLICATIONS OF ENTERAL FEEDING

Gastric Pressure Necrosis

Gastric pressure necrosis can occur from either the mushroom of the PEG tube or flange eroding the mucus layer of the stomach due to excessive tension being exerted on the PEG tube during placement. In addition, overzealous traction of the PEG tube followed by placement of the external flange flush against the skin of the patient can also cause pressure necrosis characterized by redness, swelling, and moistness of the skin. To reduce the chance that this problem will occur, the clinician should ensure that the PEG tube can be rotated after its placement and leave a 5 mm space between the external flange and the skin.

Feeding Tube Displacement

This is a relatively common problem, particularly with nasoesophageal tubes. Displacement of the tube can lead to aspiration, diarrhea, or in the case of gastrostomy tubes, peritonitis. Gastrostomy tubes should be marked with tape or a marking pen at the level of the skin to help verify the position of the tube. Detachment of the stomach from the abdominal wall with consequent intraperitoneal leakage of gastric contents can occur in large breed dogs, and an internal flange should be placed in these animals to minimize chances of tube dislodgement.

Tube Obstruction

Obstruction of the feeding tube is one of the most common complications of enteral feeding. Most obstructions are secondary to coagulation of formula, although obstruction by tablet fragments, tube kinking, and precipitation of incompatible medications can also result in tube obstruction. Nasoesophageal tubes are prone to obstruction because of their small diameters, and obstruction also occurs up to three times more frequently in patients fed by continuous versus bolus feedings. Sucralfate and antacids have been reported to precipitate with enteral formulas and cause tube obstruction. Several "remedies" have been advocated to relieve tube obstruction. Warm water injected with gentle pressure and suction will relieve most obstructions. For more unyielding obstructions, carbonated water is instilled into the tube and allowed to sit for one hour before applying gentle pressure and suction. Pancreatic enzyme infusions and meat tenderizer have also been advocated to dissolve tube obstructions. On rare occasions, the passage of an angiographic wire down the lumen is needed to unclog the tube. Clinicians can minimize obstructions by flushing the feeding tube with warm water before and after administering medications or enteral feedings. The tube should also be flushed after checking for gastric residuals, because the acid pH will cause the formula to coagulate in the tube. Elixir forms of medication should be used rather than crushed tablet forms whenever possible. Tablets should be crushed and dissolved in water prior to administration through the feeding tube, if no alternative form of medication is available.

Leakage Through Ostomy Sites

Mild leakage at the stoma site can occur for the first few days after placement of the feeding tube. Persistent leakage may

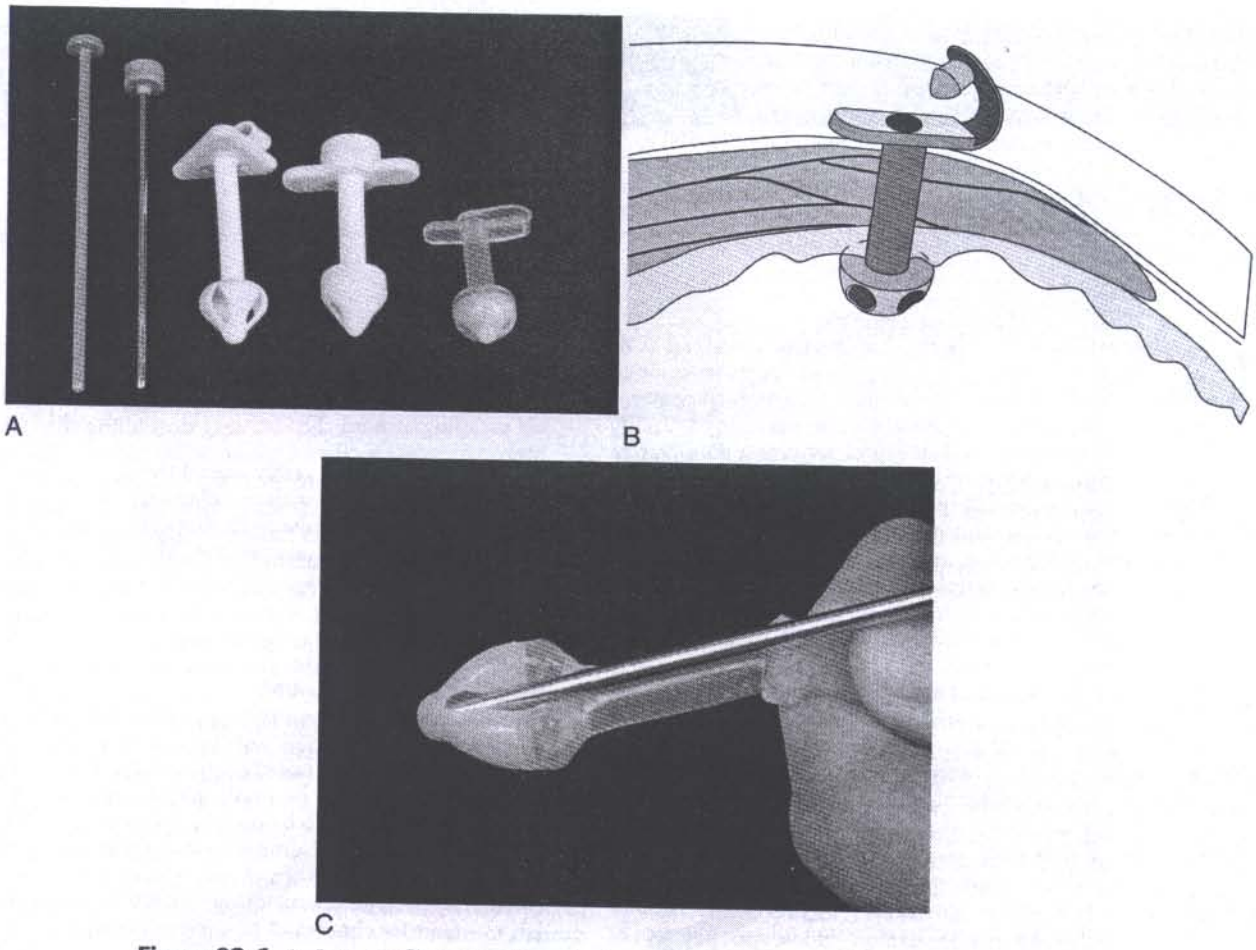


Figure 92-6 A, Low-profile gastrostomy devices and obturators used for stretching the dome-shaped tip of the device. *Left to right:* The Ross Laboratories Stomate low-profile device, the Cook low-profile device, and the Bard "Button"® low-profile device. B, Low-profile gastrostomy device with small outer wings of the device lying flush against the skin of the abdominal wall. For feedings, the small plastic plug is removed and a feeding adapter is connected to a syringe. C, Correct technique for stretching the dome-shaped tip of the low profile gastrostomy device with an obturator. The dome should not be stretched by passing the obturator through the lumen of the device as it will compromise the integrity of the anti-reflux valve located adjacent to the dome.

indicate tube dysfunction, peristomal infection, or a stoma site greater than necessary for the tube. Signs of inflammation with or without discharge or fever may indicate infection of the stoma site. This must be differentiated from fasciitis. A simple wound infection can usually be treated locally with dilute Betadine solution, topical Betadine antibacterial ointments, and more frequent dressing changes. Systemically administered antibiotics are usually reserved for animals with systemic signs of infection.

Aspiration

Pulmonary aspiration is a common complication of enteral feeding, although the actual incidence of this complication is difficult to determine due to the lack of consistency in how aspiration is defined. Risk factors for aspiration include impaired mental status, neurologic injury, absence of a cough or gag reflex, mechanical ventilation, and previous aspiration pneumonia. The source of the aspirated material should be identified because withholding gastrostomy feedings or placing a jejunostomy feeding tube will have no benefit if the pet aspirated oropharyngeal secretions. Although controversial, most authors agree that postpyloric feeding reduces the risk of aspiration. In addition, the use of continuous feedings has been shown to induce less gastroesophageal reflux than bolus feedings.

Diarrhea

Diarrhea is the most common complication associated with tube feeding in humans and animals. The incidence range is from 2.3% to 63%. The clinical implications of enteral feeding-related diarrhea are significant. Severe diarrhea leads to fluid, electrolyte, and nutrient loss, and it can cause considerable distress. Diarrhea in tube-fed individuals occurs due to multiple factors, including hypoalbuminemia, hyperosmolar or high-fat diets, infected diets, and concomitant antibiotic therapy. The incidence of diarrhea in enterally fed patients taking antibiotics far exceeds the incidence in those normally fed taking the same antibiotics. Antibiotic-associated diarrhea may arise from overgrowth of enterobacteria (*Klebsiella, Proteus, Pseudomonas)* or from proliferation of *Clostridium difficile*. Antibiotic administration is also associated with decreased concentrations of fecal short-chain fatty acids, occurring as a result of decreased colonic carbohydrate fermentation.

CHAPTER • 93

Gastric Lavage

Roger Gfeller

Gastric lavage is widely used as a gastrointestinal (GI) decontamination technique in small animals poisoned by ingestion of toxins. Removal of the stomach contents by gastric intubation and irrigation can be performed rapidly by trained staff members and does not require a cooperative patient. However, experts are beginning to question the value of gastric lavage; studies fail to confirm its value as a practical clinical procedure. Even when gastric lavage can be performed within minutes of ingestion, recovery of the toxin is limited. If the procedure is not completed before 1 hour has passed, recovery of many toxins is less than 15%. In small animal veterinary medicine, it is rare that gastric lavage would be completed within this period.

The volume of lavage fluid has also become a focus of attention. Using previously recommended volumes often results in gastric distention and complications (including fluid and electrolyte imbalances). Hypernatremia has been reported when large volumes of saline were used, whereas hyponatremia has been reported when water was the lavage solution. Further, one study found that when the volume administered resulted in gastric distention, as much as 25% of the lavage fluid passed into the small intestine carrying the ingested toxin with it. This knowledge has led experts to recommend two changes in gastric lavage protocols.

First, because a possibility exists that lavage solution may carry toxin into the duodenum, experts have begun to advise administration of activated charcoal before initiating the lavage procedure. In at least one study, administration of activated charcoal before (and after) gastric lavage resulted in reduced plasma levels of the toxin. Second, experts now agree that more attention should be paid to the degree of gastric distension allowed during lavage. It is advisable to have one staff member responsible for monitoring the amount of distension. Although visual observation of the abdomen is acceptable, it is better if one repeatedly palpates the stomach during lavage.

Additional complications of gastric lavage include aspiration pneumonia; traumatic injury of the oropharynx, esophagus, or stomach; hypoxemia; hypercapnia; and hypothermia. Gastric lavage is contraindicated in patients with an unprotected airway. Ingestion of caustic or corrosive toxins (e.g., acids, alkalis) or toxins with a high risk of aspiration (e.g., hydrocarbons) is also a contraindication to gastric lavage. A relative contraindication to gastric lavage is ingestion of a foreign body that could cause physical damage to the alimentary tract.

Gastric lavage has risks, it is messy, and it may not decontaminate the GI tract as efficiently as once thought. Before the veterinary team commits to this procedure, a scout radiograph of the stomach can be obtained. If the radiograph reveals an empty stomach, little evidence suggests that gastric lavage will decontaminate the patient more than administration of activated charcoal alone.

PROCEDURE

The patient must be anesthetized and intubated with a cuffed endotracheal tube (See Box 93-1). The cuff should be inflated just enough to create a seal between the tube and the trachea. The pop-off valve should be closed, and the rebreathing bag squeezed while filling the cuff. The clinician should listen for air escaping around the cuff and stop filling the cuff immediately when no further leakage of air occurs. The anesthetist should be able to inflate the lungs to a pressure of 15 to 20 cm of water without air leaking between the trachea and the endotracheal tube. The patient is maintained on an appropriate gas or injectable anesthetic. If injectable anesthesia is used instead of gaseous agents, the patient should be maintained on oxygen. If the patient is at risk for hypoventilation, the staff should consider ventilating the patient.

The clinician should prepare two tubes for use. The first tube is the *egress* tube. The egress tube should be as large as possible to allow rapid and complete removal of stomach contents. It should have additional side fenestrations in the end that will be inserted into the stomach. The tube should be marked with a piece of tape at a distance equal to the distance from the incisors to the xiphoid. The second tube is the *ingress* tube, through which activated charcoal and lavage solution will be instilled into the stomach. This tube should be smaller in diameter to allow the egress tube to be as large as possible. The distance from the incisors to the last rib should be measured and marked on the ingress tube with a piece of tape.

The patient is secured in right lateral recumbency. The patient's head should be positioned lower than the chest. The clinician should apply an appropriate lubricant (e.g., KY Lubricating Jelly, Johnson & Johnson, Arlington, Tex.) and insert the egress tube into the esophagus. The tube should be advanced into the stomach but not farther than the mark established previously. As much of the stomach contents as possible should be allowed to drain from the tube. If nothing drains from the stomach, the clinician should confirm that the tube is in the stomach. This can be done by several methods. In small animals, direct observation of the tube entering the esophagus and advancement of the tube to the measured distance is usually sufficient. Alternatively, one can push air through the tube while listening over the stomach. A gurgling sound can be heard in the stomach if the tube is properly positioned. A radiograph may be rarely required for confirmation.

If nothing comes from the egress tube after it has been confirmed to be in the stomach, the clinician should lubricate and insert the ingress tube. After confirming the ingress is in the stomach, the manufacturer's recommended dose of activated charcoal should be instilled. The egress tube should be clamped while the activated charcoal is infused so that the charcoal will be retained in the stomach long enough to mix with the contents. Gentle external agitation of the stomach will help the charcoal to mix with stomach contents. The egress tube should be opened to begin evacuation of the stomach contents.

Whether water or saline is to be used as the lavage solution, it should be warmed. Warming the lavage solution will slow gastric emptying and help prevent patient hypothermia. The clinician should attach the stomach pump to the ingress tube, begin to infuse the lavage solution slowly, and monitor

Box • 93-1

Materials Needed for Gastric Lavage

1. Large-bore stomach tube with additional fenestrations in one end (egress tube)
2. Small-bore stomach tube (ingress tube)
3. Lubricant
4. Stomach pump or funnel
5. Activated charcoal
6. Lavage solution (water or saline)
7. Container appropriate for laboratory submission of gastric contents, if desired
8. Disposal area for large quantities of lavage solution

gastric distension. Gentle external agitation of the stomach will help mix and remove stomach contents. If the egress tube does not allow free flow of fluid from the stomach, the tube should be withdrawn slowly. If flow begins, the lavage should continue. If no flow can be established, a small amount of water or air should be infused through the large bore tube to dislodge material. If flow is still not established, the clinician should remove the tube and check for a plug, then gently reinsert the tube to establish flow.

The procedure should be continued until the effluent is clear. In some cases, this may take large volumes of lavage solution and a great deal of time. *At no time should the patient's stomach be distended.* The patient should be lavaged in both left and right lateral recumbency. In some cases it is helpful to move the egress tube gently back and forth to help mix and dislodge stomach contents. If this is necessary, it must be done gently to avoid trauma to the pharynx, esophagus, and stomach.

When the stomach is emptied, the clinician should crimp or clamp the egress tube and remove it. He or she should ensure that the endotracheal tube is still properly placed and sealed and instill activated charcoal through the remaining tube. Then the ingress tube should be crimped or clamped and removed.

To minimize the chances of aspiration, the patient should be recovered with the endotracheal tube in place and the cuff inflated until the swallowing reflex returns. The oropharynx should be carefully checked for fluid, activated charcoal, or stomach contents and suctioned clean before the endotracheal tube is removed.

CHAPTER • 94

Transcervical Catheterization in the Bitch

Autumn P. Davidson
Bruce E. Eilts

The anatomy of the vaginal vault and cervix in the bitch has hampered access to the canine uterus. Historically, both intrauterine diagnostic sampling (for endometrial biopsy, cytology, and culture) and intrauterine insemination have required an invasive procedure (laparotomy or laparoscopy) in the bitch. In addition to an invasive approach, laparotomy requires general anesthesia, factors some clinicians and breeder clients find objectionable for an elective procedure such as artificial insemination (Figure 94-1). A laparoscopic approach to the canine uterus has been used infrequently, especially in the practice setting, because of its invasive nature and because it requires special equipment, expertise, and anesthesia. Cryopreservation and subsequent thawing diminish semen quality, necessitating special insemination technology. The process and resultant quality of canine cryopreservation have improved with time; however, insemination techniques remained suboptimal until transcervical intrauterine access was developed.

ANATOMY

The vagina of the bitch is relatively long compared with other domestic animals; the total length from the cervix to the vulva (including the vestibule) has been reported to be 10 to 14 cm in an 11 kg bitch. The canine cervix is not accessible by digital palpation per vaginum, nor can it be visualized with an ordinary vaginal speculum or otoscope. Consequently, equipment for visualizing and approaching the canine cervix must be long (e.g., up to 29 cm for larger breeds). In addition, the presence

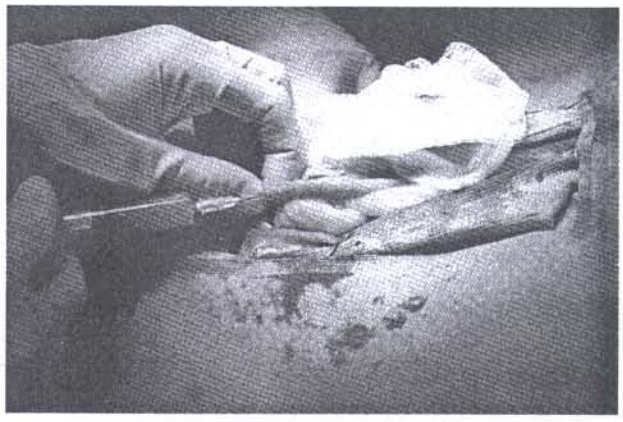


Figure 94-1 Injection of thawed semen into the lumen of the uterine horn in a bitch during laparotomy.

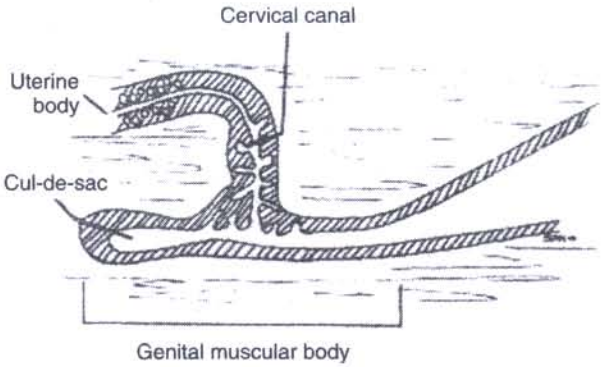


Figure 94-2 Graphic representation of the canine vagina, cervix, and paracervix.

of vaginal mucosal folds and the position of the cervix in the bitch require the use of rigid equipment to access the cervix.

The *paracervix*, the most cranial portion of the vagina, surrounds the cervix and is dominated dorsally by a well-defined mucosal ridge, the *dorsal median fold (DMF)*. Cranially, the paracervical region ends in the *fornix*, a dead-end space craniodorsal to the vaginal portion of the cervix that appears as a blind pocket when viewed endoscopically. The DMF extends from just distal to the vaginal portion of the cervix to the mid-vaginal region. It narrows the paracervix, necessitating the use of smaller diameter equipment to access the cervical area.

The DMF forms a distinct caudal tubercle where it ends in the mid-vagina. The cervix is approximately 2.5 cm cranial to the caudal tubercle of the DMF. The canine cervix is difficult to access blindly. It lies diagonally across the uterovaginal junction, with the canal of the cervix directed craniodorsally from the vagina to the uterus (Figure 94-2). The vaginal portion of the cervix appears as a large tubercle when viewed endoscopically. The internal (uterine) os of the cervical canal faces almost directly dorsally, whereas the external (vaginal) os is directed toward the ventral vaginal floor. The vaginal os is often located ventrally or laterally in the cervical tubercle, in the center of a rosette of distinct mucosal furrows. The cervical canal varies in diameter with the stage of the estrous cycle and parity; nonestrual and maiden bitches are expected to have a narrower cervical lumen. The actual appearance and general orientation of the vaginal cervix can vary from day to day during the estrous cycle.

The mid-vaginal region is characterized by a somewhat narrowed, crescentlike lumen. When viewed through a speculum, the caudal tubercle and narrowed middle vaginal lumen give the misleading appearance of tissue with an opening; this is the *false cervix* (Figure 94-3). When rigid insemination pipettes are introduced blindly into this area, often some resistance is felt, followed by advancement; this may lead some clinicians to believe they have accomplished an intrauterine insemination. In reality, insemination into the cranial vagina is more likely, often into the paracervical area.

EQUIPMENT AND METHODOLOGY

Endoscopically guided transcervical catheterization requires the use of a rigid cystourethroscope,* the components of which are a 3.5 mm forward oblique telescope with 30-degree viewing angle; a 22 French (22 F) protective sheath with two Luer-Lok adapters and an obterator; a telescope bridge with one 10F instrument channel; and a cold light source (Figure 94-4). The working length of the scope is 29 cm. The 30-degree angle is essential for visualization of the dorsally oriented cervix. A video camera can be attached to the endoscope, permitting enlarged imaging of the procedure. Videoendoscopy is preferred because it also allows the audience (e.g., the client) to watch the entire insemination procedure. Unlike with gastrointestinal endoscopy, electronic air pumps for insufflation and suction are not generally necessary. Adequate air insufflation or suction can be achieved, if needed, by connecting intravenous tubing and a syringe with a three-way stopcock to one of the working channels; this arrangement is sometimes useful for insufflation for routine vaginoscopy in a nonestrous bitch and occasionally for suctioning of copious estrual fluid to improve visualization of the vaginal lumen.

Transcervical catheterization is best accomplished with the bitch standing under light restraint and with gentle sling support of the abdomen to inhibit sitting (Figure 94-5).

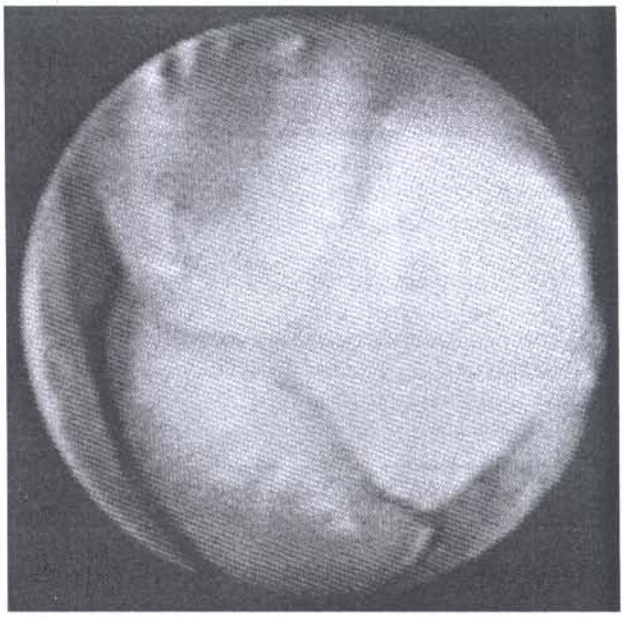


Figure 94-3 Endoscopic appearance of the false cervix.

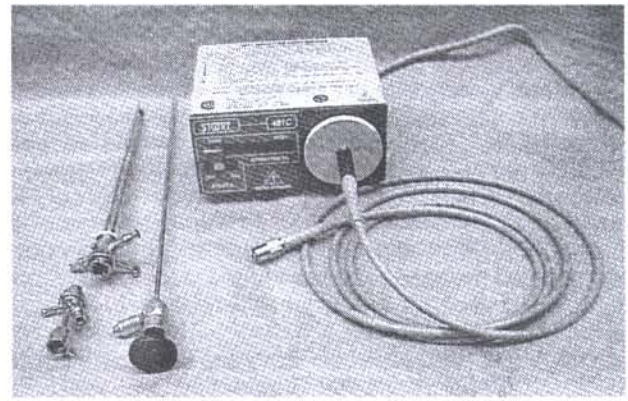


Figure 94-4 Rigid cystourethroscope: *From left*, bridge, sheath, telescope, and light source/cable.

*Storz Extended Length Cysto-urethroscope: Hookins Telescope, 30 degrees 325 B, 3.5 mm (width); 36.5 cm (length); sheath, 027KL; bridge, 0278NL. Karl Storz Veterinary Endoscopy, Galeta, Calif.

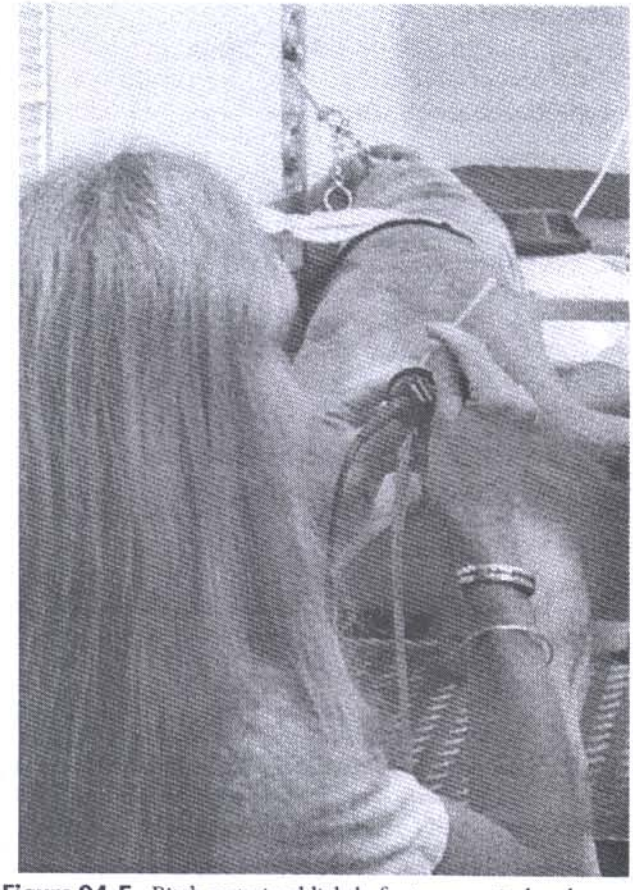


Figure 94-5 Bitch restrained lightly for transcervical endoscopy.

The operator should work from a sitting position, with the arms raised to the level of the vulva. An adjustable chair can facilitate operator comfort. Bitches tend to tolerate transcervical catheterization well, especially during estrus. With proper restraint and table setup, the procedure can be accomplished by one operator. However, the participation of the breeder client for restraint and observation generally is rewarding.

An 8 F urinary catheter is an appropriate size for most bitches for cervical catheterization, although a 6 F catheter sometimes is required for small or maiden bitches. The largest catheter accommodated offers the best rigidity for manipulation through the cervix. A smaller catheter can be placed inside a catheter if increased rigidity is required. Routine endoscopic biopsy and (guarded) culture instruments can be used for intrauterine sample acquisition.

Lubrication of the endoscope is seldom necessary. If a lubricant is used, it should be nonspermicidal and should be applied to the midportion of the sheath. Care must be taken to avoid contact with the lens, which would obscure visibility.

The endoscope is introduced through the vulva along the dorsal commissure, through the vestibule, over the brim of the pelvis, and into the vagina in a dorsal direction. To avoid the clitoral fossa and urethral orifice (Figure 94-6), the end of the endoscope must be directed dorsally. It is surprisingly easy to enter the urethra, which can be differentiated from the vagina by the characteristic smoother, more vascular appearance of the mucosa. The scope is then advanced between the vaginal folds by observing and following the direction of the vaginal lumen. During estrus, the vaginal lumen is cavernous in appearance until the false cervix is approached. Here the caudal tubercle of the DMF is commonly seen as a

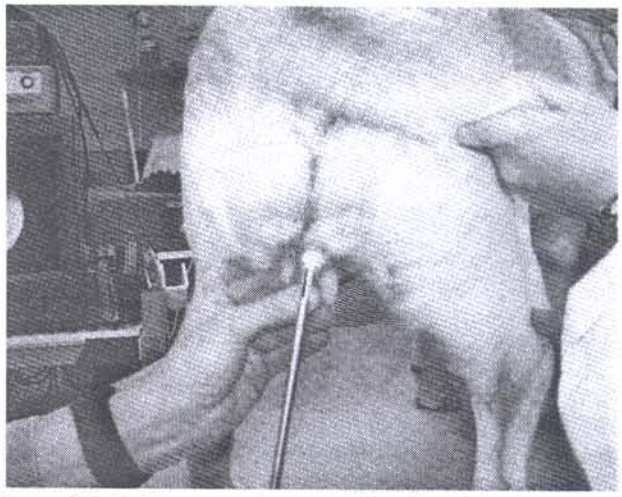


Figure 94-6 Directing the scope dorsally when entering the vestibule avoids entry into the urethra, facilitating passage into the vaginal lumen.

prominent landmark. Following the DMF facilitates passage into the cranial vagina. The vaginal portion of the cervix appears as a distinct tubercle with a cobblestone appearance due to a rosette of mucosal furrows converging at the os (Figure 94-7). The false cervix, by comparison, is smooth and has a single horizontal fissure. The actual cervical os sometimes can be identified by serosanguineous to hemorrhagic fluid of uterine origin flowing from the cervical canal.

The vaginal cervical os can be difficult to visualize, because it tends to be located ventrally or laterally on the cervical tubercle. The scope can be used to manipulate the somewhat moveable cervix into a position that permits better visualization of the os. If a large amount of estrual fluid impedes visualization of the cranial vagina, removal of the scope and having the bitch sit for a few moments can be helpful. The tip of the polypropylene catheter or endoscopic instrument is advanced into the cervical os by simultaneous manipulation of

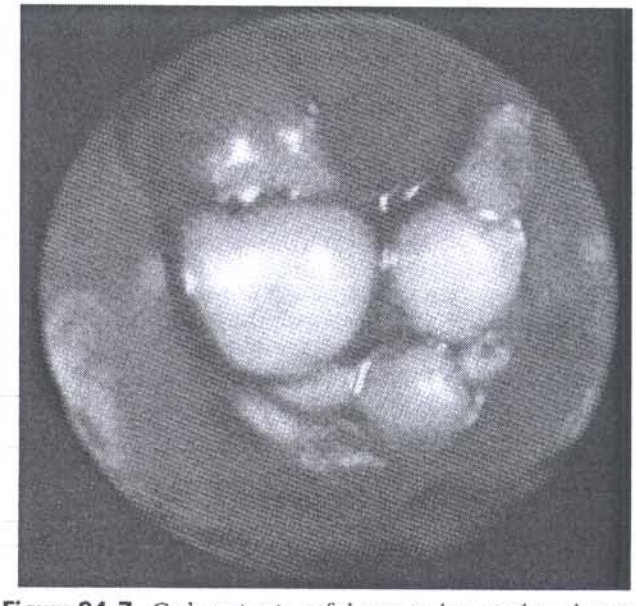


Figure 94-7 Catheterization of the vaginal cervical os, showing the rosette appearance of the cervix.

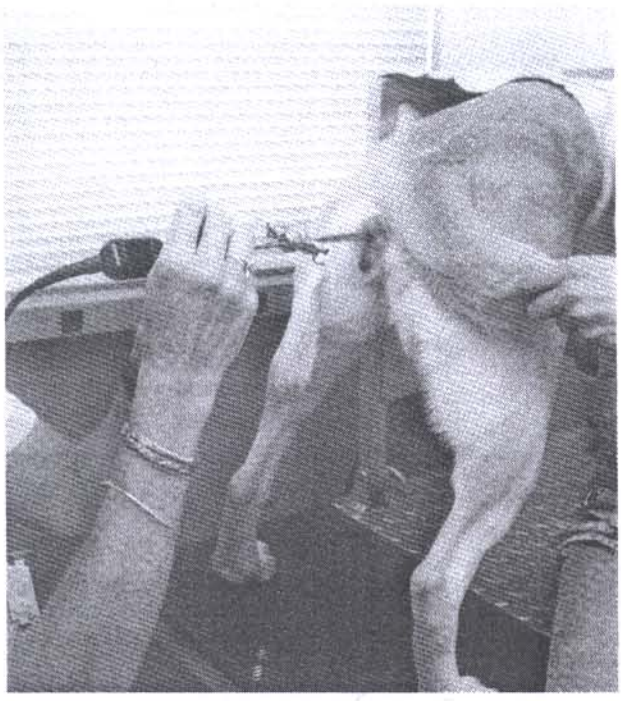


Figure 94-8 Passage of the catheter into the uterine lumen is accomplished by having one hand on the cystourethroscope and the other on the catheter.

Figure 94-9 Injection of semen through the catheter; afterward, a small amount of air is injected to clear all fluid from the catheter lumen.

the cervix using the endoscope and catheter (Figure 94-8). The rigidity of the endoscope permits manipulation of the cervical tubercle to access the os and start insertion of the catheter. If access to the cervical os is difficult because of its position, bending the tip of the polypropylene catheter beforehand may be helpful.

After insertion of the tip of the catheter, the viewing end of the scope should be dropped significantly to align the catheter parallel to the direction of the cervical canal. Once the scope position is parallel to the cervical canal, the catheter can be steadily advanced through the cervix with a twirling motion. For intrauterine insemination, the catheter is passed in as far as possible without meeting resistance. The uterine lumen of the average-sized bitch in estrus can accommodate approximately 2 mL of semen, and semen has been shown to distribute throughout both horns even when inseminated into only one. Minimal backflow of semen occurs with proper catheter placement. In the event of semen backflow, the insemination should be stopped and the catheter repositioned cranially or caudally. Minimizing the amount of air introduced into the uterine lumen before semen reduces backflow. A small amount of air (1 to 2 mL) is used to flush all the semen from the catheter into the uterus (Figure 94-9). For intrauterine diagnostics, culture and biopsy instruments are similarly advanced until contact is made with the uterine mucosa. Saline can be infused in and out of the uterine lumen through a polypropylene catheter for cytologic specimen acquisition.

The ease of transcervical catheterization can be recorded for each bitch (1 = very easy, less than 5 minutes; 5 = not achievable). Rarely, access to the cervical canal cannot be achieved. A repeat attempt should be made in 24 hours, because the morphology of the cervix changes under hormonal influence. For this reason, frozen semen should not be thawed until successful catheterization of the cervix has been accomplished. The practitioner and client should agree on a plan for vaginal or alternate intrauterine insemination beforehand, in the rare event that catheterization cannot be accomplished by the end of the bitch's fertile window. Repeat inseminations may provide better semen availability during the fertile period of the estrous cycle and may improve conception and litter size. The minimal inseminant dose in the dog has not been established.

Concerns about the introduction of vaginal flora into the uterine lumen through transcervical catheterization have not been realized. Normal vaginal flora can be found transiently in the uterus during proestrus and estrus, and vaginal flora is known to be introduced into the uterine lumen with natural breeding with no impact on fertility.

Unless rigid endoscopy is already a part of their practice, clinicians must make a substantial investment in equipment for video-endoscopic transcervical catheterization. However, the investment is soon returned, because the transcervical approach is popular with breeder clients who prefer to avoid surgery and anesthesia for intrauterine inseminations. Additional use of the equipment for diagnostic procedures, such as endometrial biopsy and intrauterine culture and cytology, may enhance its value.

Maintenance of the equipment is minimal; a 10-minute soaking of the immersible parts in 0.2% chlorhexiderm in solution, and through rinsing with distilled water followed by air drying, is optional. Techniques for sterilization are described by the manufacturer. The use of stronger disinfectants raises concern because of their spermicidal potential. Sterility does not appear to be necessary, because the vagina harbors normal flora.

Published pregnancy results for endoscopic insemination are not abundant, but some reported conception rates have been 100% when breeding twice with 200×10^6 sperm/breeding; 85% using as few as 50×10^6 sperm/breeding; and 57% using a total of 452×10^6 sperm in 2.4 breedings/cycle. The wide acceptance of frozen insemination by practitioners implies acceptable conception rates in field situations. As with all reproductive procedures, success is greatly influenced by the dogs' inherent fertility, by the timing of ovulation in the bitch, and by the quality of the semen. Collaborative multicenter studies to determine the minimal inseminant dose for conception in the bitch, as well as the utility of intrauterine diagnostic and therapeutic efforts, will be facilitated by the endoscopic transcervical technique.

CHAPTER 95

Laparoscopy

Keith Richter

INTRODUCTION

The use of laparoscopy for diagnostic and therapeutic purposes has increased tremendously in human medicine during the last 10 years. This acceptance of laparoscopy stems from technologic advances in equipment and impressive results achieved with this noninvasive modality. Though many procedures performed in human beings will have little applicability in veterinary medicine, many of the procedures will gain acceptance due to their ease, effectiveness, and lack of morbidity.

EQUIPMENT

Light is transmitted from a remote light source via a fiber-optic light cable to the rigid fiber-optic laparoscope (telescope). Size and viewing angles of laparoscopes vary. A forward-viewing (0 degrees), 5.0 to 10 mm outer diameter, 35 cm long scope is preferred. Smaller scopes have a smaller image with less field of view. In addition, a greater light intensity is needed for smaller scopes. A 6.5 mm scope is suitable for examining any dog or cat. Scopes are available in various degrees of angulation of view, including zero degree (direct forward viewing) up to 70 degree. The zero-degree angle is easier to use and generally preferred for most procedures. A 30-degree angle scope can be used to view structures to the side of the tip, and through rotation, to expand the field of view. Angled scopes are more difficult for inexperienced operators. Most scopes have no biopsy channel. Operating scopes have a 5 or 6 mm channel, with an eyepiece extending from the proximal end. These scopes allow introduction of instruments through the same puncture as the scope. The disadvantage of operating scopes is the limited ability to manipulate instruments passing through the channel. Usually the accessory or secondary puncture technique is preferred.

Video capabilities can be achieved with a handheld charged coupling device (CCD) video camera mounted on the eyepiece. These cameras have high resolution, magnify images 5 to 15 times, and provide a clear image. Three-chip cameras are superior to one-chip cameras in terms of clarity, light sensitivity, and color. The use of video is essential for operative laparoscopy. A bright light source (usually 150 to 300 watts) is required to adequately illuminate the abdomen.

To visualize abdominal structures, a pneumoperitoneum must be created to lift the abdominal wall away from the viscera. This is accomplished by insufflating gas through tubing attached to a Veress needle. The latter has a spring-loaded blunt inner portion and an outer cannula with a sharp point. The sharp point is used to penetrate the abdominal wall; then the inner blunt portion is protruded past the sharp point and left in that position to avoid traumatizing abdominal viscera. Gas can then be continually insufflated as needed throughout the procedure.

Three gasses can be used: carbon dioxide (CO_2), nitrous oxide (N_2O), or room air. Carbon dioxide is recommended because it has the advantage of being rapidly absorbed, and thus the risk for air embolism is minimized. The latter is a reported complication of laparoscopy using room air (the gas absorbed most slowly). The disadvantage of CO_2 is that it is slightly more irritating to the peritoneal surface and therefore requires a slightly higher plane of anesthesia. Nitrous oxide is intermediate in its rate of absorption. Gas is infused with an automatic insufflator. These devices regulate flow rate and intra-abdominal pressure. Ideally, intra-abdominal pressure should not exceed 15 mm Hg. Excessive pressure decreases venous return to the heart and causes decreased ability to ventilate.

The laparoscope is introduced into the abdomen with the use of a trocar/cannula assembly. The cannula is a metal or hard plastic sleeve with a one-way valve that permits passage of instruments (such as the trocar and laparoscope) and prevents the escape of gas. The trocar is a sharp-pointed stylet that is used to penetrate the abdominal wall. It is then removed leaving the cannula in place so that the laparoscope can then be introduced. Accessory puncture sites are made for introduction of additional trocar/cannula assemblies. This allows the introduction of blunt metal probes, suction tips, cautery instruments, grasping forceps, "spoon," or "clamshell" style biopsy forceps, and a wide variety of surgical instruments. These instruments are elongated, narrower versions of standard surgical instruments. The use of stapling equipment has enabled surgeons to perform procedures such as vessel ligation and bowel resection.

TECHNIQUE

It is preferred to perform laparoscopy with the animal under general anesthesia. The position of the dog or cat and location of the various puncture sites will depend on the procedure and organ being examined. Because the liver is the most common organ examined and biopsied, this procedure will be described in detail.

LAPAROSCOPY-GUIDED LIVER BIOPSY

The main advantage of laparoscopy-guided biopsy is the ability to obtain large biopsy samples and to visualize the liver, biliary tree, and other abdominal organs. With experience, the gallbladder can be examined, palpated with a blunt probe, and the bile duct traced to its entry into the duodenum. In this manner it can be determined whether a common bile duct or cystic duct obstruction exists. In addition, because focal lesions of the liver can be directly visualized, an appropriate biopsy site can be selected while avoiding other intrahepatic structures (gallbladder and portal vessels). Hemorrhage can be observed and, when excessive, controlled with direct compression with a blunt probe over the biopsy site. Alternatively, electrocautery or application of a hemostatic material (Gel-Foam®) can be used to control hemorrhage. Compared with laparotomy,

much less anesthetic time exists. A complete laparoscopic examination can be completed and multiple hepatic biopsies obtained in 10 to 15 minutes. Because only a 1.0 cm incision is made, less risk exists for wound dehiscence.

The animal is placed in left dorsal oblique recumbency at a 45-degree angle. This position allows visualization of both sides of the liver, gallbladder, bile duct, pancreas, duodenum, and much of the abdominal viscera, and avoids the falciform ligament (which may be encountered with a midline approach). The puncture sites should be surgically prepared and draped. The Veress needle (for insufflation) is inserted through a small incision (using a No. 11 blade) on the midline near the umbilicus. Prior to insufflation, the Veress needle is aspirated to confirm that no viscus has been entered. Saline (6 to 8 cc) is then infused to ensure free flow into the abdominal cavity. The abdomen is then insufflated with gas to an appropriate pressure. This amount can be determined by a pressure gauge on an automatic insufflator (usually 10 to 15 mm Hg) or when the abdominal wall is tympanic to the touch. Overdistension should be avoided so as not to decrease venous return or cause impairment in ventilation. Once the desired degree of pneumoperitoneum is reached, a 1.0 cm skin incision is made on the right side between the last rib and the flank. The incision is adjusted in a cranial direction for larger animals, in a caudal direction for smaller animals, and should take into account the size of the liver. The trocar and cannula assembly is then "popped" into the abdominal cavity with a twisting motion. Grasping the cannula ~3 cm from the tip with the free hand will prevent inadvertent insertion of the assembly too far into the abdomen. The trocar is removed and laparoscope inserted into the abdominal cavity through the cannula. The remote light source is connected to the laparoscope with a fiber-optic cable and the liver examined. If a video camera is available, this should be placed on the eyepiece of the laparoscope. A secondary puncture site is made to the left of midline at the level of the umbilicus. Through this site, a second cannula can be introduced so that a blunt probe can be used to palpate the liver and gallbladder. The probe should also be used to lift up each lobe of the liver to examine the dorsal surface and to get the omentum out of the way so the bile duct can be traced to its entry into the duodenum. The pancreas should also be examined.

Once the abdomen has been examined, a suitable place on the liver is selected for a biopsy site. The author prefers using a laparoscopic spoon or clamshell type of biopsy instrument. This can be placed through the same accessory cannula as the blunt probe, thus avoiding an additional puncture site. These types of instruments result in less hemorrhage than biopsy needles. Repeated twisting of the shaft or retracting the closed jaws into the cannula will prevent ripping of liver tissue and result in less bleeding. If a laparoscopic biopsy instrument is not available, an automated needle biopsy instrument can be used to obtain hepatic tissue. This is inserted into the abdominal cavity just caudal to the xiphoid cartilage and can be directly visualized to enter the liver. It is then operated in the standard manner under direct visualization to obtain hepatic tissue. The number of biopsies obtained depends on the risk of bleeding and the anticipated need of adequate tissue. Multiple samples from various areas of the liver are recommended (observing for hemorrhage after each sample). If excessive bleeding occurs, the blunt metal probe is used to put direct compression over the biopsy site. Suction can also be applied to clear the field if bleeding cannot be adequately assessed. If bleeding is not controlled, an electrocautery probe can be used to stop the bleeding. Alternatively, laparoscopic forceps can be used to place a piece of a hemostatic material (Gel-Foam®) on the bleeding biopsy site. Once the biopsy samples are obtained, the clinician completes the procedure by removing all instruments, evacuating all the gas through opened cannula valves, and suturing the puncture sites.

Potential complications of the procedure include those related to a general anesthetic, excessive bleeding, inadvertent organ damage during instrument introduction, overdistention of the abdomen with gas, air embolism, and a tension pneumothorax if the diaphragm is inadvertently punctured (as abdominal gas enters the thoracic cavity). Meticulous attention to details of technique together with experience will minimize the probability of these complications. Postoperative pain should be anticipated, and this should be addressed with appropriate analgesics.

OTHER USES OF DIAGNOSTIC LAPAROSCOPY

Laparoscopy can be used to diagnose and stage abdominal tumors through direct visual assessment and allowing directed biopsies. Laparoscopy can detect lesions less than 1 mm in diameter on the peritoneal surface. Laparoscopy can be also used to examine and biopsy the pancreas, an organ that can be difficult to image with radiographs and ultrasound. Other organs that can be biopsied via laparoscopy include the kidney, spleen, prostate, intestine, mesentery, omentum, and the parietal peritoneum. Laparoscopy can guide aspiration of the gallbladder, loculated ascites, and abdominal cysts or abscesses. Laparoscopy can guide transabdominal intrauterine artificial insemination. Laparoscopy can also be used in evaluation of abdominal trauma. Such injuries as hepatic and splenic laceration, diaphragmatic hernia, bladder rupture, renal rupture, and abdominal hernia can be assessed.

LAPAROSCOPIC SURGERY

Many laparoscopic surgical procedures are currently being performed on humans. These include cholecystectomy, ovariectomy and hysterectomy, adrenalectomy, appendectomy, bile duct exploration, hernia repair, bowel resection, gastropexy, pyloromyotomy, and others. Many of these are applicable to veterinary medicine. Limitations of laparoscopic surgery include the two-dimensional image, restricted freedom of movement of the instruments, restricted sense of touch, and the need for extensive training. Controlled studies are necessary to substantiate the role of all laparoscopic procedures in veterinary medicine. As clinicians and equipment manufacturers address technical limitations, many surgical procedures performed within a body cavity should be amenable to laparoscopic surgery.

CHAPTER 96

Fine Needle Aspiration and Lung Biopsy

Lynelle R. Johnson

Airway samples are often valuable in determining the underlying cause of respiratory signs in dogs and cats. They can be collected by means of tracheal aspiration, bronchoalveolar lavage, fine needle aspiration, or lung biopsy. The use of a particular technique depends on the results of the physical examination, the animal's stability for procedures that require anesthesia, the type and distribution of radiographic infiltrates, and the list of most likely differential diagnoses.

Fine needle aspiration (FNA) and lung biopsy are most useful for investigating the etiology of diffuse interstitial disease, mass lesions, or focal infiltrates. In general, fine needle aspiration or surgical lung biopsy should be performed when bronchoscopy or other noninvasive tests have failed to yield a diagnosis or to provide sufficient information to guide therapy.

Fine needle lung aspiration can be performed in a conscious animal, under light sedation, or during anesthesia. The technique may be done blindly or with ultrasound guidance. Lung biopsies are performed under general anesthesia and can be accomplished percutaneously with ultrasound guidance, via thoracoscopy, with a keyhole surgical approach, or during thoracotomy. Typically, thoracoscopic and keyhole biopsies provide evaluation of peripheral lung segments only. Focal histologic abnormalities or lesions in more central regions of the lung can be missed. Diagnostic yield can be improved by using preoperative computed tomography to identify and localize appropriate regions for aspiration or biopsy.

Contraindications for FNA include bleeding disorders, intractable tachypnea or hyperpnea, and mechanical ventilation. Standard contraindications for general anesthesia would preclude lung biopsy.

FINE NEEDLE LUNG ASPIRATION

In animals that are relatively eupneic, percutaneous FNA of the lung can be performed without sedation. Local anesthesia generally is not helpful, because infiltration with lidocaine often causes more discomfort than the single pass of the aspiration needle through the skin. The equipment for FNA includes a 23- to 27-gauge needle ¾ to 1½ inches long and a 6- to 10-cc syringe. Microscope slides should be readily accessible for preparation of the sample for cytologic evaluation, and aspirated material can be applied to culture swabs for microbiologic analysis if sufficient quantity is obtained.

For FNA, a small region of the chest is shaved and minor surgical preparation is completed. The needle is passed through the skin and subcutaneous tissue and into the thoracic cavity cranial to the border of the rib. With respiration halted, the needle is directed swiftly into the lung perpendicular to the lesion. It is inserted back and forth gently and quickly, and one or two gentle aspirations are applied to the syringe. The needle and syringe are removed together for preparation of cytologic specimens.

A second method uses an inverse aspiration technique. The needle (attached to syringe) is inserted through the rib muscles until it is close to the pleural cavity. To enter the lung, the barrel of the syringe is advanced toward the chest wall while the plunger is held stationary. Release of the plunger aspirates material into the hub of the needle. The syringe and needle are removed for preparation of the sample.

Generally, only a small aspiration sample is visible in the hub of the needle. The syringe is detached from the needle and filled with air, and the contents of the needle hub then are gently sprayed onto a slide or cover slip for cytologic examination and Gram staining. Additional material can be applied to a culturette swab. If aspiration with an empty syringe fails to yield material, the syringe can be filled with 1 to 2 mL of sterile saline. The aspirated material in the hub of the needle is drawn back into the syringe to create a suspension of the aspirant. A cytospin preparation can be done; however, this technique may result in excess dilution of the sample.

For more central or focal lesions, ultrasound-guided percutaneous aspiration is performed with the animal under heavy sedation or anesthesia. Balanced anesthetic protocols that maintain cardiopulmonary support are preferred, and narcotic agents are often used. If a larger instrument (18 to 21 gauge) is used, the aspiration biopsy needle is preferred over a cutting biopsy needle because the former technique has a lower incidence of complications.

LUNG BIOPSY

Lung biopsy can be achieved through video-assisted thoracoscopic surgery (VATS), keyhole biopsy, or thoracotomy. Samples are submitted for histology and bacterial cultures (aerobic and anaerobic). Fungal cultures should be considered in some cases, and impression smears of biopsy samples may be helpful for early assessment of cytologic lesions.

Thoracoscopy is the least invasive surgical technique that provides an opportunity for visualized lung biopsy or lung lobectomy. General anesthesia with endotracheal intubation is used, and close anesthetic monitoring is required because a moderate pneumothorax is induced during the procedure. VATS is performed more commonly in dogs than cats because of their larger body size. This technique requires specialized rigid telescopes, trocars, and endoscopic instruments, a light source, and a video monitor. Formal training is required to develop expertise in this procedure. Peripheral biopsies of a distal lung segment can be obtained with a stapling instrument or an endoscopic loop ligature. Alternatively, a lung lobe can be resected. The most serious complication of thoracoscopic biopsy is hemorrhage.

Lung biopsy of a peripheral segment can also be obtained through a modified (keyhole) thoracotomy. The animal should be placed under general anesthesia and surgically prepared. An intercostal thoracotomy is performed, and a wedge of lung is exteriorized. A biopsy is obtained by applying loop ligatures around the segment or by using a stapling device.

In an animal with a solitary mass lesion, consolidated lung lobe, central pulmonary infiltrate, or focal abnormality,

exploratory thoracotomy with lung biopsy, partial lobectomy, or lung lobectomy may be required to obtain a diagnosis. A lateral intercostal approach on the side of the lesion provides the best access to structures in the immediate area and usually has the advantage of an uncomplicated approach and closure. The technique is associated with less postoperative discomfort than a sternotomy; however, it does not allow access to the entire contents of the chest cavity. Median sternotomy is performed when a complete thoracic cavity exploratory is required, but it is difficult to perform lung lobectomy by this approach. In addition, access to hilar structures through a median sternotomy is limited in large, deep-chested dogs.

COMPLICATIONS

The most common complications of fine needle lung aspiration and percutaneous lung biopsy are pneumothorax and hemorrhage, although seeding of the pleural cavity with neoplastic cells is also of theoretical concern. Complications can occur when the technique is done either blindly or with ultrasound guidance, but the occurrence rate is substantially lower when small needles are used. Proper patient selection is also of critical importance, because animals with marked tachypnea and/or pronounced respiratory distress are more likely to develop pneumothorax. Highly agitated or fractious dogs or cats that are difficult to restrain are prone to hemorrhage, as are animals with coagulopathies or pulmonary hypertension. Sedation or anesthesia of fractious animals might improve the safety of the procedure. After a lung aspiration procedure, the animal should be encouraged to lie on the side of the aspiration to promote the development of a seal at the site. Radiographs should be taken if an increase in respiratory rate or effort develops or if an absence of lung sounds is noted, which could suggest pneumothorax.

Complications of open lung biopsy are those associated with duration of anesthesia or respiratory depression. Chest tubes are placed after surgery, thus limiting the occurrence of pneumothorax. Hypotension, hypoxemia, and poor ventilatory recovery are potential postoperative problems.

CHAPTER 97

Lymph Node Aspiration and Biopsy

David M. Vail

Lymph node aspirates, biopsies, or both are indicated when lymph nodes are clinically enlarged or are suspected of being involved in a disease process where their histologic assessment would be helpful in diagnosis or staging the extent of disease involvement. Whether a fine needle aspirate, incisional, or excisional biopsy is chosen depends on the disease process under consideration, the tissue volume requirements for assessment, and the condition of the dog or cat.

LYMPH NODE ASPIRATION

This simple, rapid, and low-morbidity assessment of lymph nodes can be performed several ways; the technique used will depend on operator preference and location of the node in question. For peripheral lymph nodes, sedation is rarely necessary; however, sedation or general anesthesia may be necessary if a dog or cat is fractious, or an intracavitary node is to be aspirated either by palpation or by ultrasound guidance.

For most accessible nodes, the author prefers the "needle without the syringe" approach to fine needle aspiration. This technique is well suited for lymph nodes because, in general, they readily exfoliate their cells. This allows the operator to experience a fingertip feel of the node texture; it also decreases blood admixture and cellular disruption secondary to vacuum aspiration (Figure 97-1). Alternative techniques for lymph node aspiration include aspiration with the needle attached to a 10-cc syringe. In this case, upon insertion of the needle (20 gauge) into the node, suction is created by rapid, repetitive aspiration of the syringe. Metal or plastic commercially available mechanical aspiration devices can also be used to create vacuum, but they are rarely necessary for lymph node samples.

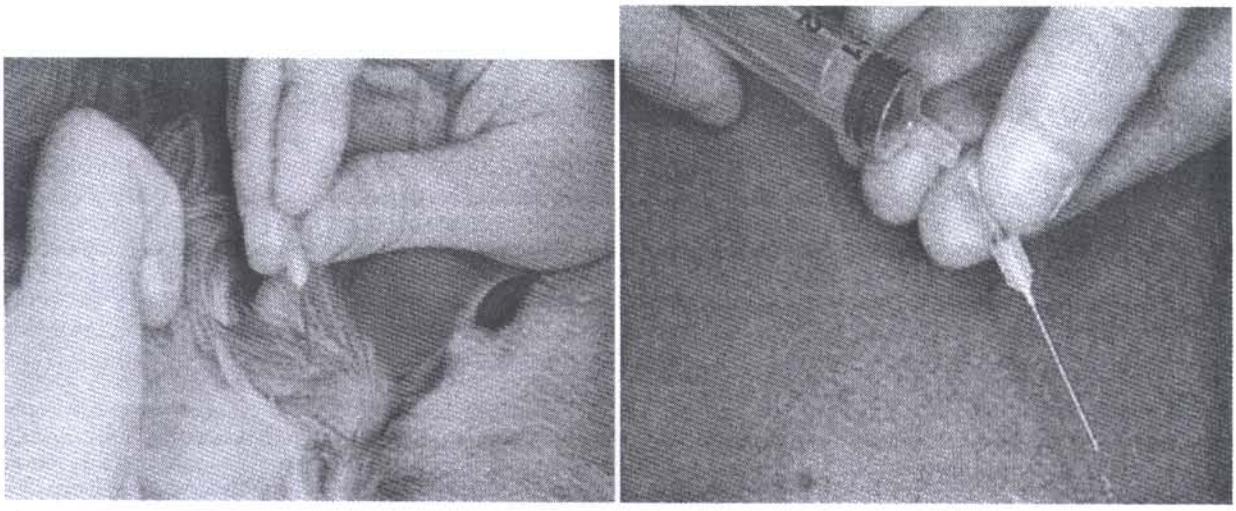
No preparation is necessary for peripheral lymph nodes other than swabbing the site of penetration with alcohol. If the node is within a body cavity, then surgical preparation of the site of entry is recommended. Instrumentation includes a 20-gauge needle, a 10-mL syringe, and cytology slides. The process is as follows (see Figure 97-1, *A* and *B*).

While holding the node in an off hand, the operator holds the needle with one finger over the hub. The needle is passed once through the skin and into the node, followed by several quick thrusts in and out of the node without exiting the skin each time. The needle is then removed from the node, placed on an air-filled 10-cc syringe, and the contents are gently expressed onto several slides. The sample is smeared out and submitted for appropriate staining and analysis.

LYMPH NODE BIOPSY (INCISIONAL)

If a larger sample for histopathology is required, a needle core biopsy (e.g., Tru-Cut®) is recommended and outlined in Figure 97-2. Usually, only sedation and local anesthesia is required. Rarely, intravenous or gaseous anesthesia is necessary if a dog or cat is fractious or an intracavitary node is to be biopsied. Mechanical, spring-loaded needle biopsy instruments are also commercially available.

Instrumentation includes a No. 11 blade to make a stab incision for needle biopsy entry, a Tru-Cut® biopsy instrument, a specimen cassette, and suture material (only necessary if entry hole is large or if excessive hemorrhage occurs).



A B

Figure 97-1 Fine needle aspiration—lymph node.

The Tru-Cut® core biopsy instrument can be set in one of two positions (see Figure 97-2, *A*): The first, the *closed* or sheathed position, has the inner canula within the outer sheath. This is the position used when placing the needle into the node. The second, or *open* position, occurs when the outer sheath is held in place and the inner cannula is thrust forward by pushing the handle plunger (indicated by the thick arrow in Figure 97-2, *A*) forward. This opens the specimen or sample trough (indicated by the narrow arrow in Figure 97-2, *A*).

After a No. 11 blade is used to make an entry hole in the surgically prepped area, the biopsy needle is passed through the skin just into the node while in the *closed* position (see Figure 97-2, *B*).

Next, the operator thrusts the plunger forward to place the instrument in the *open* position (see Figure 97-2, C), thereby allowing nodal tissue to fill the needle trough. While the biopsy plunger is held in a steady position, the operator slides the outer sheath forward over the inner cannula, thereby cutting the core sample off within the specimen trough (i.e., the biopsy instrument is again in the *closed* position); the entire instrument is then withdrawn from the node while in the *closed* position (see Figure 97-2, *D*). The biopsy needle is then *opened*, and the specimen (i.e., core sample) is placed in a biopsy cassette for processing (see Figure 97-2, *E*).

LYMPH NODE BIOPSY (EXCISIONAL)

In the case of low-grade lymphoma in dogs or when lymphoma is considered in cats where several well-documented benign lymphadenopathies may mimic lymphoma, the entire lymph node should be removed for histologic assessment. This is important for the pathologist to determine architectural changes and capsular invasion. The reader is referred to a general surgical textbook for techniques for whole-node extirpation.

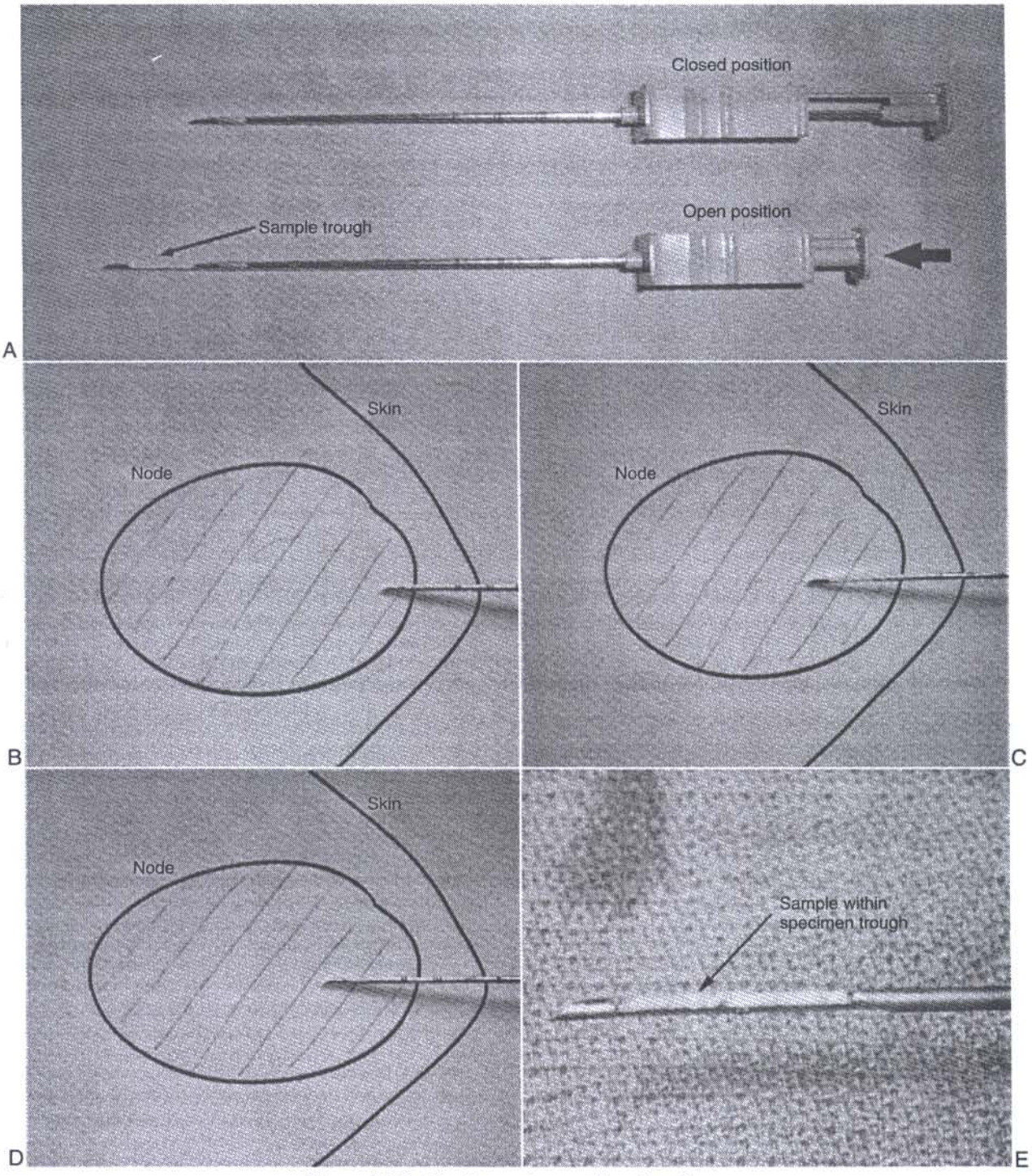


Figure 97-2 Needle core biopsy—lymph node.

CHAPTER 98

Pacemaker Implantation

Daniel F. Hogan

INTRODUCTION

Artificial pacing (AP) for the treatment of symptomatic bradyarrhythmias in veterinary medicine began over 30 years ago and is now considered the standard level of care for such patients. The most common conditions requiring AP include third-degree (complete) atrioventricular block (3AVB) and sinus node dysfunction (sick sinus syndrome [SSS]). Other less common conditions include high-grade second-degree atrioventricular block (2AVB), persistent atrial standstill, vasovagal syncope, reduction of obstruction gradient in hypertrophic obstructive cardiomyopathy (HOCM), and biventricular pacing in congestive heart failure patients. Pacing systems are varied and can range from simple to complex, depending on what the requirements are for the individual patient. The vast majority of pacing systems implanted today consist of single-chambered systems where one pacing lead is placed, usually into the right ventricle (RV), and programmed to deliver an electrical stimulus when intrinsic electrical activity is absent. A single-chambered system could also use a lead placed within the right atrium (RA), as sometimes used to treat SSS, but this requires a competent atrioventricular node (AVN). However, it is well recognized that maintenance of atrioventricular synchrony in pacemaker patients is preferable and results in increased cardiac output, improvement in neuroendocrine profile, and reduced incidence of the pacemaker syndrome. For these reasons, there has been increased use of dual-chambered systems in veterinary medicine over the past 5 years. These systems usually consist of two leads: one in the RA and one in the RV. Dual-chambered pacing can be established by use of a special single lead where free-floating electrodes reside within the RA that sense intrinsic atrial electrical activity. However, atrial pacing is precluded in this system.

PACING COMPONENTS

The pacing system consists of (1) a pulse generator that contains a lithium-iodide power source and magnetic switches that determine how and when the electrical stimulus is delivered and (2) lead or leads that deliver the electrical stimulus and sense intrinsic electrical activity. These components must be compatible; the clinician can determine this by consulting with a local pacemaker representative, by reading publications such as the *Pacemaker* and *Connector Encyclopedia*, or by obtaining the components from the Companion Animal Pacemaker Registry and Repository (CANPACERS).*

Pulse generators have two main categories: (1) single or dual chambered and (2) unipolar or bipolar. Dual-chambered generators have two channels or connectors for the leads. Unipolar generators serve as the anode to complete the electrical circuit and are only compatible with unipolar leads. The noninsulated surface of the unipolar generator must be in contact with body tissues to allow pacing. Bipolar generators can be programmed as unipolar, allowing compatibility with unipolar and bipolar leads that results in greater flexibility of such systems. Generators also differ with respect to their programmability, with the newer generators having more functions that can be modified by the user.

Leads are classified as (1) endocardial or (2) epicardial. Endocardial leads contact the endocardial surface of the RV or RA and are implanted by the transvenous route, whereas epicardial leads are implanted by thoracotomy or celiotomy and contact the epicardial surface of the left ventricle (LV). As already mentioned, leads are classified as unipolar (epicardial leads are always unipolar) or bipolar, and this will influence compatibility issues. The clinician can identify bipolar leads by the distal ring electrode on the lead that functions as the anode or by the two ring electrodes on the connector pin. In addition, the size of the connector pin on the lead can vary, but this must match the connector size of the generator. Older leads can have connector sizes of 5 or 6 mm, whereas newer components have been standardized (these leads are listed as IS-1 UNI or IS-1 BI for unipolar and bipolar, respectively). However, adapter sleeves can be used to allow a smaller-diameter lead connector to fit into a larger generator channel. Leads also have two different types of fixation to the myocardium. Active fixation leads penetrate the myocardial wall with a corkscrew mechanism, whereas passive fixation leads have silicone or polyurethane tines that become entangled within the trabeculae of the endocardial surface. Epicardial leads must have some form of active fixation either through a corkscrew mechanism, suture disc, or both. Either fixation technique can be used for endocardial leads, because the dislodgement rates from the ventricle are similar. However, the author prefers to use active fixation for atrial leads for more secure myocardial engagement. Most of the newer leads have steroid-eluting tips that reduce the risk of excessive fibrosis around the contact site that could result in exit block and loss of pacing.

It is important to have access to a pacing system analyzer (PSA) on site, through a pacemaker representative, or from a local hospital. However, most PSAs are only compatible with generators from the same manufacturer as the PSA, and compatibility needs to be confirmed prior to pacemaker implantation. The PSA allows programming of user-modified parameters through the application of a magnet over the generator. After implantation, the magnet can be applied on the skin surface

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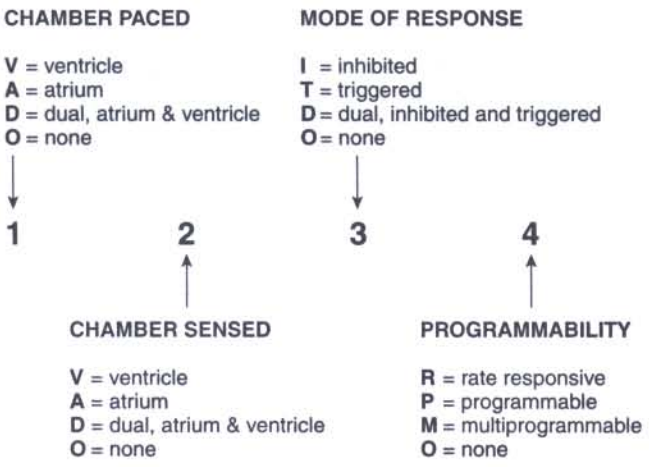

Figure 98-1 Pacemaker programming code.

overlying the generator, allowing noninvasive programming of the pacing system.

Pacing systems in veterinary medicine are most commonly coded by a four-letter system (Figure 98-1). The first letter represents the chamber paced, the second letter the chamber sensed, the third letter is the mode of response to sensed intrinsic electrical activity, and the fourth letter indicates the programmability of the generator. In veterinary medicine, the most common pacing modality is VVI, with a fixed pacing rate ranging from 70 to 100 pulses per minute (ppm). However, over the last 5 years there has been increased use of dual-chambered pacing systems where DDD or VDD pacing modalities are used. A PSA is used prior to implantation to estimate battery life and to program nominal pacing parameters. During implantation the PSA allows evaluation of the surface ECG, atrial or ventricular electrograms (or both), determination of lead impedance, and optimal pacing parameters. Postimplantation, the PSA is used to interrogate the pacing system for changes that occur over time that could require the pacing parameters to be altered. In addition, the PSA can program in-stock generators to nonpacing modes such as OAO or OVO to prolong the battery life of the generator prior to implantation. If a PSA is not routinely available, then a pulse generator can be programmed to the following parameters: pace amplitude 5 V, pacing pulse width 0.5 ms, sensitivity 2.5 mV, ventricular refractory period 250 ms, and pacing rate 70 to 100 ppm within a VVI pacing system. The author does not recommend implanting a dual chambered pacing system without having a PSA readily available because these systems are more complex and often require multiple adjustments during implantation.

PREIMPLANTATION DIAGNOSTIC EVALUATION

Preimplantation diagnostics should include a complete blood count, serum chemistries, and urinalysis to identify possible underlying causes of the rhythm disturbance and determine overall health of the animal. An electrocardiogram is necessary to accurately diagnose the arrhythmia. Thoracic radiographs and echocardiograpy should be performed to identify any possible underlying causes of the rhythm disturbance and any concurrent cardiac disease and to assess baseline cardiac function. It is important to determine baseline cardiac function because a small subset of animals with 3AVB develop myocardial failure after pacemaker implantation, either from an adverse effect of the pacemaker or extension of the disease process that resulted in the arrhythmia requiring pacemaker implantation (Figure 98-2). Additional diagnostics may be performed to identify diseases that have been associated with arrhythmias requiring pacemaker implantation such as Lyme disease and myasthenia gravis.

PACEMAKER IMPLANTATION

Perioperative antibiotics are routinely used on a prophylactic basis. First-generation cephalosporins such as cefazolin (22 mg/kg IV q 2 hours) are most commonly used. However, the use of antibiotics does not replace good aseptic techniques. Controversy exists as to whether a temporary pacing system should be placed prior to general anesthesia for permanent pacemaker implantation. The procedural time is increased, there is no significant decrease in adverse events and no clear consensus from cardiologists if temporary pacing systems should be placed on a routine basis. However, it is generally agreed that animals with unstable escape rhythms should be temporarily paced. The author routinely uses temporary pacing in all cases with propofol anesthesia, which allows a more controlled and relaxed environment for permanent pacemaker implantation.

The vast majority of pacing systems use endocardial leads placed via the transvenous approach. However, epicardial leads are routinely placed in cats due to complications with transvenous systems and in the rare instances of persistent single left cranial vena cava in dogs.

TEMPORARY PACEMAKER IMPLANTATION

When implanting a temporary pacemaker, the clinician can use the following as a guide:

- A large area over the left or right jugular vein is clipped and surgically prepared.
- Anesthesia is induced with propofol intravenously to effect (4 to 6 mg/kg), and the animal is intubated and given oxygen.
- A 5 or 6 F vascular introducer is placed in the jugular vein via percutaneous technique.
- A 4 to 6 F temporary pacing lead is advanced into the RV under fluoroscopic guidance.
- The lead is attached to the external generator and paced as VVI with 5 V amplitude, 0.5 ms pulse width duration, 2.5 mV sensitivity, and 60 to 90 ppm.

Note: Alternatively, the femoral vein can be used for venous access using the previously described procedure.

PERMANENT TRANSVENOUS PACEMAKER IMPLANTATION (JUGULAR VEIN)

Ventricular Lead

When preparing a ventricular lead via the jugular vein, the clinician should do the following:

- Surgically prepare a large area over the right or left jugular vein, ipsilateral neck extending dorsally just to the contralateral side from the base of the skull to the midlevel of the scapula.
- Isolate a jugular vein segment via surgical cut-down and temporary encircling sutures or sterilized rubber bands.
- Perform a horizontal venotomy.
- Advance a straight or curved, appropriately sized stylet through the inner channel of the endocardial lead.

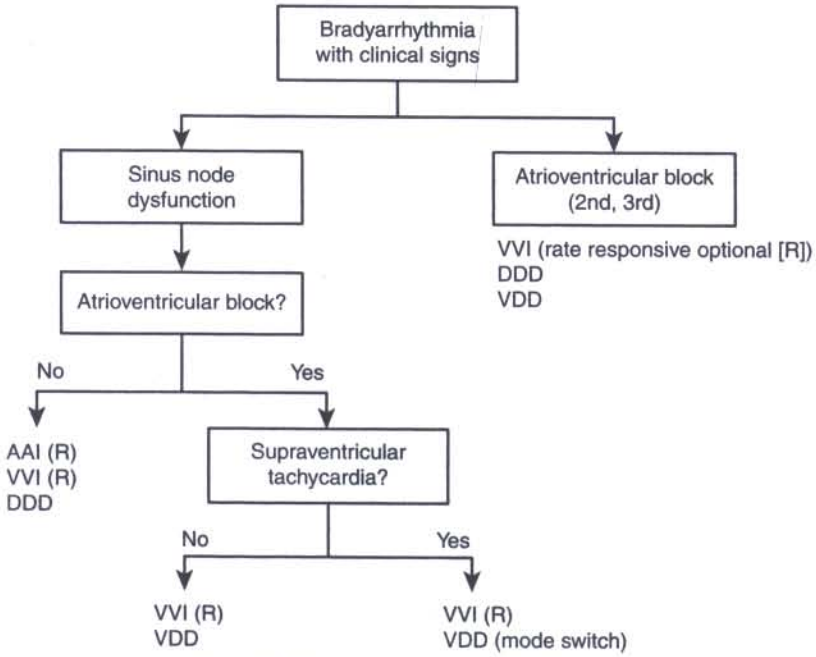

Figure 98-2 Bradyarrhythmia with clinical signs.

- Verify performance of extrusion-type active fixation leads by connecting the fixation tool to the connector pin and advance the corkscrew electrode by rotating the fixation tool clockwise.
- After extrusion, rotate the fixation tool counterclockwise to return the corkscrew into the lead. (The tool should not be overrotated counterclockwise or the mechanism may break.)
- Advance the endocardial lead through the venotomy site to the RA under fluoroscopic guidance. When using a curved stylet, the lead can often be directed into the apex of the RV. If using a straight stylet, withdraw some of the stylet to render the distal aspect of the lead more flexible and advance the distal tip to the apex of the RV.
- Advance a straight stylet to the end of the lead and gently advance the lead tip against the endocardial surface. With active fixation, connect the fixation tool to the connector pin and rotate clockwise to extrude the corkscrew under fluoroscopic guidance. Two radiopaque markers present at the lead tip touch when the corkscrew is fully extruded. With passive fixation, the lead is gently advanced to entangle the tines within the trabeculae of the RV.
- Ideally, at this time a PSA will be used to determine lead impedance and pacing thresholds. The lead can be placed at a different location within the ventricle if the pacing thresholds are determined to be inadequate for effective and safe pacing.
- Perform a "tug test" by gently pulling on the lead to verify that the endocardium is engaged.
- If a dual-chambered system is to be employed, insert the atrial lead prior to proceeding to the next step.
- Slide the suture sleeve on the lead distally and insert it into the distal aspect of the venotomy site. Place two to three circumferential nonabsorbable sutures around the jugular vein and the suture sleeve, taking care to advance enough lead to allow some slack for neck movement.
- Double ligate the proximal portion of the jugular vein.
- Make an incision over the dorsal neck. (Blunt dissection is used to create a pocket just large enough for the pulse generator.)
- Using a long, straight hemostat, tunnel to the venotomy site, grasp the proximal aspect of the lead, and pull until the lead enters the pulse generator pocket.
- Insert the connector pin into the ventricular lead channel of the pulse generator and tighten the screw or screws with a manufacturer-supplied wrench tool (overtightening should be avoided). If using a unipolar system, the pulse generator must be in contact with the tissues for pacing to occur. Temporary pacing should either be turned off or the rate dramatically slowed to not interfere with the permanent system.
- Place any excess lead underneath the generator, place a nonabsorbable suture through the suture sleeve on the generator, and anchor it to the deep fascia of the dorsal neck.
- Close incisions routinely, taking care to close as much dead space as possible to avoid possible seroma formation.

Atrial Lead

When placing an atrial lead via the jugular vein, the clinician should do the following:

- When used with a dual-chambered system, the ventricular lead is placed first. Care is taken when manipulating the atrial lead because dislodgement of the ventricular lead could result.
- If using a straight lead, insert a straight stylet into the lead and advance the lead tip under fluoroscopic guidance just until it enters the RA.
- Replace the straight stylet with a *J*-shaped stylet to direct the lead tip into the cranial-lateral aspect of the right auricle.
- If using a preformed *J*-shaped atrial lead, insert a straight stylet into the lead and advance the lead tip under fluoroscopic guidance just until it enters the RA.

- Slowly retract the stylet while advancing the lead; this should allow the tip of the lead to move into the cranial-lateral aspect of the right auricle.
- *Note:* Proper placement of the lead tip is verified by dorsoventral movement or "wagging" in concert with the beating heart.
- Regardless of the lead used, a *J*-shaped stylet should then be advanced to the lead tip and fixation performed as with the ventricular lead.
- When removing the stylet, the clinician should advance some of the atrial lead while the stylet is removed to reduce the risk of dislodgement.
- Place circumferential sutures around the jugular vein and suture sleeve as with the ventricular lead.

PERMANENT TRANSVENOUS PACEMAKER IMPLANTATION (COSTOCERVICAL VEIN)

When implanting a permanent transvenous pacemaker via the costocervical vein, the clinician should do the following:

- Perform a thoracotomy at the right second intercostal space.
- Isolate the costocervical vein (CCV) and ligate it 2 to 3 cm distal to the cranial vena cava.
- Perform a venotomy and advance the lead into the RV as with the jugular technique.
- Create the generator pocket deep to the external abdominal oblique muscle by a vertical incision over the seventh rib.
- Tunnel the lead deep to the subcutaneous tissues and over the lateral thorax to enter the generator pocket.
- Close all incisions in routine fashion.

PERMANENT EPICARDIAL PACEMAKER IMPLANTATION

When implanting a permanent epicardial pacemaker, the clinician should do the following:

- Perform a ventral midline celiotomy extending from just caudal to the umbilicus to the xiphoid.
- Make a vertical incision in the diaphragm, left of midline, to expose the cardiac apex.
- Incise the pericardium and retract with tissue forceps to expose the apex of the LV.
- Implant an active fixation epicardial lead into the apex of the LV by using the manufacturer-supplied lead tool.
- Create the generator pocket between the transverse abdominis and internal abdominal oblique muscles along the lateral abdominal wall.

Note: The clinician should not suture the pericardium; instead, the diaphragm and abdominal incisions should be closed in routine fashion.

POSTOPERATIVE CARE AND MONITORING

Thoracic radiographs and electrocardiography are performed postoperatively to verify lead placement and record QRS morphology, respectively. The animal is generally placed in an intensive care unit (ICU) overnight with continuous ECG monitoring for possible arrhythmias and loss of capture. With endocardial systems placed via the jugular route, a padded bandage is placed around the neck to cover both the jugular and generator incisions to protect the incision sites and prevent excessive fluid accumulation. The bandage is changed every 2 to 3 days until the sutures are removed in 10 days. Antibiotics such as cephalexin (22 mg/kg q 12-8 hrs) or amoxicilin with clavulanic acid (13.75 mg/kg q 12 hrs) are continued orally for 7-10 days. Strict exercise restriction is required for the first month to reduce the risk of lead dislodgement. After 1 month, the lead is usually anchored firmly in place and the animal can resume normal activity.

The author follows a monitoring protocol of 1 month, 3 months, and 1 year after implantation with annual or biannual rechecks scheduled thereafter. Thoracic radiographs, surface ECG, and programmer interrogation by a PSA are performed to evaluate lead placement and function. Appropriate adjustments are made to the generator via the PSA as needed; end of battery life for the generator can also be identified.

CHAPTER • 99

Peritoneal Dialysis

Cathy Langston

Peritoneal dialysis is used to treat acute renal failure, occasionally poisoning by a dialyzable toxin (i.e., ethylene glycol, phenobarbital, ethanol), or chronic renal failure. Some peritoneal dialysis techniques can also be applied for peritoneal drainage (i.e., uroabdomen) or peritoneal lavage (i.e., pancreatitis, hypothermia, hyperthermia).

PERITONEAL DIALYSIS CATHETERS

Access to the peritoneal cavity is accomplished via a peritoneal catheter. The general design of percutaneously placed catheters includes multiple fenestrations at the tip of the catheter to allow fluid ingress and egress. A variety of catheters are available that are made specifically for this purpose (i.e., Peritoneal Lavage Catheter, Cook Veterinary Products, Spenser, Ind.; Pediatric Peritoneal Dialysis Catheter, Baxter Healthcare Corp., Deerfield, Ill.), or fenestrated chest tubes may be used. For percutaneous placement, local anesthesia in conscious animals or a short-acting injectable anesthetic may be used. The patient is placed in dorsal recumbency, and the abdomen is sterilely prepped and draped. A stab incision through the skin lateral to the midline at the level of the umbilicus allows introduction of a trocar threaded through the dialysis catheter. The trocar is tunneled under the skin for 1 to 2 cm before puncturing the abdominal musculature. The trocar should be directed toward the opposite hip. Having the abdomen slightly distended with fluid facilitates percutaneous placement. After the trocar has been introduced, the catheter is advanced off the trocar. The tip of the catheter should rest near the urinary bladder to facilitate fluid drainage. If a trocar is not provided with the catheter, the tip of the catheter can be grasped with curved hemostats, which can be used to tunnel the catheter under the skin and then puncture the abdomen.

The coaxial catheter (Cook Veterinary Products, Spenser, Ind.) and the fluted-T catheter (Ash Advantage Peritoneal Dialysis Catheter, Medigroup, Inc., Aurora, Ill.) are less likely to occlude with omentum. The fluted-T catheter has two limbs, each with channels extending the length of the catheter, to minimize the chance for complete occlusion. These catheters are placed surgically or via laparoscopy. Both have a Dacron cuff that allows attachment of fibroblasts in the subcutaneous portion to enhance stability and diminish leaks and infection. With surgical placement, the catheter is placed in the abdomen via a small caudal abdominal incision. The catheter should exit the ventral body wall through a separate stab incision (not through the abdominal incision), and tunnel under the skin lateral to the midline. The tip of the catheter should rest near the urinary bladder. A partial omentectomy is performed to diminish catheter occlusion. If omentectomy is not desired due to recent intestinal surgery, an omentopexy should be performed.

With both percutaneous and surgical placement, the catheter is secured to the skin at the exit site via a purse string suture. A sterile dry bandage is placed over the catheter. Ideally, the catheter would not be used for 24 hours after placement to allow formation of a fibrin seal, but the animal's condition rarely allows this. When the catheter must be used immediately, a small volume of dialysate (half of the standard volume) should be used for each exchange for the first 24 hours.

DIALYSATE SOLUTIONS

Dialysate is the fluid that is introduced into the abdomen. Uremic toxins (e.g., blood urea nitrogen [BUN], creatinine, potassium) diffuse from the area of high concentration (the patient's bloodstream) across the peritoneal membrane into the area of low concentration (dialysate). The dialysate is then drained and discarded and the process is repeated. Dialysate should be similar in content to plasma and should contain physiologic concentrations of readily diffusible substances like sodium, chloride, calcium, and magnesium. It should also contain dextrose, which may be varied in concentration to create an osmotic gradient to either promote or retard fluid removal, based on the animal's needs. If no fluid removal is desired, a dextrose concentration of 1.5% is typically used. If the dog or cat is overhydrated, dextrose concentrations of 2.5% or 4.25% can be used to promote movement of water into the hypertonic dialysate in the abdomen—a process called *ultrafiltration*. Commercially prepared dialysate is available, or dialysate can be improvised from intravenous fluids. Dextrose is added to lactated Ringer's solution or saline to create the desired dextrose concentration (30 mL of 50% dextrose per liter for 1.5% solution, 50 mL per liter for 2.5% solution, or 85 mL per liter for 4.25% solution). Heparin (250 to 1000 U/L) should be added to the dialysate for the first few days after catheter placement to minimize fibrin clot formation. Magnesium should be added after the first several days of dialysis to achieve a concentration of 1.5 mEq/L. If saline is used, sodium bicarbonate should be added to achieve a concentration of 30 to 45 mEq/L. Each additive to the dialysate increases the risk of contamination and formulation error.

EXCHANGE PROCEDURE

Frequent dialysate exchanges are necessary in dogs or cats with acute oliguric or anuric renal failure, with hyperkalemia, or those that are overhydrated. Initially, exchanges may be as frequent as every 45 to 60 minutes. As the uremia improves (typically after 24 to 48 hours), the frequency of exchanges can be gradually decreased to four times a day, with the goal of maintaining the BUN concentration between 60 to 100 mg/dL. The volume of dialysate to instill is 40 mL/kg per exchange. With small volumes of dialysate, weighing the dialysate bag or using a burette is recommended to increase the accuracy of measurement. Dialysate should be warmed to 38° C to maintain body temperature and to improve peritoneal permeability. Dogs and cats need to be closely observed for signs of abdominal discomfort or respiratory compromise.

Because peritonitis is a frequent complication of peritoneal dialysis, the catheter and all connections should be handled as aseptically as possible. The connection ports should be covered with antiseptic-soaked gauze and should be scrubbed prior to any connection or disconnection. Sterile gloves should be worn when handling the connections, and the frequency of connections and disconnections should be kept to a minimum. Most contamination occurs when connecting to the dialysate bags. A Y connector (or stopcock) can be placed on the catheter and connected to a multidose bag of fresh dialysate and to an empty bag to collect spent dialysate. A small amount of fresh dialysate is flushed into the drain bag with the catheter closed to the animal in an attempt to flush any contaminant that may have been introduced during the connection process into the drain bag and not into the abdomen. The dose of dialysate should then be instilled into the abdomen by gravity feed, usually taking less than 10 minutes. The fresh dialysate bag should then be clamped and the catheter closed to the dog or cat during the dwell time. After the appropriate dwell time, the catheter is opened to allow drainage of the abdominal fluid into the drain bag. It is important that the drain bag be positioned lower than the catheter to allow gravity drainage. Gentle ballottement of the abdomen and repositioning the animal can facilitate more complete drainage. After draining ceases (approximately 15 to 30 minutes), fresh dialysate is again instilled into the abdomen. If the entire volume of the fresh dialysate bag is infused per exchange, the empty bag should be clamped after infusion and left attached. After the dwell time, the clamp should be opened and the bag used as the drain bag.

The volume of dialysate instilled and the volume recovered should be monitored carefully, as should urine output and volume of administered fluids, medications, and feedings. When hypertonic dialysate is used (i.e., 4.25% dextrose), a larger volume of dialysate should be recovered than instilled, indicating net fluid removal from the animal. The dog or cat should be monitored for evidence of dehydration. If less dialysate is being recovered than is being instilled, the catheter tubing should be checked for kinks or occlusion and the animal repositioned. The catheter can be forcefully flushed with heparinized saline, or 15,000 U of urokinase can be instilled in the catheter for 2 to 3 hours to dislodge fibrin clots or omentum. If these measures do not restore flow, the catheter may need to be repositioned or replaced. If the dog or cat is dehydrated, fluid may be reabsorbed from the peritoneal cavity, decreasing the volume of dialysate recovered.

In addition to meticulous attention to fluid balance, several other parameters should be monitored routinely. Blood glucose concentration should be monitored once or twice daily. If hyperglycemia is documented, low doses of insulin may need to be administered. Packed cell volume (PCV), total solids, and electrolytes should be monitored twice daily. Initially, BUN, creatinine, and albumin should be monitored once or twice daily. Cytology should be performed on the spent dialysate on a daily basis, and the dialysate should be cultured weekly or if it becomes cloudy.

COMPLICATIONS

Peritonitis is a major complication of peritoneal dialysis. Meticulous attention to aseptic technique is necessary to decrease this risk. Diagnosis is made by presence of clinical signs (e.g. abdominal pain, fever), cloudy dialysate, or greater than 100 inflammatory cells per mL of dialysate. Because *Staphylococcus* is the most common organism isolated, systemic cephalosporins are recommended pending culture results. Intraperitoneal administration of antibiotics may be helpful (i.e., 125 mg cephalothin per liter of dialysate). Although peritonitis may be successfully managed while continuing dialysis, removal of the peritoneal dialysis catheter may be required to allow resolution of unresponsive peritonitis.

Catheter occlusion is a common problem with peritoneal dialysis. The omentum has tremendous migratory capability and can rapidly encompass the catheter. Acute peritoneal dialysis catheters may occlude within 24 to 72 hours of placement. The fluted-T and coaxial catheters fare better, but occlusion can still occur with these. A partially occluded catheter drains more slowly and incompletely. Incomplete emptying of the dialysate decreases efficiency of toxin removal and risks overdistension of the abdomen, with concomitant problems (abdominal or respiratory distress). Flushing the catheter with saline in the first 24 hours after placement may help delay this problem. If the catheter occlusion cannot be dislodged with flushing or urokinase, the catheter may need to be replaced. Other catheter-related complications include dialysate leakage or exit site and subcutaneous tunnel infections.

Hypoalbuminemia is one of the most common complications of peritoneal dialysis and can be partially addressed by providing adequate nutrition either enterally or parenterally. Enteral feeding is frequently difficult, due to anorexia or vomiting. Gastrostomy or jejunostomy tubes are contraindicated in peritoneal dialysis due to exit site leaks and increased risk of infection. Dialysate containing amino acids may provide partial nutrition but should not be used unless adequate nonprotein calories are being provided.

DISCONTINUING DIALYSIS

Intermittent rest periods, in which no dialysate dwells in the abdomen, with close evaluation of the animal's clinical and biochemical status can be used to determine when dialysis can be discontinued. When the dog or cat can maintain homeostasis without dialysis, the catheter should be removed surgically. Unfortunately, survival with peritoneal dialysis has been low, with most reports around 30%.

CHAPTER 100

Veterinary Nuclear Medicine

Brian A. Poteet

INTRODUCTION

Nuclear imaging (scintigraphy) has been used in veterinary medicine as a primary or secondary modality to aid in the diagnosis of disease processes and for therapy. The utility of nuclear medicine procedures lies in the fact that they enable the imaging of physiologic processes. Nuclear medicine is to physiology as radiographs are to anatomy. Table 100-1 lists six nuclear medicine studies and their primary indications for use. Although these studies and others have been used in animal patients, the thyroid scan, portal scan, bone scan, and glomerular filtration rate (GFR) scan are the most commonly performed scans in a clinical setting. The *Handbook of Veterinary Nuclear Medicine*[1] further describes these and other types of scans.

Nuclear imaging differs from radiographic imaging in that the instrumentation (a gamma camera) emits no radiation. Instead the patient emits gamma radiation after a dose of radiation has been intravenously administered. The most common radionuclide used for diagnostic purposes is ^{99m}Technetium (^{99m}Tc, Tc, Tech, or pertechnetate). ^{99m}Tc is eluted using sterile saline in liquid form from its parent isotope, ^{99}Molybdenum (^{99}Mo), in a lead-encased generator system (also known as the "cow"); the whole process commonly referred to as "milking the cow." The eluate (^{99m}Tc suspended in saline) is then placed in a small lead-encased dosing bottle (known as the "pig") and kept for use either alone (as a radionuclide) or it tagged to a pharmaceutical (to form a radiopharmaceutical). The amount of radioactivity obtained with each elution is variable and will depend on the size of the generator system, its age, and the timing of each elution. The most common unit of a dose of radioactivity is the Curie (Ci), with most fresh eluates being around 1 Ci in strength. Most patient doses are in the millicurie (MCi) range (1 Ci = 1000 MCi). An individual or institution must have a radioactive materials license (RML) from either the state in which they practice (an "agreement state") or from the Nuclear Regulatory Commission (NRC). Qualifications and experience required to obtain an RML varies, but it generally requires proven experience and training in nuclear medicine procedures and radiation safety. The regulations concerning the use of radioactive materials in veterinary patients are often different from that of human patients. The major differences usually pertain to patient release criteria and safety requirements. For example, human patients are allowed to leave the hospital if they have been administered 30 MCi or less, as compared with animal patients that must typically be hospitalized for 24 hours until their exposure levels are below a specific level that the state has set (typically 0.5 mR/hour at 1 m. The overall dose of radiation that a patient is exposed to from a typical nuclear medicine procedure is minimal, and adverse side effects are rarely seen.

Table 100-1

Commonly Performed Nuclear Medicine Studies in Veterinary Medicine

SCAN NAME	INDICATIONS FOR USE
Thyroid scan	Feline hyperthyroidism, occult hyperthyroidism
Portal scan	Macroscopic portosystemic shunt detection
Bone scan, three-phase bone scan	Occult lameness, differentiate septic arthritis or osteomyelitis vs. severe chronic degenerative joint disease (DJD), metastatic bone disease
Glomerular filtration rate (GFR) scan	Quantitative evaluation of differential renal function
Perfusion lung scan	Pulmonary thromboembolic disease
Multigated acquisition cardiac scan (MUGA)	Subjective and objective evaluation of cardiac performance

The site and method of tissue localization depends on several factors, the more important of which are blood flow, the type of radiopharmaceutical used, and individual species differences. When administered intravenously to a patient as a radionuclide (pertechnetate ion), localization will mimic that of halogenated compounds, such as iodine, and occurs in glandular tissues, such as the thyroid gland, choroid plexus, salivary glands, and mucosal glands that line the stomach. When administered as a radiopharmaceutical, the method and site of localization depend on the physical or chemical characteristics of the radiopharmaceutical itself. Table 100-2 lists commonly used radiopharmaceuticals, their various sites and methods of tissue localization, and their various uses.

Instrumentation required in a basic veterinary nuclear medicine lab will vary, but includes a gamma camera, an interfaced computer with acquisition and processing software, an exposure meter, safety equipment including a radioactive materials spill containment and clean-up kit, shielding material such as lead bricks, and a properly shielded and ventilated radiation isolation ward. New gamma cameras and computers are expensive, but good quality used and refurbished equipment is available.

Radiation safety is extremely important when performing nuclear medicine procedures. The word "nuclear" often conjures up thoughts of nuclear weapons, mushroom clouds, and genetic defects. In fact, many owners are surprised to find out that their animals will not "glow in the dark" after a scan. Four basic premises to radiation safety are considered universal: First, is the as low as reasonably achievable (ALARA) concept, which states that individuals should never allow themselves to be exposed to any more radiation than is absolutely required to do their jobs. The last three radiation safety guidelines that should be remembered are time, distance, and shielding. One should always minimize the time exposed to a radiation source, maximize the distance from it, and when

Table • 100-2

Commonly Used Radiopharmaceuticals

RADIOPHARMACEUTICAL OR RADIONUCLIDE	SITE OF LOCALIZATION	METHOD OF LOCALIZATION	TYPICAL USE
^{99m}Tc-Methylene diphosphate	Hydroxyapatite	Chemiadsorption	Bone scan
^{99m}Tc-Diethylene triamine pentaacetic acid	Glomerular filtrate	Active transport	GFR scan
^{99m}Tc-Macroasgregated albumin	Pulmonary capillary bed	Capillary blockade	Perfusion lung scan
^{99m}Tc-HIDA xxx	Hepatocytes and bile	Active transport	Hepatobiliary scan
^{99m}TcO4 xxx	Glandular tissue		Thyroid scan
^{67}Gallium xxx	Sarcoma tissue, abscess	Transferring analog	Sarcoma imaging, FUO
^{123} or ^{131}MIBG xxx	Neuroendocrine cells	Active transport	Pheochromocytoma

possible place protective shielding (lead, cement walls) between him or herself and the radiation source when possible. For all nuclear medicine procedures performed in veterinary medicine, the users should always wear disposable exam gloves, a lab coat, and should always be monitored (properly wearing a radiation exposure detection device) with a film badge, thermoluminescent dosimeter (TLD) badge, or pocket dosimeter. For most institutions, employees working strictly with nuclear medicine patients will have about one tenth the dose of other employees who work in radiology sections.

THYROID SCINTIGRAPHY

Introduction and Basic Techniques

The thyroid scan is the most commonly performed diagnostic scan in veterinary nuclear medicine and is used to confirm and diagnose feline hyperthyroidism. The diagnostic thyroid scan is considered to be the "gold standard" means of diagnosing feline hyperthyroidism. Because technetium behaves as a halogen (iodine) when administered, it is actively trapped by thyroid cells. However, unlike iodine, technetium is only trapped and does not progress through the remaining steps of thyroid hormone synthesis (organification, coupling, storage, and release).[2,3] The trapping of technetium is competitive with iodine (recent administration of iodinated contrast material may hinder the uptake by the thyroid) and is also influenced by thyroid-stimulating hormone (TSH) levels.[4] Adenomatous hyperplasia of the feline thyroid results in a hyperfunctional gland in two ways. First, the gland synthesizes and releases too much thyroxine, resulting in an elevated T4 value and (more fundamentally) the gland has increased ability to trap iodine (and therefore technetium). This is not always true in the canine species as will be discussed later.

Although the thyroid scan can be performed with either ^{123}I or ^{99m}Tc, technetium has the advantages of being more economical, readily available, and it has a shorter half-life. If disparate imaging between the two radionuclides occurs, they are typically insignificant.[5] The dose of ^{99m}Tc used for a feline patient is typically 4 MCi (+/– 2 MCi) and is administered intravenously into a cephalic or medial saphenous vein. It has been shown that the maximal uptake by thyroid cells is at 45 to 60 minutes after injection[6]; although approximately 90% of cats will demonstrate positive scans in just seconds after injection. Normal salivary gland to thyroid gland ratios are 1:1.2 or less[7] and can be obtained by calculating the count density within a region of interest (ROI) encircling the respective glands. For practical purposes, however, the zygomatic salivary glands and thyroid gland should have very similar degree of uptake in normal cats. In hyperthyroid cats, a portion or all of one or both of the thyroid lobes will have significantly more uptake than that seen by the salivary glands.

Indications for Performing a Thyroid Scan

A thyroid scan should be performed for several reasons. The scan can be used to confirm suspect hyperthyroidism in feline patients that have elevated circulating thyroxine levels prior to administration of radioiodine. The majority of centers routinely perform thyroid scans on all patients prior to administration of radioiodine (^{131}I), thus preventing wrongful treatment of normal patients that have a false-positive elevated T4 or fT4 assays. Negative results of a thyroid scan will prevent an unnecessary surgery or inappropriate administration of radioiodine. The amount of uptake and size of the glands may also aid the clinician in determining the dose of radioiodine to be used, thus allowing some degree of individual tailoring of the dose of radioiodine. Lastly, by routinely performing a diagnostic thyroid scan on all patients, one may be able to exclude a patient whose scan suggests an aggressive thyroid carcinoma, the presence of which may change the owner's decision-making process.

Thyroid scanning may also diagnose patients with "occult" hyperthyroidism. In these cases a diagnostic thyroid scan can quickly diagnose hyperthyroidism in a patient that may otherwise be missed.

A thyroid scan can also be used before or after attempts at surgical resection of both or one lobe of the thyroid in clinically persistent hyperthyroid cats. In these cases, foci of ectopic thyroid tissue can be easily localized within the cervical region (incomplete resection) or within the cranial mediastinum. Once located, the persistent hyperfunctional thyroid tissue can be removed or ablated with radioiodine.

Image Acquisition

A minimum of three views should be taken during acquisition of a routine feline thyroid scan (Figure 100-1). The first image should be a ventral view, which includes both lobes of the thyroid gland and the mandibular and zygomatic salivary glands. This view is used to confirm the diagnosis of hyperthyroidism because the amount of uptake by the thyroid glands can be easily compared with that of the salivary glands, either by drawing ROIs around the individual glands and comparing count density or by subjective comparison. The second ventral view should be a close up view of just the thyroid gland itself, taking care to include any area of uptake. This view is important in evaluation of the morphology of the thyroid itself. The last view that should be acquired is a lateral view (right or left), including the entire thorax. To ensure that the entire thorax is included, the thyroid should be seen on one side of the image and stomach uptake on the opposite side. This view

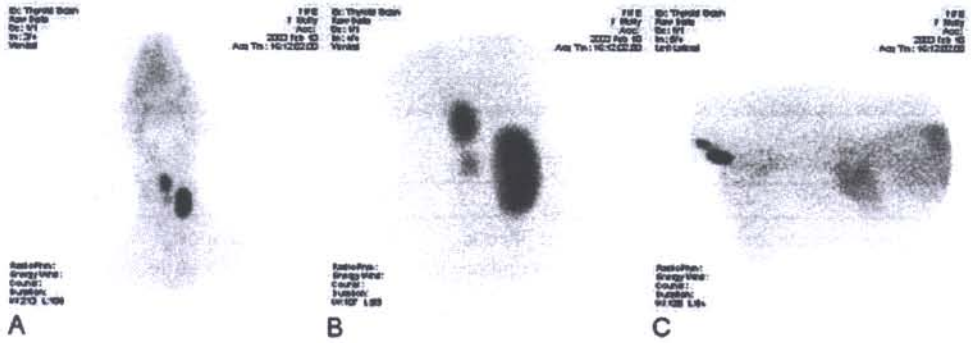

Figure 100-1 Thyroid Scan. Hyperfunctional thyroid adenoma, bilateral, in a fourteen-year-old domestic shorthair, male castrated technetium injected with 4 MCi of ^{99m}Tc. Images shown are 200,000-count static images with pinhole collimation. **A,** Ventral neck view. Focal intense activity is seen by both lobes of the thyroid glands, more so than that seen by the salivary glands. The right thyroid has a "hot" nodule in the cranial and caudal pole. **B,** Ventral thyroid view. Both glands exhibit benign scanning characteristics (intense center, homogeneous uptake, tapering margins, no evidence of regional tissue invasion). **C,** Left lateral thorax view. No abnormal areas of uptake in the thorax are seen.

is important in evaluating for possible uptake within the cranial mediastinal region and lung fields. If uptake is seen in these regions, a ventral view of the thorax and opposite lateral should also be obtained. All images should be acquired on a count basis (as opposed to a time acquisition) for approximately 200,000 counts using pinhole collimation. Each image acquisition should take approximately 3 minutes, giving a total scan time of about 10 minutes (assuming a ^{99m}Tc dose of 4 MCi).

Interpretation and Analysis

In normal cats (not hyperthyroid) the amount of uptake seen by the salivary glands and thyroid gland is very similar. Placement of ROIs around the salivary glands and thyroid tissue with comparison of the amount of uptake should yield a thyroid to salivary gland ratio of less than 1.2 in normal animals. In most cases the placement of ROIs is not needed to confirm the diagnosis of hyperthyroidism, and subjective evaluation of significantly more uptake within the thyroid tissue versus that of the salivary gland tissue is all that is needed (Figure 100-2).

False-positive ^{99m}Tc thyroid scans can be seen in hyperthyroid cats secondary to recent administration of methimazole because it may cause false increased uptake by the thyroid tissue due to stimulation by an elevated TSH concentration.[10] This same phenomenon has not been evaluated in normal euthyroid cats. False-negative thyroid scans are extremely rare but may be due to severe thyroiditis, recent intake of iodinated contrast material, or ingestion of excess dietary or administered iodine[11] overlying and attenuating soft tissues or malfunctioning nuclear medicine equipment.

Several classifications of feline hyperthyroidism exist based on the location of uptake. Unilateral uptake by one lobe with complete suppression of the contralateral lobe is reportedly seen in approximately one third of patients[3] (Figure 100-3, *A*). Bilateral uptake in both lobes is seen in the remaining two thirds[3] (Figure 100-3, *B*). Bilateral uptake is defined as uptake, regardless of the amount, seen in both thyroid lobes. It is common for one lobe to have more uptake, be larger than the contralateral lobe (incomplete suppression), or both; however, this is still considered to be bilateral because a normally functioning thyroid should demonstrate no evidence of autonomous function and be completely suppressed (thus not seen at all) (Figure 100-3, C).

Hyperfunctional ectopic tissue can occur anywhere from the base of the tongue to the base of the heart; the incidence is estimated to be as high as 10%[14] (Figure 100-4). The presence of ectopic hyperfunctional thyroid tissue does not imply malignancy. It is also very common to detect adenomas with intense focal uptake by very small (2 to 3 mm), nonpalpable, thyroid nodules (Figure 100-5).

A thyroid scan can also be used to help differentiate benign adenomatous hyperplasia versus a malignant thyroid carcinoma. Close examination of the morphologic scanning characteristics of each thyroid lobe may give clues that help distinguish nonaggressive disease versus an infiltrative carcinoma. Pinhole collimation is very helpful in evaluating the morphology of thyroid disease because it magnifies the appearance of the otherwise small lobes. Characteristics of a simple adenoma (benign) include round to oval shape, smooth or homogeneous uptake, margins that taper uniformly, and no evidence of regional tissue invasion. Malignant thyroid carcinomas often exhibit very abnormal shapes with poorly defined, irregular

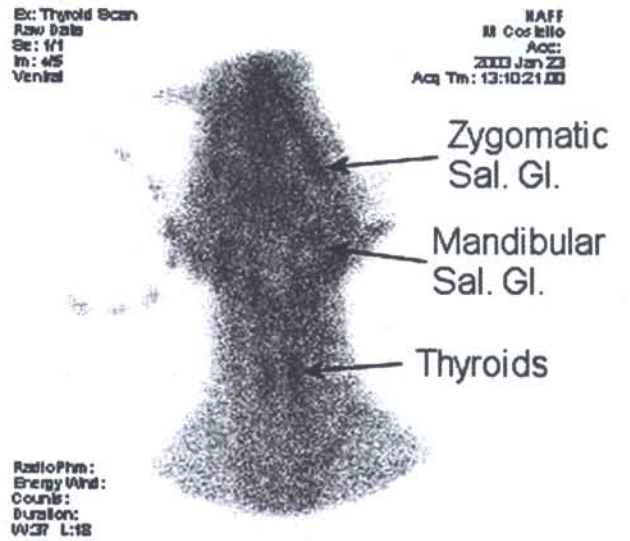

Figure 100-2 Normal feline thyroid scan. The amount of uptake by the thyroid gland is similar to that seen by the salivary glands.

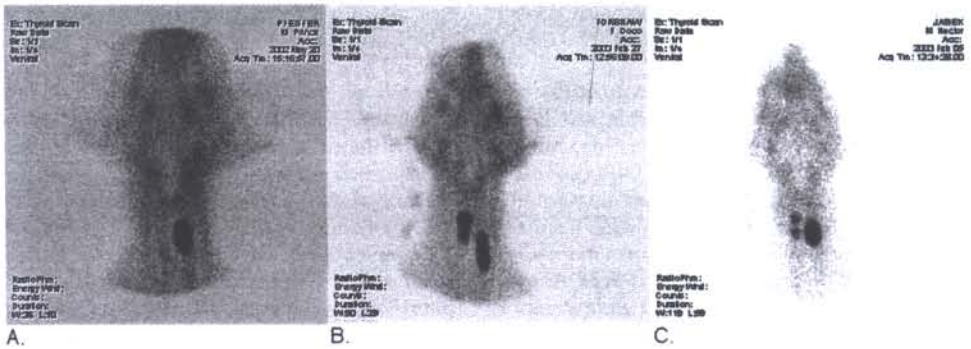

Figure 100-3 Variations of feline hyperthyroidism. Three commonly seen morphologic variations of feline hyperthyroidism exist. **A,** Unilateral with complete suppression of normal contralateral thyroid lobe. **B,** Bilateral hyperthyroidism. **C,** Bilateral hyperthyroidism with incomplete suppression of one thyroid lobe.

margins, heterogenic uptake, and evidence of invasion into surrounding tissue facial planes (Figure 100-6).

Common findings that occur in adenomas that can be confused with a carcinoma include nodular to multinodular uptake, photopenic areas caused by thyroiditis, follicular cyst or parathyroid adenoma, or ectopic hyperfunctional tissue within the thoracic inlet or cranial mediastinum. In these cases it is important to examine each focal area of uptake individually for evidence of benignancy or malignancy. If the cat has undergone previous attempts at thyroidectomy, caution must be exercised because the surgical intervention can cause a very abnormal morphologic appearance of the persistent or recurrent thyroid tissue that can mimic a thyroid carcinoma (Figure 100-7).

In cats with suspected thyroid carcinoma, ultrasound is often the next step because it can often detect the reason for photopenic areas caused by follicular cysts or an enlarged parathyroid gland and evaluate if the thyroid appears to be well encapsulated. If none of the aforementioned are true, if the thyroid gland appears of mixed echogenicity, or if it appears invasive into surrounding tissues, surgical intervention usually follows.

After a diagnostic thyroid scan using ^{99m}Tc, the feline patient must be housed in a radiation isolation ward until it clears the individual clinics release criteria, which is typically set by the issuer of the RML (the author's practice requires 0.5 mR/hour at 1 m). This is measured using an appropriate monitoring device such as a Geiger counter or "Cutie Pie"

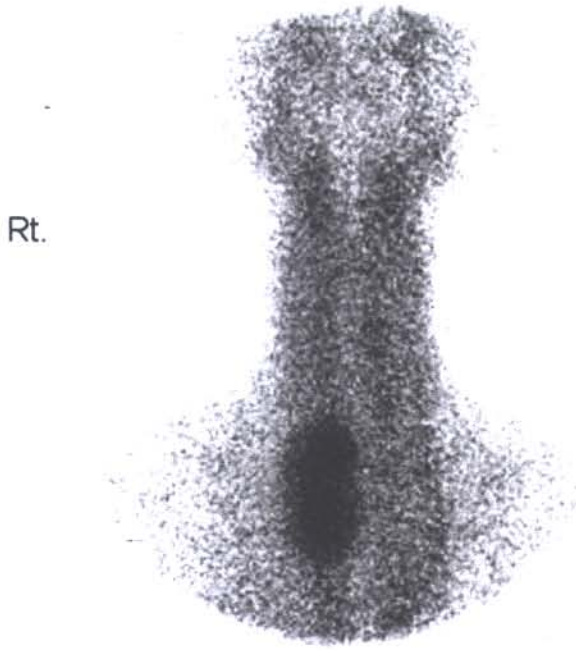

Figure 100-4 Ectopic thyroid tissue. Ventral view shows focal intense uptake in functional thyroid tissue located within the cranial mediastinum on the right.

Figure 100-5 Extremely small, nonpalpable thyroid tissue. Focal intense uptake is evidenced by a very small foci of thyroid tissue on the left side. This nodule was not palpable even in retrospect after the scan localized it.

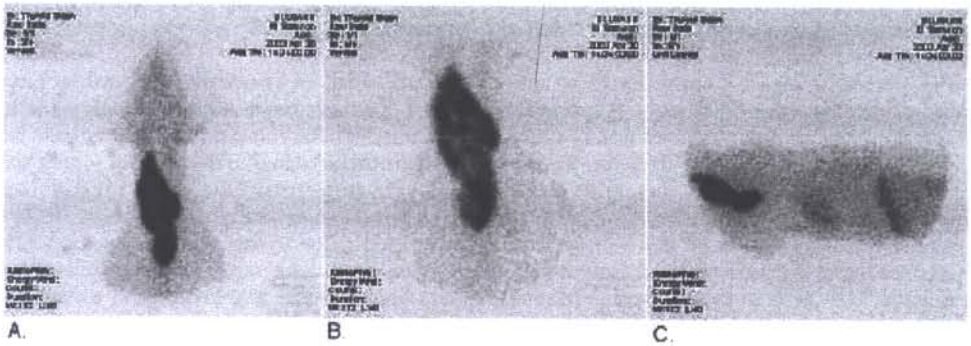

Figure 100-6 Feline thyroid adenocarcinoma. The right thyroid lobe shows very heterogeneous uptake with irregular margins. Extension of functional malignant tissue can be seen into fascial planes and into the cranial mediastinum. Numerous photopenic areas are present.

exposure meter. Once the animal returns home, the owner is instructed on how to care for the pet physically, told to minimize time holding the cat for the next week or so, and instructed how to handle the very small amount of radioiodine that will still be excreted in the cat's urine. (The specifics of these requests often vary from state to state.)

Radioiodine Therapy for Feline Hyperthyroidism

Three treatment options exist for feline hyperthyroidism: (1) medical therapy with methimazole, (2) surgical removal of the thyroid glands, and (3) radioiodine therapy. All methods have pros and cons, which will be discussed.

Radioiodine therapy using ^{131}I also has both advantages and disadvantages. Radioiodine therapy is extremely targeted in that once injected the iodine is preferentially trapped and organified by the hyperfunctional thyroid cells (little to know uptake is seen by normally suppressed thyroid cells) and once there, the high-energy beta particles that are emitted during the decay process cause irreparable damage to the cells. The distance of beta particle travel, and therefore the area of tissue damage, is confined to 1 to 2 mm; thus concurrent damage to adjacent parathyroid tissue is not seen. Administered radioiodine is taken up by all hyperfunctional thyroid tissue, regardless of its anatomic location. Because feline hyperthyroidism is not an autoimmune form of thyroid disease (human Grave's disease) and most closely resembles toxic nodular goiter (multinodular goiter), the great majority of cats that are diagnosed with hyperthyroidism retain some suppressed (but otherwise normal) thyroid cells. The advantage is that approximately 95% of cats treated with radioiodine will be euthyroid after treatment, requiring no supplementation. It is relatively common for cats to have subnormal total thyroid hormone levels immediately after radioiodine therapy, but it is extremely rare for any of these cats to demonstrate any signs of hypothyroidism. In these cats, a recheck of the thyroid hormone levels in 1 to 3 months after therapy will often demonstrate normal values.

Care must be taken regardless of the form of therapy chosen if the patient has concurrent renal compromise. Readers are encouraged to review the many studies that pertain to the correlation of the treatment of hyperthyroidism and renal disease.[15–17] In general, cats that have normal renal function based on normal serum blood urea nitrogen (BUN) and creatinine (CR) values should have few problems with

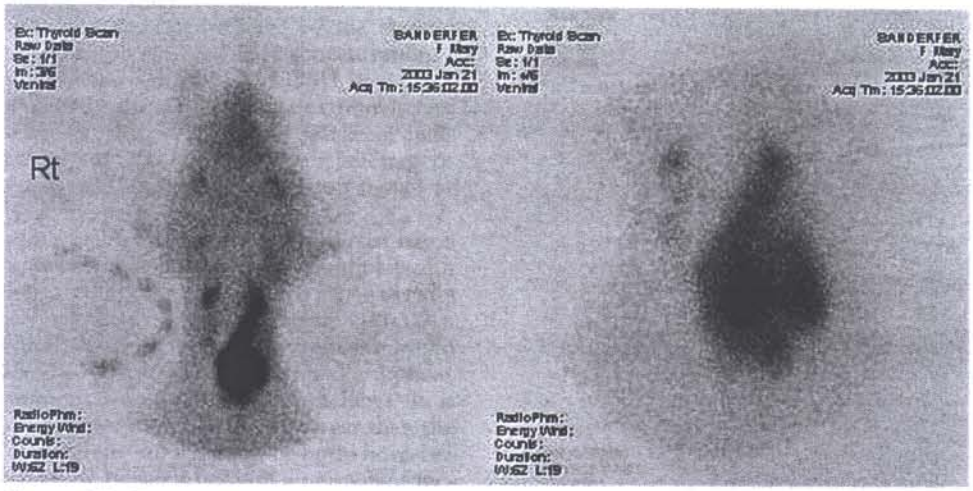

Figure 100-7 Postsurgical thyroid. Fifteen-year-old domestic shorthair, female spayed. Patient is persistently hyperthyroid despite two attempts at bilateral subcapsular thyroidectomy. The left thyroid lobe is irregular in shape and bulbous in appearance secondary to previous surgical intervention (left-sided subcapsular thyroidectomy) and subsequent recurrence. The right thyroid lobe is incompletely suppressed.

any form of therapy for hyperthyroidism. In patients that are both hyperthyroid and show equivocal or definitive evidence of renal failure (azotemia and inability to concentrate urine), a 3- to 4-week trial period using methimazole is recommended. If at the end of this time the BUN and CR levels are not increased, the animal is not showing signs of renal failure, and the total T4 values have dropped to within the normal range, a more definitive form of therapy can be safely considered. In these patients a lower dose of radioiodine may be used in an effort to minimize any effects on the kidneys and, at the same time, control hyperthyroidism. Radioiodine itself is not toxic to the kidneys. The cause of the worsening of renal disease that can accompany any form of hyperthyroid therapy is unknown but may relate to changes in hemodynamics within the kidney and glomerular filtration. Supplementation of thyroid hormone in cats that experience manifestation of renal failure after definitive thyroid therapy may be of benefit; however, no such studies have been undertaken to prove this theory.

Thyroid Scan and Canine Thyroid Disease

The parotid salivary glands in dogs demonstrate much more uptake compared with those of cats; however, the amount of uptake by the salivary glands and thyroid should be very similar in individual animals of either species (Figure 100-8). The indications to perform thyroid scans in dogs are fewer than in cats but may include presurgical evaluation of the degree of regional tissue invasion (which may aid the surgeon in evaluating the degree to which one rejects the cervical mass). A thyroid scan can also confirm that a cervical mass is indeed thyroid in origin and identify functional distant metastasis. Canine thyroid carcinoma is different from that seen in cats in that approximately one third of affected patients will demonstrate decreased or no uptake (inability to trap ^{99m}Tc), one third of patients will have relatively normal amounts of uptake (normal ability to trap ^{99m}Tc), with the last third demonstrating increased uptake (increased ability to trap ^{99m}Tc). Uptake by distant metastasis appears to have similar patterns. The same scanning characteristics of malignancy can be applied to the canine patient in that most carcinomas will demonstrate heterogeneous uptake, very irregular gland shapes, and often evidence of regional tissue invasion (Figure 100-9). Thoracic radiographs are more sensitive than a thyroid scan for the detection of pulmonary metastasis, and as such they should always be obtained whenever thyroid carcinoma is suspected.

Radioiodine Therapy for Canine Thyroid Carcinoma

^{131}I has also been used as therapy for canine thyroid carcinoma.[18,19] Radioiodine therapy is best suited for therapy for micrometastatic disease in cases where the primary carcinoma is proven to retain the ability to trap iodine (technetium); as such a diagnostic thyroid scan using ^{99m}Tc or ^{123}I should be performed prior to surgical intervention. The thyroid-associated mass should be removed or debulked surgically followed by radioiodine therapy. Presurgical external beam radiation therapy may also be used in certain cases in an attempt to shrink the primary tumor prior to intervention. If the primary tumor exhibits no ability to concentrate iodine, then conventional chemotherapeutics may be preferential for potential or known micrometastatic disease in combination with external beam radiation therapy for any incompletely resected margins. The dose used for canine thyroid carcinoma varies widely but may range from 20 MCi to 100 MCi or more. The dose is usually administered intravenously through a preplaced catheter. After administration, the animal must be kept in a radiation isolation ward until it has cleared release criteria. Strict radiation safety practices must be instituted during the entire stay, and it is not uncommon for these patients to contaminate their exterior surfaces with iodine. The typical hospital stay for these patients in the author's practice ranges from 10 to 21 days. Side effects seen with large-dose radioiodine therapy are rare but may include transient neutropenia that lasts only a few days.

PORTAL SCINTIGRAPHY

Background and Basic Techniques

Nuclear portography (portal scan) has been used as first introduced in the canine by Caride.[20] A portal scan greatly aids in the diagnosis of a macroscopic portosystemic shunt. The scan can rarely differentiate the types of portal shunts (it typically cannot differentiate if the shunt is intrahepatic versus extrahepatic or if a shunt is a single-vessel extrahepatic shunt or from a multivessel extrahepatic shunt). Hepatic microvascular dysplasia will result in a normal portal scan because the radioactive bolus is transported in normal fashion to the liver prior to the cardiac ROI.

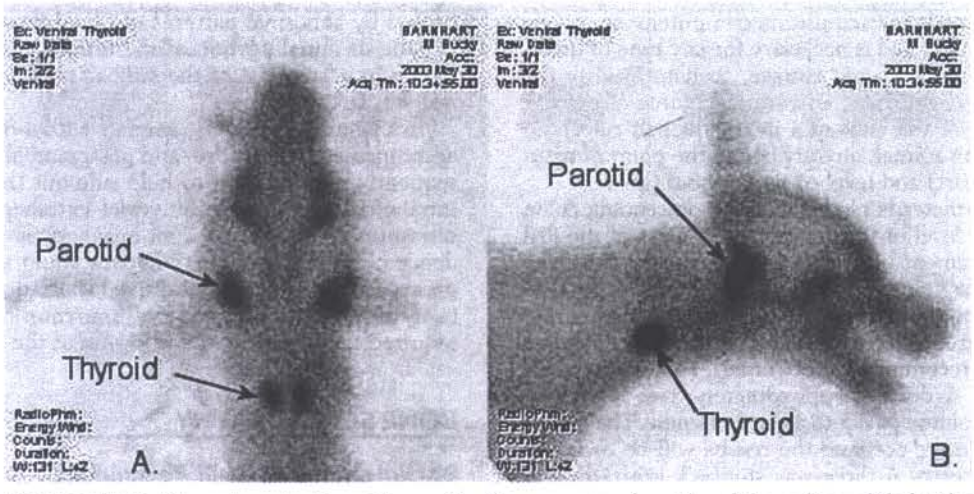

Figure 100-8 Normal canine thyroid scan. Similar amounts of uptake of the radionuclide by the parotid salivary glands and the thyroid tissue occur. Both thyroid lobes are normal in size, shape, and location.

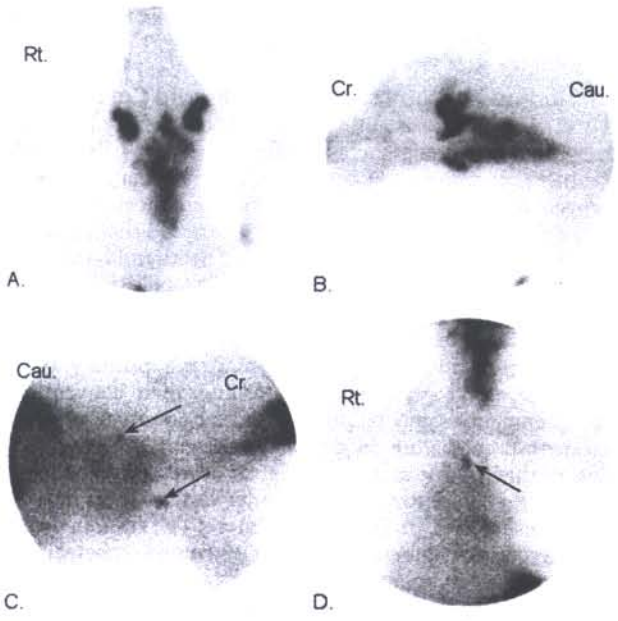

Figure 100-9 Canine thyroid adenocarcinoma. **A,** Ventral neck view shows heterogeneous, ill-defined uptake associated with the left thyroid lobe. Invasion into the caudal and cranial neck region and into fascial planes is seen. **B,** Lateral view of neck. **C,** Right lateral view of the thorax. The arrows are demonstrating two functional pulmonary metastatic lesions. **D,** Dorsal view of the thorax. The arrow points to a visible functional metastatic pulmonary nodule.

Indications for Performing a Portal Scan

The usefulness of a portal scan appears to be in patients that are suspected of having a portosystemic shunt based on clinical signs and high bile acid levels. The portal scan is performed to confirm the existence of a macroscopic shunt prior to surgical exploratory and subsequent ligation or coil placement.

Image Acquisition

A portal scan is performed on a tranquilized or (preferably) anesthetized animal in right lateral recumbency with the diaphragm centered over a gamma camera. The field of view (FOV) should include the entire heart and liver region. Although the scan can be performed without the aid of an interfaced nuclear medicine acquisition computer system, one is highly recommended and is necessary for any type of quantitative analysis and subsequent storage. To help localize the position of the heart and liver, an external source of activity (μCi point sources or the ends of a flexible cobalt ruler) are placed ventral to the animal, directly below the point of maximum intensity (heart) and level of the xiphoid (liver).

A red rubber catheter is placed into the descending colon and inserted to the level of the cranial most aspect of the ilial wings. Careful placement of the tip of the catheter along the ventral aspect of the colon is helpful in preventing a "fecal-o-gram." It is preferable to perform a portal scan with an empty colon and administration of a cleansing enema 2 to 3 hours prior to the scan is recommended by some[21]; however, it is not routinely required. A dose of approximately 3 to 8 MCi of ^{99m}Tc is used in a volume of 0.5 to 1.0 ml of saline. The higher the dose used, the more accurate the results will be owing to better counting statistics. A three-way stopcock is attached to the preplaced catheter, the dose syringe, and a 12-cc syringe filled with room air. A ⅛-inch thick piece of lead is placed between the camera top (imaging table) and the patient, directly under the tip of the catheter and caudal abdomen. Care must be taken to avoid placement of the lead under the liver region or too caudally so that it allows a "bloom" artifact from the radioactive bolus within the colon. The bolus of radiation is injected first, followed by a small amount (3 to 10 ml) of room air at a slow to moderate rate. A dynamic acquisition should be obtained, starting just prior to injection of the bolus of radiation, and continued at 4 seconds per frame for a total of about 3 minutes. Once the pertechnetate is placed within the colon, a small percentage (10% to 20%) is absorbed across the colonic mucosa and is taken up within the portal venous system.

Interpretation and Analysis

In normal patients, activity should be seen within the liver ROI prior to activity seen within the cardiac ROI (Figure 100-10). In animals with macroscopic shunts, the cardiac ROI is seen at the same time or preceding the liver ROI (Figure 100-11). With the aid of a computer and appropriate software, percent shunt fractions can also be obtained using the following formula:

$$\text{Percent shunt fraction} = \frac{(\sum \text{total heart counts over time i})}{[\sum(\text{total heart counts} + \text{total liver counts})\text{over time i}]} \times 100$$

Normal animals will have a shunt fraction of less than 20%. A positive scan is considered to be one with a shunt fraction of greater than 50%. Values obtained between 20% and 50% are considered to be abnormal and may be caused by a less severe shunt. In these cases the scan should be repeated or the animal should be explored. A shunt fraction of 0% is not physiologic, owing to the hepatic arterial blood supply. Calculation of a shunt fraction is not necessary for the diagnosis of the existence of a shunt. False-negative scans may be caused by improper placement of the radionuclide bolus in the colon cranial to the level of the shunt, incomplete absorption of the bolus across the colonic mucosa due to infiltrative disease of the colonic wall itself, or if the bolus is lodged in a ball of feces. Incorrect results (falsely elevated shunt fraction) may be seen if the bolus is administered too far cranially within the colon where a bloom artifact may overlie the liver ROI. This is commonly seen if the colon is filled with liquid, such as just after administration of an enema. The majority of the technetium is excreted in the feces (that which remains in the colon) and in the urine (that which was absorbed systemically) within the first 12 hours after the scan.

Portal streaming, as reported by Daniel,[22] is the phenomenon seen in a small portion of animals that causes only one or two lobes of the liver to scintillate. Portal streaming is caused by abnormal patterns of blood flow within the extrahepatic or initial portion of the intrahepatic vasculature that results in a "steering" of the radioactive bolus into only a section of the liver.

In the author's facility, animals with a positive portal scan accompanied by high pre- and postprandial bile acids are subsequently ultrasounded to help rule out the possibility of an intrahepatic shunt or multivessel extrahepatic shunt. If the ultrasound is negative for an intrahepatic shunt and no evidence of a multivessel extrahepatic shunt is seen, the patient proceeds to surgery for definitive localization and repair. Only in rare cases, intraoperative mesenteric portograms are required for definitive identification of the shunt vessel.

BONE SCINTIGRAPHY

Background and Basic Techniques

Bone scans are highly sensitive and equally highly nonspecific. Evaluation of the extent, pattern, and anatomic origin of an area of abnormal uptake, coupled with other factors such as

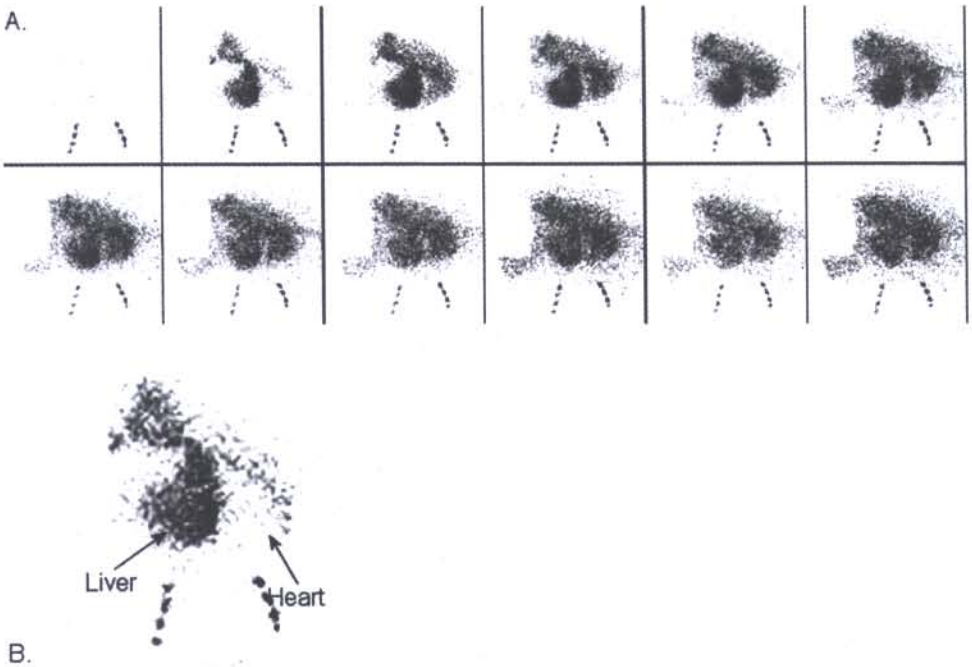

Figure 100-10 Normal portal scan. Dynamic image acquisition shows uptake within the liver region of interest (ROI) preceding that seen within the cardiac ROI.

the animal's age, sex, breed, history, physical examination, and radiographic findings can increase the specificity; in many cases a diagnosis can be made. Most images are acquired with the gamma camera head placed underneath a Plexiglas scanning table. Care should always be taken to ensure that the camera face is placed as close as possible to the underside of the imaging table and that the camera face is exactly parallel to the tabletop. By imaging from under the animal, positioning is easier and the patient feels less threatened than if the camera were placed above it. Dorsal and ventral dynamic or static images can be easily obtained on most, if not all, small animals. Using a large FOV gamma camera, a whole-body bone scan can be obtained on a large breed canine in approximately 30 to 45 minutes.

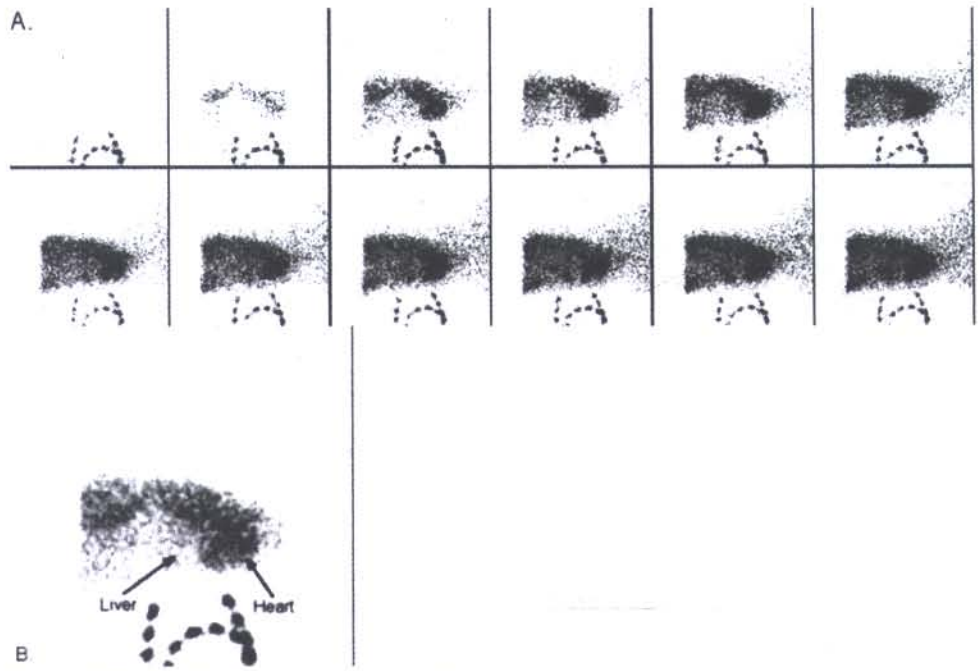

Figure 100-11 Abnormal portal scan. Dynamic image acquisition shows uptake within the cardiac region of interest (ROI) preceding that seen within the liver ROI.

Indications for Performing a Bone Scan

Bone scintigraphy has multiple uses in small animals. These include evaluation for primary and metastatic disease, septic arthritis, osteomyelitis, prosthetic implant loosening or infection, soft tissue and bone viability, occult lameness, and fracture healing. Bone scanning can often times localize subtle lesions not seen radiographically until days or weeks later.

Image Acquisition

In small animals, all static images should be acquired on a count basis, as opposed to a timed acquisition. Timed acquisitions often result in images with low count densities and poor target-to-background ratios, which renders less than optimal image quality. The higher count density and high target-to-background ratio images that are obtained using count acquisition parameters are usually of much higher quality than those obtained on a time acquisition basis. The longer scan time needed per image (1 to 3 minutes) is only significant if the animal is not under general anesthesia and patient movement is likely.

Patient preparation prior to scanning is not needed. The radiopharmaceutical ^{99m}Tc-MDP is used commonly and results in high-quality images with good target-to-background ratios. Nonradioactive ("cold") MDP is sold in a kit form and is easily made using a fresh eluate of reduced (Sn) $^{99m}TcO_4$, which allows the labeling ("tagging") of the short chain polyphosphate. Because little binding of the radiopharmaceutical to plasma proteins takes place, urinary excretion is rapid, with 59% of the dose excreted within 24 hours.[23] Adequate blood flow is necessary for delivery of the radiopharmaceutical; however, once delivered, skeletal uptake is not a function of perfusion.[24] The exact mechanism of binding is not well understood, but it is known that the phosphate itself is merely the delivery vehicle for the ^{99m}Tc; once arriving at the hydroxyapatite surface, the ^{99m}Tc is released and then chemiadsorbs to the hydroxyapatite surface as ^{99m}Tc-oxide.[24,25] Uptake of the MDP is directly proportional to osteoblastic activity and can be affected by decreased perfusion and regional sympathetic tone.[26] Maximum bone uptake is at 65 minutes postinjection, with the maximum target-to-background ratio (highest activity in the bone and lowest activity in the soft tissues) occurring at 6 hours postinjection.[27]

Radiopharmaceutical dose ranges from approximately 5 MCi to 30 MCi, depending on the animal's size (Table 100-3).

Dosing of small animals for nuclear medicine procedures will vary; however, small breed canines (e.g., toy poodles) and cats are administered 5 MCi doses, medium-sized canines (e.g., Beagles) are given 10 to 15 MCi doses, large breed dogs (e.g., Labradors) are given 20 MCi doses, and giant breed dogs are given 30 MCi doses. As with all radiopharmaceuticals, intravenous routes of administration are used. If the dose is injected through a preplaced catheter, the catheter should be flushed well after the dose is given. Even a small amount of extravasated dose will result in an injection site hot spot on subsequent imaging. Because injection site hot spots occur, it is recommended to inject in a limb that is not in question for diagnosis or to inject into a rear limb if imaging a front limb, for example. For single-phase scans, bone phase images should be acquired no earlier than 3 hours after administration. During this incubation time, care should be taken to minimize external contamination of the animal by urine. When possible, the urinary bladder should be emptied just prior to scanning by passing a urinary catheter, manually evacuating the urine, and safely disposing of the radioactive waste when done. Emptying of the bladder should be done in a careful manner to minimize contamination in the surrounding area. Clinicians should adhere to the ALARA concept in all cases; personnel that will handle the patient or urine should wear examination gloves to avoid exposure.

Routine bone scan images should be obtained using a general all-purpose (GAP), parallel hole collimator with a 20% window centered over the 140 keV gamma photo peak of ^{99m}Tc. Occasionally, a pinhole collimator is helpful in acquiring high-resolution images of small parts, such as the coxofemoral joints (Legg-Calve-Perthes Disease), elbows, carpi, and sesamoid bones associated with the extremities. If a pinhole collimator is used, the number of acquired counts will need to be decreased because the acquisition time becomes prohibitively long.

As with thyroid imaging, all static images should be acquired on a count basis. Generally speaking, the more counts that can be acquired, the higher quality the image will be. The following are suggestions regarding recommendations for static acquisitions for different body parts (Table 100-4).

During acquisition, the animal should not be allowed to move. Movement associated with respiration cannot be avoided; however, panting artifact can be minimized by manually holding the animal's muzzle closed.

Positioning of the animal for a particular body part to be imaged can be critical in obtaining a high-quality scan that is free of artifact. The following recommendations are an attempt to aid in positioning (Table 100-5).

Two methods for accurately comparing two similar ROIs (e.g., the elbows) are available. The easiest way is to place both limbs or ROIs in the middle of the camera in the same field of view. Care must be taken to ensure that both limbs are positioned exactly the same and not rotated. It is also very important to make sure that both limbs or ROIs are equally distant from the camera face, ideally in contact with the camera face. If one limb is further from the camera than the other, it will appear artifactually more intense. The second method for comparison of similar ROIs is to image the areas separately. This is accomplished by imaging one ROI for a preset number of counts and recording the time of acquisition. The contralateral ROI should then be imaged for the amount of time it took to

Table • 100-3

Small Animal Bone Scan Doses

ANIMAL SIZE	DOSE (MCi)
Toy breeds and cats	5
Medium breeds	10-15
Large breeds	20
Giant breeds	30

Table • 100-4

Recommendations for Bone Scan Count Acquisitions

ANATOMIC SECTION	COUNTS TO ACQUIRE
Thorax	750,000 (750 k)
Pelvis*	500,000 (500 k)
Skull or C-spine	350,000 (350 k)
Lumbar spine*	350,000 (350 k)
Elbow or stifle	200,000 (200 k)
Distal extremity	100,000 (100 k)

*Assumes the urinary bladder is empty.

Table • 100-5

Positioning Recommendations

ANATOMIC SECTION	RECOMMENDATIONS
Dorsal or ventral skull, spine or pelvis	Animal is placed in radiolucent V trough, legs are extended out, and symmetrical placement is ensured
Lateral skull	Neck is extended, head is rotated axially so that eyes are perpendicular to tabletop, and forelimbs are pulled caudally
Lateral C-spine	Traction is applied to neck, head is rotated axially to straighten skull, and front limbs are pulled caudally
Lateral shoulder	Neck is extended, shoulder to be imaged is placed down with the ipsilateral front limb extended and pulled cranially, and contralateral limb is pulled caudally
Lateral thorax Lateral lumbar spine	Front limbs are pulled cranially
Lateral pelvis	Urinary bladder is evacuated (or shielded), rear limbs are pulled caudally, pelvis is rotated axially until ilia are superimposed
Lateral stifle	Urinary bladder is evacuated (or shielded), stifle to be imaged is placed down, rear limb is pulled caudally (placing stifle in center of the camera), and contralateral stifle is abducted out of field of view (FOV)
Distal limbs	Palmar/plantar view—both paws are placed side-by-side in same field of view, centered, and rotated until symmetrical Lateral view—limbs are extend, one limb is done for counts (note time of acquisition), contralateral limb is done for time of first acquisition (clinician should note total counts acquired and compare to contralateral limb)

acquire the first ROI image, then recording the total number of counts. For this method to be accurate it is very important to make sure that the two images used for comparison appear exactly the same on the field of view.

Interpretation and Analysis

Without experience the normal bone scan in small animals can be difficult to interpret. Skeletally immature animals have very focal intense uptake in metaphyseal regions of long bones and at costochondral junctions (Figure 100-12). Normal areas of increased skeletal uptake in all (immature and mature) small animals include areas of thick bone (ends of long bones), temporomandibular joints (TMJs), occiput, the first cervical vertebrae (on the lateral image), sinuses, and costochondral junctions (Figure 100-13). Normal areas of soft tissue accumulation include kidney and urinary bladder. Activity in the kidneys can be minimal to marked. Activity in the bladder is marked, requiring evacuation prior to imaging or lead shielding.

Nonskeletal distribution of bone-seeking radiopharmaceuticals include calcinosis cutis, pulmonary mineralization, renal infarcts, acute rhabdomyolysis, lymph node uptake (after extravasation of the dose),[28] thyroid uptake of free pertechnetate, or dystrophic mineralization of soft tissues.[29] Tracer uptake has also been reported in lactating breast tissue of women[30–32] and the pregnant uterus.[33]

Several reasons exist for generalized poor skeletal uptake that results in poor image quality. These include decreased cardiac output, an increased overlying mass of soft tissue (edema formation), renal failure, or simple old age.

Neoplastic Disease

Bone scanning is the most common nuclear medicine procedure performed at many human hospitals, making up over nearly half of the nuclear medicine caseload. By far, the most common indication to order a bone scan is for evaluation of possible or known metastatic bone disease.[34] Bone scanning has been shown to be a sensitive indicator for the detection of skeletal metastasis.[35,36] The majority of these patients have primary prostatic or breast cancer. In these patients, a whole-body bone scan is obtained using a moving gamma camera (or moving patient gantry) that acquires a static image of the entire human body in less than 30 minutes. If an abnormal area of uptake is seen, additional "spot" images can be obtained. In veterinary medicine, overall rate of occurrence of skeletal metastasis is not known but is considered low (<10%).[37] Tumors that have shown a propensity for bone metastasis include prostatic adenocarcinoma, transitional cell carcinomas, primary bone osteosarcoma, thyroid adenocarcinoma, and mammary carcinomas (Figure 100-14).[37,38] Bone scans have been shown to be 30% to 50% more sensitive for the detection of metastatic bone disease than radiographs.[39] Because of this, the bone scan may pick up metastatic disease before the animal shows skeletal pain.[38] In many cases, bone scans allow for earlier detection of metastatic bone disease, which can significantly alter the owner's decision to proceed with further therapy or change treatment options. Several patterns of metastatic bone disease have been described, the most common of which is variably sized, multiple, focal, intense hot spots, randomly distributed throughout skeleton.[40] The axial skeleton is most commonly affected (skull, vertebral bodies, ribs, and pelvis), followed by the femur and humerus.[41] In the skull the metastatic lesions are usually associated with suture lines. Rib uptake should be randomly distributed—uptake at the same level on adjacent ribs is most often due to previous trauma, not metastatic disease. If this is seen, a careful history should be obtained from the owner and radiographs of the ROI should be obtained. In the ribs the normal increased uptake of costochondral junctions should also be differentiated from metastatic bone disease. If the appendicular skeleton is involved, metastatic bone disease will typically spread to the diaphyseal portions of long bones, especially at the sites of nutrient foramen. False-negative bone scans are uncommon

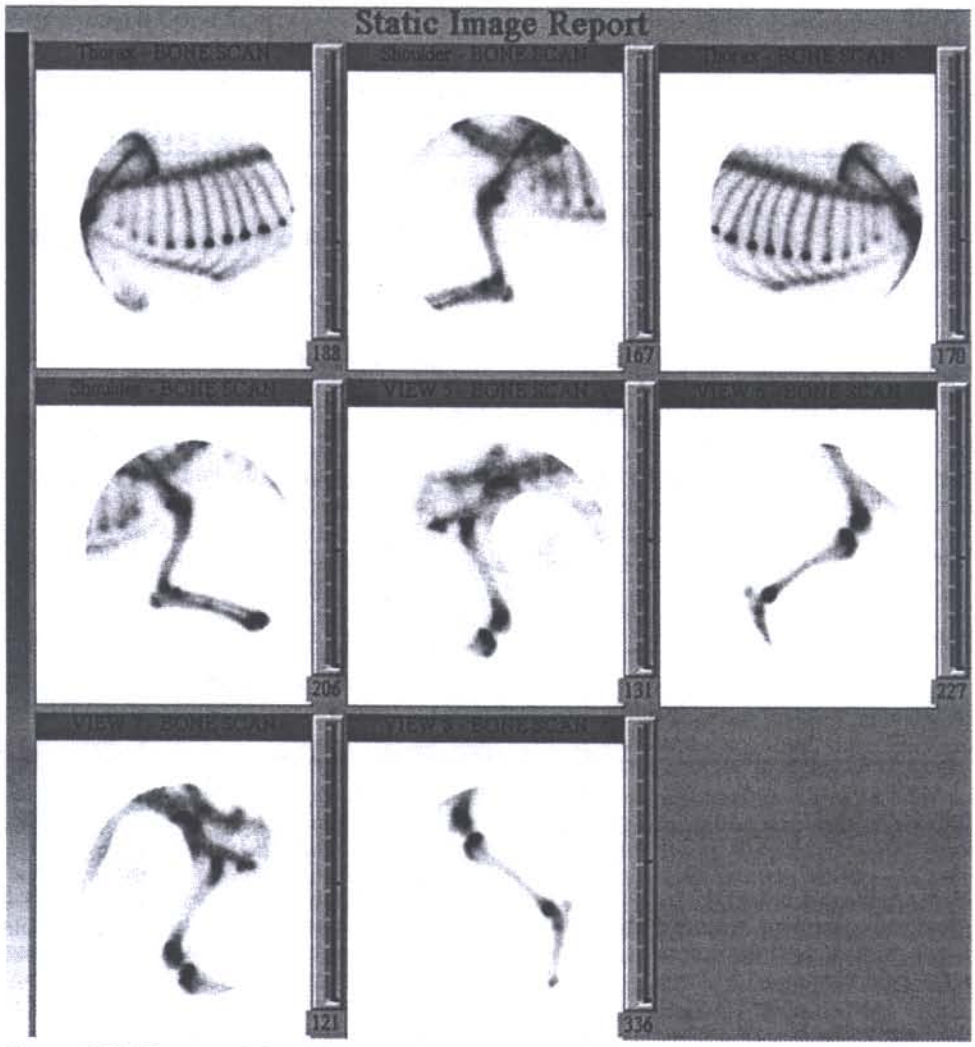

Figure 100-12 Normal bone phase images from skeletally immature canine. The reader should note the marked areas of normal uptake in the metaphyseal regions of long bones and the costochondral junctions.

but can be due to the fact that up to 5% of bone metastasis are "cold," showing little to no uptake.[42] In most cases multiple myeloma or other purely lytic tumors are generally negative (although ^{99m}Tc-Sestamibi or ^{201}Tl may be positive), owing the fact that little osteoblastic activity takes place. Other benign lesions that may have similar focal intense uptake include sepsis, osteophytes, enthesiophytes, spondylosis deformans, and chronic healed fractures. These lesions can usually be differentiated based on the location of uptake (metaphyseal, diaphyseal, or within a joint space) and the history, signalment, and physical examination findings.

A persistent problem in both human and veterinary medicine is that of a solitary focus of increased uptake in a patient known to have a primary tumor elsewhere. Although a similar study does not exist in veterinary medicine, Tumah and colleagues[43] reported only 10% of solitary rib lesions were due to metastatic disease in a group of patients with known breast cancer. In these cases radiographic correlation is essential, and demonstration of benign radiographic features can sometimes answer the question definitively. In some cases histological confirmation may be required.

Primary bone neoplasia such as osteosarcoma, chondrosarcoma, fibrosarcoma, or synovial cell sarcoma most commonly is seen first on radiographs. Scanning characteristics associated with primary bone tumors include metaphyseal location, extremely intense uptake, and extension toward the diaphyseal portion of the involved bone; many may have photopenic centers or heterogeneous uptake (Figure 100-15).[44,45] The usefulness of a bone scan in these patients is to rule out the presence of metastatic bone disease prior to costly amputation, chemotherapy, radiation therapy, or limb-sparring techniques. Magnetic resonance imaging (MRI) has proven to be superior to radiography, computed tomography (CT), and scintigraphy in evaluating the extent and degree of invasiveness of neoplastic bone tumors.[46-48] Bone scans tend to overestimate the extent of primary bone tumors due to the "bloom" effect (Figure 100-16).[44] Pulmonary metastasis may demonstrate a faint blush on bone scans, and areas of mineralized soft tissue (metastatic or dystrophic mineralization) will also be positive (Figure 100-17).

In rare cases a "super scan" is seen (Figure 100-18).[49,50] Although the exact mechanism is not clear, these scans are felt to be related to paraneoplastic hypercalcemia. Such scans will have marked, diffuse, symmetrical skeletal uptake; the kidneys are not seen; little-to-no soft tissue uptake occurs; and obvious bone activity is seen on soft tissue phase images. The significance

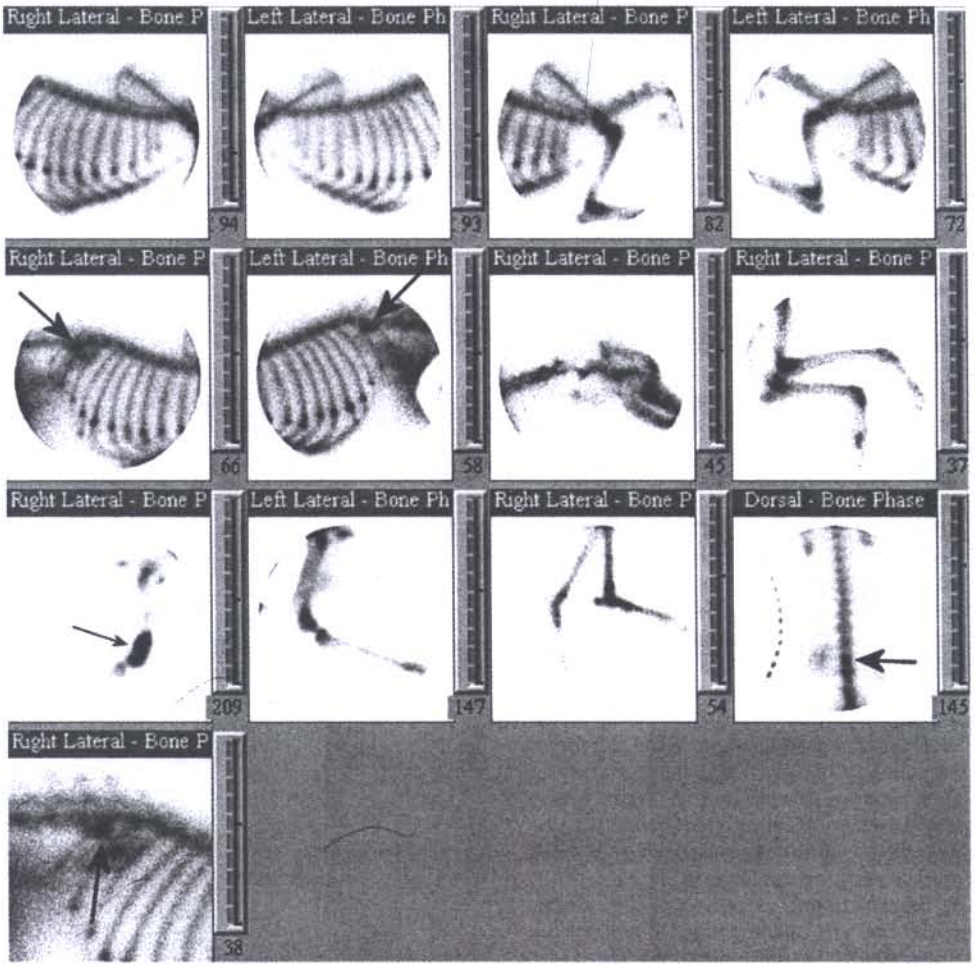

Figure 100-13 Normal bone scan in an adult canine. The reader should note the location of normal "hot spots" including C1 (end-on spinous processes), occiput, temporomandibular joints (TMJs), metaphyseal regions, and costochondral junctions. A primary bone tumor (osteosarcoma) is seen in the distal right humerus *(small-headed arrow)*. The hot spot on the ventral aspect of T13-L1 is spondylosis deformans *(large-headed arrow)* and should not be confused with a metastatic lesion.

of the "super scan" is not known, and it does not appear to be correlated to one particular tumor type.

Non-Neoplastic Disease

In small animals, acute hematogeneous osteomyelitis is relatively rare; however, septic arthritis, physitis, and discospondylitis are more common. Hematogeneous osteomyelitis will typically demonstrate intense linear cortical uptake within 24 to 48 hours[51] (radiographs are positive at 10 to 21 days).[52] The bone scan will often remain positive for weeks to months after the infection has resolved.[53] Because of this, bone scanning cannot confirm presence of *active* disease, but a negative scan excludes it. Septic arthritis (Figure 100-19), septic physitis, and discospondylitis will all demonstrate extremely focal intense uptake on bone phase images and in some cases may be positive prior to radiographs.[54, 55]

Occult lameness can be defined as a persistent, often subtle, undiagnosed lameness that cannot be localized on physical or orthopedic examination. If anatomic localization is possible, radiographs are often normal or inconclusive. Causes for an occult lameness often include mild panosteitis, fragmented medial coronoid processes, partial tear of the cranial cruciate ligament, meniscal injury, stress fractures, fractures of the sesamoid bones, and small avulsion fractures (Figure 100-20). Both single-phase and three-phase bone scanning may be useful in definitively localizing these conditions.

Panosteitis appears on bone scans as intense linear uptake within the medullary cavity of the diaphysis on bone phase images, as well as having minimal-to-marked uptake on the soft tissue phase images (Figure 100-21). Bone scans can often diagnose panosteitis on animals with subtle, nonlocalizable lameness or may be helpful when radiographic findings are equivocal.

Although radiography is typically the primary imaging modality to assess abnormalities associated with the medial coronoid process, radiographs can often be inconclusive in the early stages of this developmental disease because many of the Roentgen signs include degenerative changes associated with the anconeal process and ulnar trochlear notch.[56-58] CT has also been shown to have excellent sensitivity in diagnosis of fragmented medial coronoid processes; however, the availability of CT may be limited.[57] Bone scan findings that suggest a fragmented medial coronoid process are dependent on the animal's age. In puppies the medial coronoid process overlies the proximal radial physis on the lateral view. Because this physis demonstrates typical physeal uptake, a focal intense

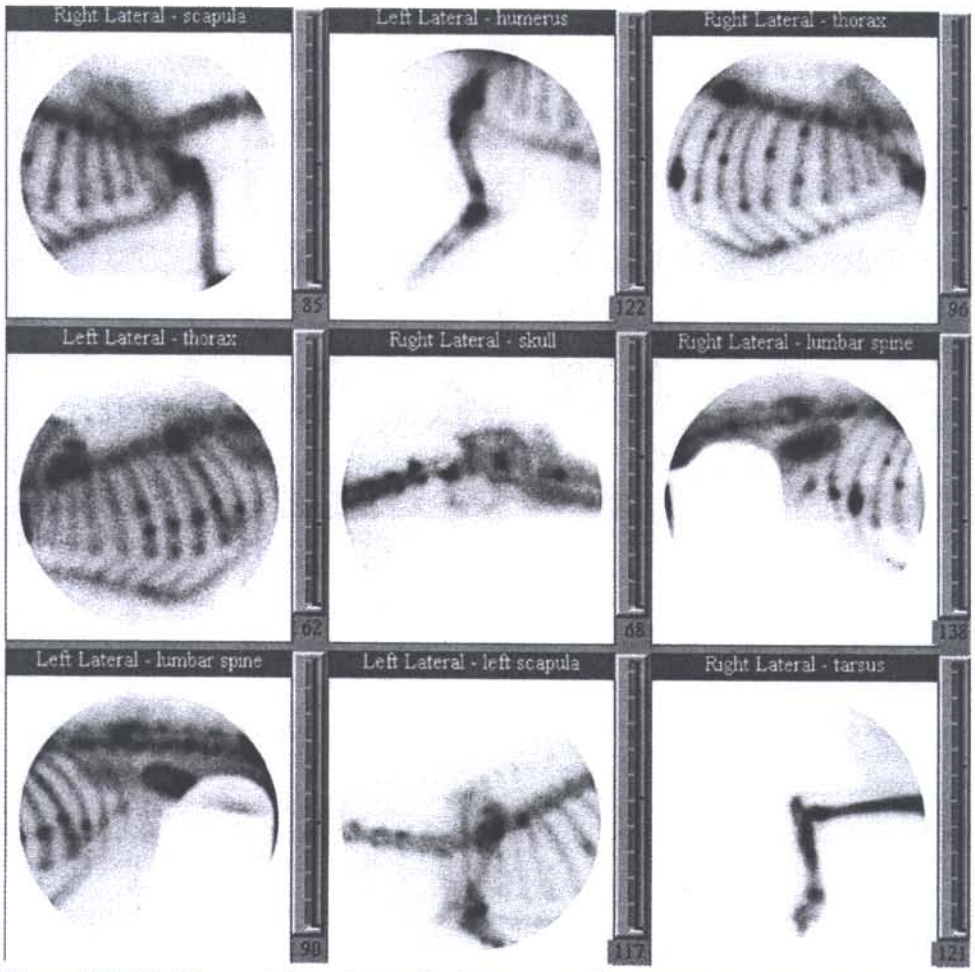

Figure 100-14 Metastatic bone disease. Focal intense uptake is seen that is associated with multiple ribs and proximal aspect of right scapula in an animal with a transitional cell carcinoma of the urinary bladder.

"hot spot" in this region may be due to either a fragmented medial coronoid process or the proximal radial physis. In these dogs, however, comparison of the amount and pattern of uptake bilaterally can be helpful in diagnosing a unilateral fragmented medial coronoid process. Focal intense uptake associated with the proximal radial physis should be symmetrical. Asymmetrical uptake suggests a diagnosis of fragmented

A. B.

Figure 100-15 Primary osteosarcoma distal left tibia. An irregular area of focal intense heterogeneous uptake is seen in the distal metaphyseal region of the left tibia **(A)**. With the intensity turned down, a photopenic center is visible, suggestive of a central area of necrosis **(B)**.

Figure 100-16 Primary osteosarcoma of the left humerus. A large, poorly defined area of intense uptake is seen in the proximal metaphyseal region of the left humerus. The reader should note that the lesion has marked heterogeneous uptake, does not appear to cross the scapulohumeral joint space, and appears to extend to the mid-diaphyseal region ("bloom" effect).

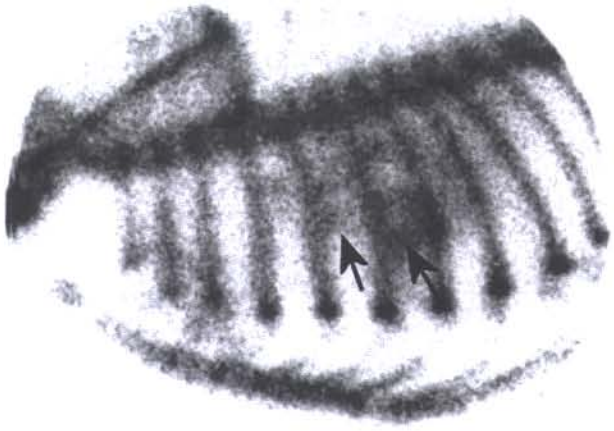

Figure 100-17 Pulmonary metastatic nodules seen on a bone scan. Areas of radiopharmaceutical uptake are seen between the ribs. The amount of uptake ranges from faint to marked. "Shine through" from rib lesions on the opposite side of the thorax should be differentiated from areas of uptake in the lung.

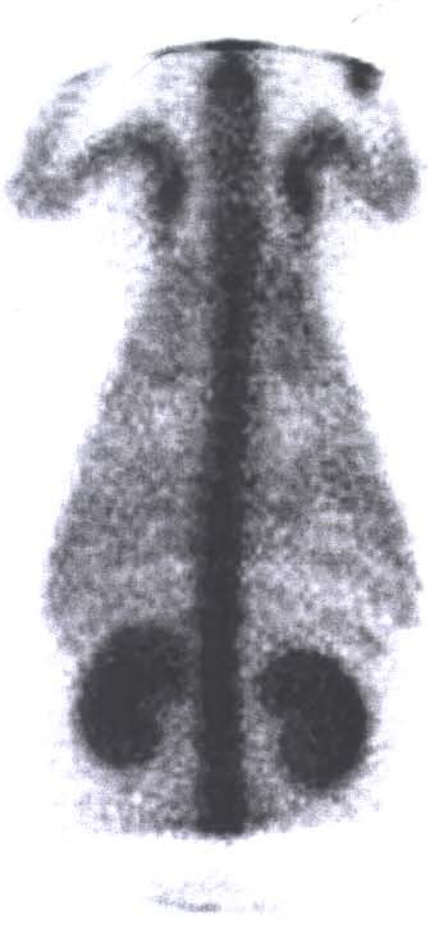

Figure 100-18 Super scan. The reader should note the "pretty bone scan" appearance with marked skeletal uptake within all portions of the skeleton and prominent kidney uptake.

medial coronoid process. Because the diagnosis is dependent on asymmetrical activity in these young dogs, the scintigraphic diagnosis of bilateral fragmented medial coronoid processes may be insensitive using bone scan findings alone. Although rare, fragmented medial coronoid processes can occur in middle-aged to older dogs (Shetland Sheepdogs). In these animals the scintigraphic diagnosis is often easier because no focal increased uptake of the proximal radial physis occurs. In skeletally mature animals, the amount of uptake by the radial head and medial coronoid process region should be similar to that of the distal humeral condyles (in the lateral projection). Focal increased uptake by the region of the medial coronoid process that is significantly more than that seen by the distal humeral condyles is highly suggestive of a fragmented medial coronoid process (Figure 100-22).[59] In both young and older animals, anterior-posterior (AP) views or pinhole collimation (or both) may also be helpful in differentiating uptake by the radial head and the medial coronoid process.

Three-phase bone scans may also be helpful in diagnosing partial (incomplete) tears of the cranial cruciate ligament (Figure 100-23).[60] In these cases the soft tissue phases may be helpful in differentiating acute (active) synovitis from chronic (inactive) intracapsular soft tissue swelling. In the normal canine stifle, a distinct photopenic area is seen within the cranial aspect of the stifle joint that corresponds with the shape and location of the infrapatellar fat pad. In animals with active synovitis, this area demonstrates a faint uptake (blush). Comparison to the contralateral stifle is usually helpful. This same "blush" is not seen in animals with chronic effusion or joint capsule thickening. Bone phase images are not typically helpful in evaluating potential acute cruciate disease.

Stress fractures result from repetitive, prolonged muscular action on bone that is unaccustomed to such stress. Typical symptoms include mild to marked lameness, bone pain, minimal soft tissue swelling, and bone pain that are relieved by discontinuing the exercise. In dogs, stress fractures are seen in athletic and working species and most commonly occur within the diaphyseal portions of long bones, particularly the tibia (Figure 100-24). Bone scintigraphy has proven to be highly sensitive in the early detection of stress-related bone disease[61-63] and is often positive prior to radiographic abnormalities.

In human beings the incidence of bipartite sesamoid bones is approximately 10% to 33%. Although the incidence in small animals is unknown, breeds such as Rottweilers, Greyhounds, Dobermans, and Labradors may have higher incidence of sesamoid disease.[64,65] A bone scan can also differentiate bipartite sesamoid bones from fractured sesamoid bones. Bipartite sesamoids will have no abnormal uptake, whereas recently fractured sesamoid bones will have marked focal uptake (Figure 100-25).

Evaluation of fracture and fracture healing can also be performed using bone scanning. Bone phase images are very sensitive to fracture, and it can be difficult to differentiate acute pathologic conditions from healed previous fracture. It has been reported that bone scans (bone phase images) are 80% positive by 24 hours, 95% positive by 72 hours, 98% positive by 7 days.[66] It has also been shown that 90% of patients with previous fracture are negative on bone phase images at 2 years.[26] Bone scans may also be helpful in the evaluation of the nonunion fracture (lack of progressive healing at 6 months postfracture). Focal intense uptake at fracture ends indicates viable tissue and shorter time to union, whereas little uptake at fracture ends indicates nonunion is likely.[67]

Avascular necrosis of the femoral head (Legg-Calve-Perthes disease) has a unique appearance, depending on the maturation of the disease. Within 12 to 48 hours after injury, a focal photopenic area within femoral head is seen, which is

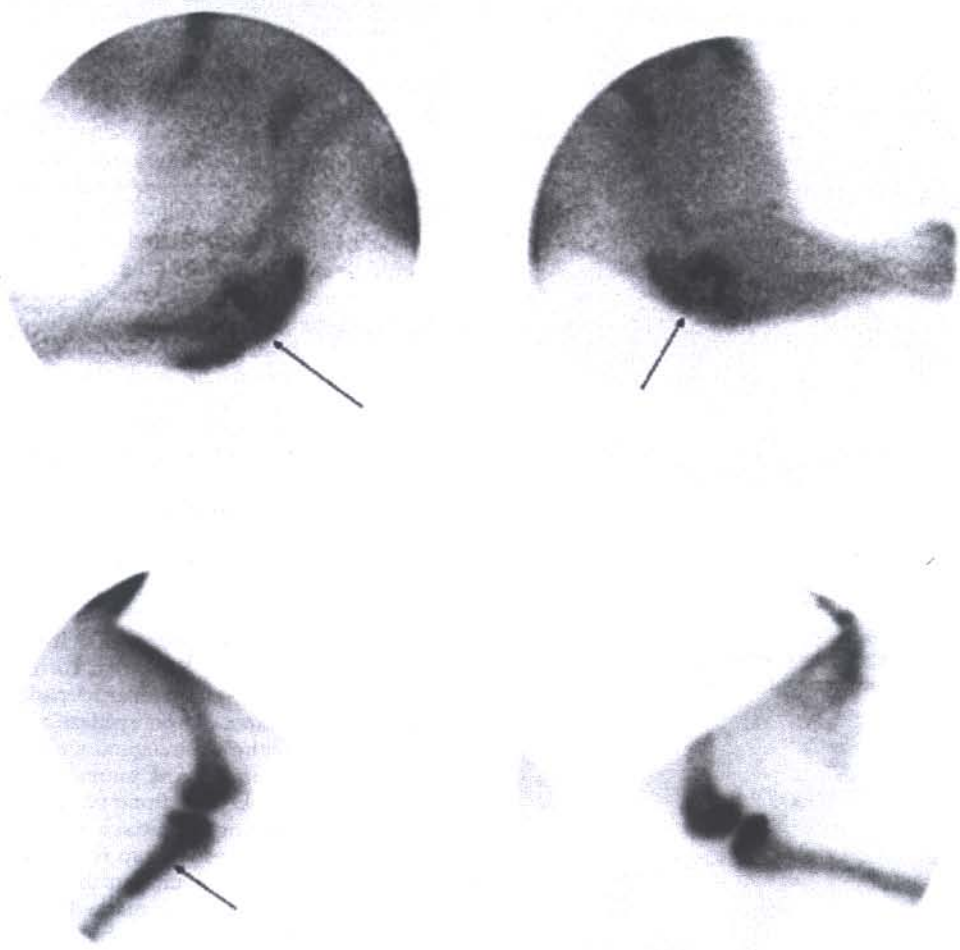

Figure 100-19 Osteomyelitis. Soft tissue phase and bone phase images of the right and left stifle joints obtained 3 months after bilateral cruciate surgery. On the soft tissue phase images, marked uptake is seen in the proximal metaphyseal and diaphyseal regions of the right tibia and within the cranial aspect of the stifle joint. The bone phase images show very intense uptake of the distal metaphyseal regions of the femurs and proximal metaphyseal regions of the tibias. *Staphylococcus aurous* was isolated from a joint fluid.

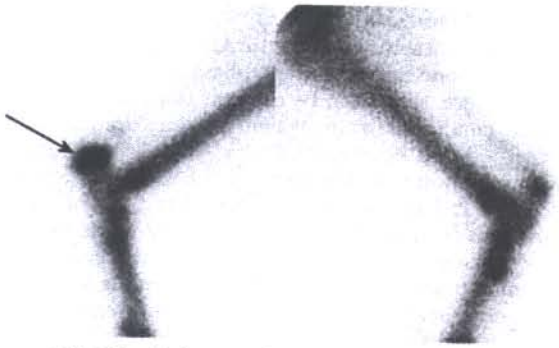

Figure 100-20 Enthesiopathy and syndesmitis of the insertion of the tendon of the gastrocnemius on the right tuber calcaneus. Bone phase images show marked focal uptake in the region of the right tuber calcaneus. The comparison view of the left tibial tarsal region is normal.

then followed by a rim of moderately focal intense activity around a central photopenic core at 1 to 3 weeks. As the condition becomes chronic, the photopenic central core will fill in and have similar activity to the remainder of the femoral head.[68]

Three-Phase Bone Scanning

Multiphase bone scanning is extremely helpful in differentiating active septic from nonseptic conditions.[69] The three-phase bone scan (Table 100-6) consists of an initial "arterial phase" dynamic study (2 seconds/frame for 30 frames) of blood flow (Figure 100-26). The imaging sequence is started immediately upon injection of the radiopharmaceutical into a peripheral vein. The injection should be made as far away from the area of interest as possible to minimize any injection site hot spots that would interfere with interpretation. It is recommended that the dose be injected in bolus fashion (within 2 seconds) into a preplaced intravenous catheter followed by 12 ml of saline flush. The use of an extension set and three-way stopcock is preferred. Because of the dynamic acquisition, the arterial phase is limited to one ROI. Because of the

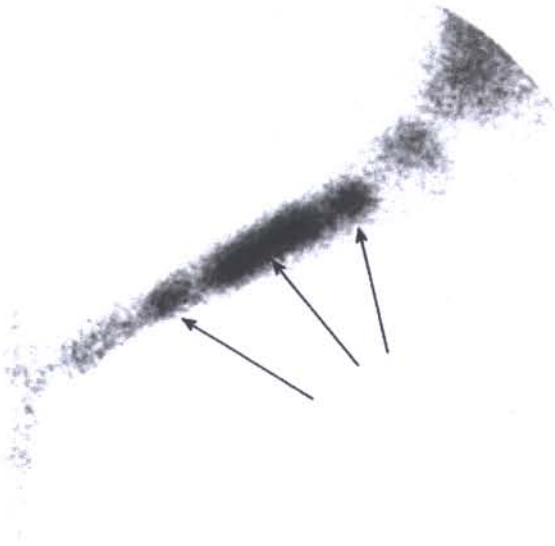

Figure 100-21 Canine panosteitis. Soft tissue and bone phase images of the right tibia demonstrate marked focal intense uptake in a linear pattern in the mid-diaphyseal region.

number of images that are acquired over a short period of time, matrix sizes (in pixels) of 64 × 64 or 128 × 128 are used. Postprocessing of these images include viewing a cine loop and summing pertinent images together to render a high total count static image.

Phase two is termed the *blood pool phase* and is obtained by acquiring static images over the ROI at minutes postinjection (Figure 100-27). Blood pool (sometimes called *venous phase*) images include 1 to 2 static, 500 K images over the ROI and contralateral area for comparison.

Phase three represents the "bone phase" images. Static spot bone phase images of the ROI, comparison views of the contralateral side and remaining skeleton are obtained at 3 to 4 hours postadministration. A matrix size (in pixels) of 256 × 256 is recommended for both the blood pool phase and bone phase images.

The three-phase bone scan helps to differentiate noninflammatory versus inflammatory conditions. The technique can be helpful in differentiating a loosened versus a septic

Table 100-6

Three-Phase Bone Scan

	PHASE 1 (ARTERIAL)	PHASE 2 (POOL)	PHASE 3 (BONE)
Cellulitis	+	+/−	−
Septic arthritis	+	+	+
Osteomyelitis	+	+	+
Fracture	+/−	+/−	+
Chronic DJD	−	−	+

total hip prosthesis. The typical appearance of a loosened femoral component includes a normal vascular and blood pool phase with focal increased activity of moderate intensity seen at the level of the distal tip of the metallic stem, usually in the mid-diaphyseal region on the bone phase images (Figure 100-28). Loosening of the acetabular component is seen as curvilinear area of focal, moderately intense uptake in the acetabulum on bone phase images and normal soft tissue phase images. A septic prosthesis is suspect when moderate to marked uptake occurs on all three phases in and around the acetabular component or diffusely surrounding the femoral component (Figure 100-29).[70] When comparing with the contralateral limb on the same dorsal image, close attention to symmetrical positioning should be made to ensure both acetabuli and femoral shafts are equidistant to the camera face and that no foreshortening of the limb occurs.

Three-phase bone scanning is also helpful in assessing tissue viability secondary to injury such as gunshot[71] and frostbite.[72] Decreased perfusion (soft tissue phase images) and uptake (bone phase images) indicate nonviable tissue, which usually necessitates amputation. Decreased perfusion but normal to slightly decreased uptake on bone phase images can often be successfully treated with débridement surgery and medical therapy.

QUANTITATIVE RENAL IMAGING (GFR SCANS)

Background and Basic Techniques

In contrast to radiographic intravenous pyelography that demonstrates well-defined morphology of the kidney and collecting system but little functional information, the GFR scan yields poor structural information but clinically important functional information. The importance of the

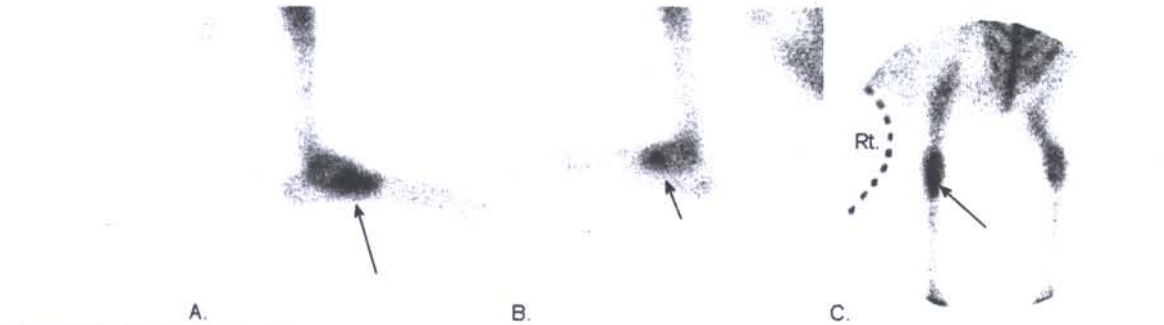

Figure 100-22 Fragmented medial coronoid process. Focal intense uptake is seen in the region of the right medial coronoid process *(long arrow)* greater than that seen by the adjacent humeral condyles. Comparison normal left elbow shows normal amount of uptake associated with the distal humeral condyles and less uptake seen by the normal medial coronoid process.

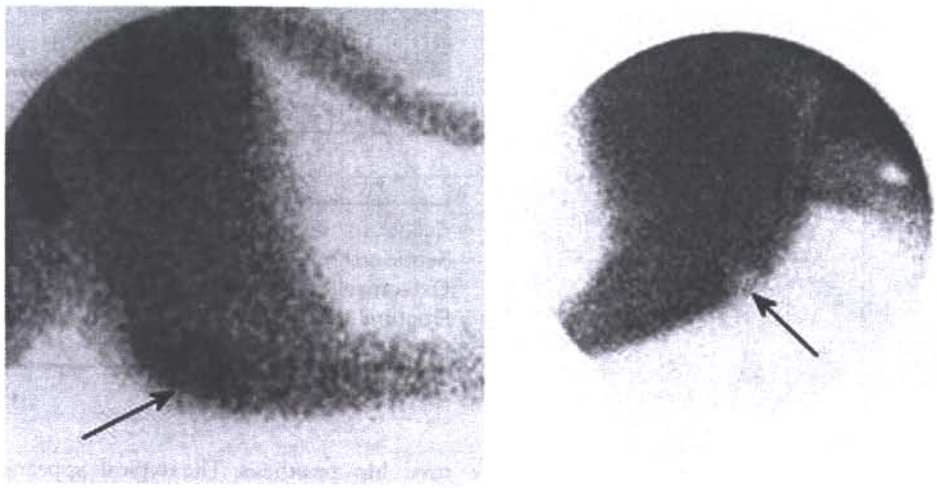

Figure 100-23 Partial tear of the cranial cruciate ligament. Regional increased uptake is seen within the left stifle joint *(long arrow)* on soft tissue phase images. The normal right stifle shows the typical photopenic triangle that corresponds to infrapatellar fat pad *(short arrow)*.

GFR scan lies in the fact that individual renal function can be assessed and compared. The correlation between inulin clearance and a GFR scan using ^{99m}Tc-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) has been reported to be 0.94 in dogs[73] and 0.81 in cats.[74]

The glomerulus acts similar to a sieve type of filter, only allowing particles of a certain very small size to pass into the ultrafiltrate. Renal function is commonly assessed with BUN and serum CR assays; however, it is known that up to 75% of the nephrons must be destroyed before these values may increase. Plasma clearance can be used to express the ability of the kidneys to remove a substance from the blood and is more accurate in assessing renal function. The plasma clearance of a substance can be calculated using the following equation:

$$\text{Clearance}_x = \frac{(U_x\text{mg/mL}) \times (\text{VmL/min})}{(P_x\text{mg/mL})}$$

Where Clearance_x = rate of clearance of substance_x per unit time (mL/min)
U_x = concentration of substance_x in urine (mg/mL)
V = volume of urine per minute (mL/min)
P_x = concentration of substance_x in plasma (mg/mL)

For plasma clearance to be accurate, the substance must be (1) completely filtered at the glomerulus; (2) not synthesized, destroyed, reabsorbed, or secreted by the renal tubules; (3) physiologically inert; and (4) not significantly bound to plasma proteins. Classically, inulin clearance has been used to measure GFR; however, it is cumbersome and usually reserved for the research setting. CR clearance has also been used but is not as accurate, owing to the small amount of

Figure 100-24 Stress fractures of the left tibia. Focal areas of intense uptake are seen in the mid- to distal diaphyseal region of the left tibia. Normal areas of focal uptake exist in the metaphyseal regions in this young animal.

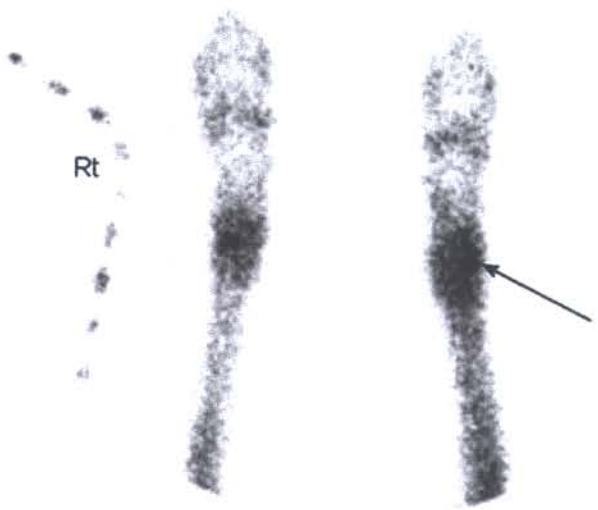

Figure 100-25 Fracture of the ulnar carpal bone, left limb. A focal intense area of uptake is seen in the lateral aspect of the left carpus secondary to a small chip fracture of the ulnar carpal bone.

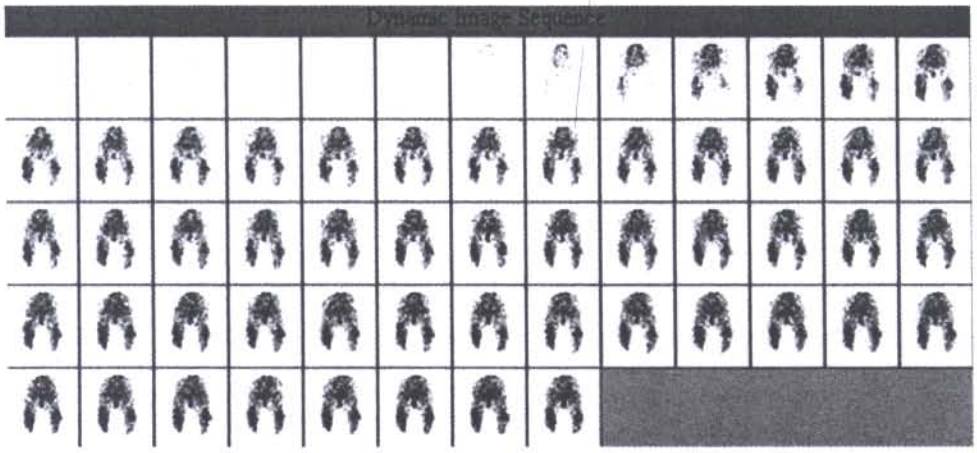

Figure 100-26 Dynamic ("arterial") phase images. Dorsal pelvic images obtained immediately after injection of a bolus of ^{99m}Tc-MDP. Images were obtained at 2 seconds per frame.

tubular secretion and its ability to only measure total GFR, not individual kidney GFR. Radionuclide techniques have been developed to measure both total GFR and differential GFR.

^{99m}Tc-DTPA is a radiopharmaceutical that diffuses evenly throughout and stays within the vascular space; it satisfies the requirements as a glomerular agent and can be used to accurately estimate total GFR (comparable to inulin clearance). By using a gamma camera, interfaced computer system, and proper software, both total and differential GFR (right kidney and left kidney) can be determined. Nuclear processing software uses the integral activity within ROIs placed over each kidney and separate ROIs for background subtraction during the 1- to 3-minute or 2- to 3-minute time period after the initial bolus of activity is seen within the kidney ROIs. Gates[75] first introduced this method that uses the following equation:

$$\text{GFR} = \frac{\left\{\left[\left(\frac{\text{RKid ROI counts} - \text{bkgd}}{e^{-0.153 \times \text{kid depth in cm}}}\right)\right] + \left[\left(\frac{\text{LKid ROI counts} - \text{bkgd}}{e^{-0.153 \times \text{kid depth in cm}}}\right)\right]\right\}}{(\text{Preinjection counts} - \text{postinjection counts}) \times 100 \times 9.756 - 6.198 \text{ for CR clearance}}$$

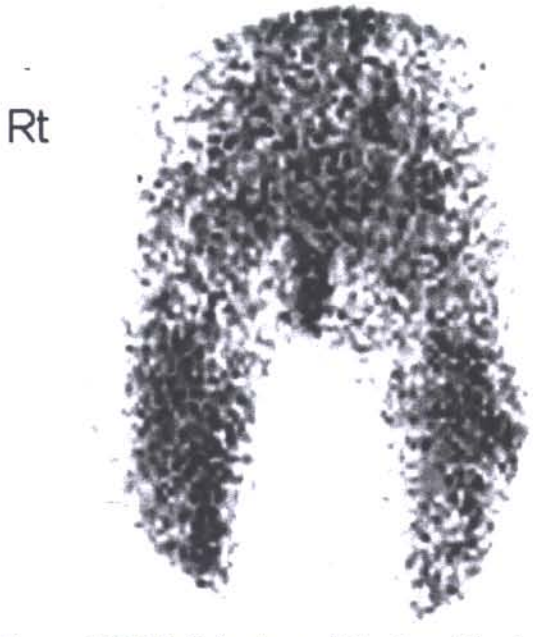

Figure 100-27 Soft tissue ("blood pool") phase image. Static images of the bilateral rear limbs and pelvis obtained 3 to 5 minutes postinjection of ^{99m}Tc-MDP.

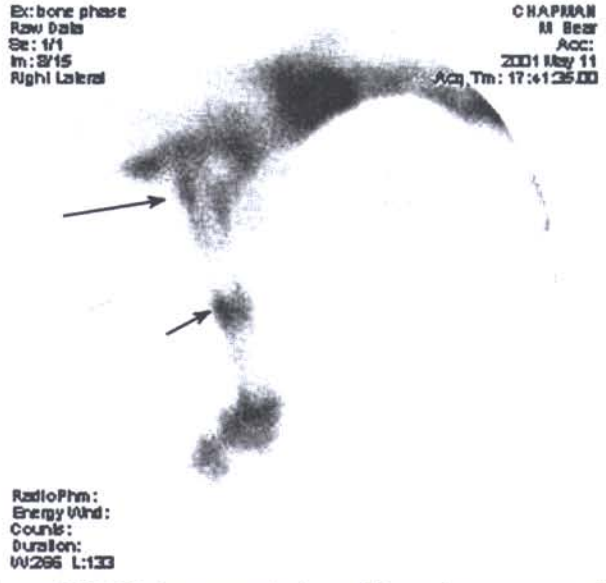

Figure 100-28 Loose acetabular and femoral components after total hip replacement. Focal areas of intense uptake of radiopharmaceutical are seen in the caudal cortex of the mid-diaphyseal region of the right femur *(short arrow)*, which corresponds to the level of the distal tip of the femoral stem, the caudal cortex of the proximal femur, and acetabular rim *(long arrow)*.

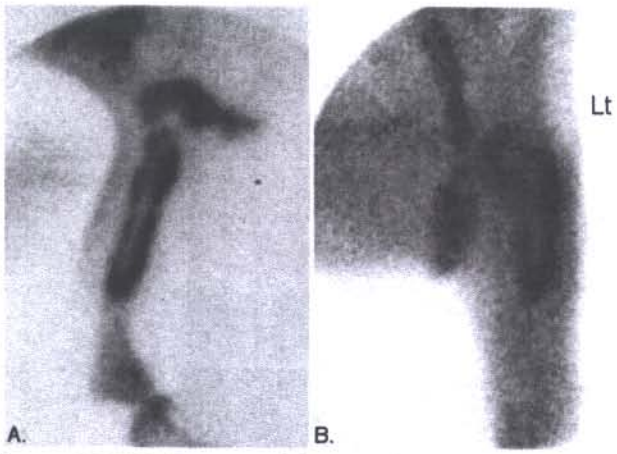

Figure 100-29 Septic total hip prosthesis. Left lateral bone phase image (A) and ventral soft tissue phase image (B) demonstrate marked uptake associated with the entire portion of the left femoral and acetabular prosthetic implants.

With minor modifications to the acquisition and processing, the same can be used for noninvasive estimates of renal function in dogs[73] and cats.[74] In human medicine, GFR results are reported in milliliters per minute and uses the assumption that all humans are approximately the same size (1.75 m^2). Due to the wide range of size differences in animals, it has become convention to normalize these values and report the GFR quantification as milliliters per minute per kilogram. Caution should be taken in that if nuclear medicine processing software designed for evaluation of human GFR scans is used in dogs and cats, the results will not be accurate for these species because the "r" value used to correct the mathematic formula used to calculate GFR is different for dogs and cats as compared with humans.

Indications for Performing a Glomerular Filtration Rate (GFR) Scan

Although the GFR scan will yield a total GFR that is more sensitive to abnormalities in the kidneys than elevated BUN or CR values, the primary indication for performing a GFR scan in small animals is to evaluate differential (individual) renal function in cases where a known abnormality exists that has altered the function of one kidney. The GFR scan is performed to correlate a suspected lack of function for the abnormal kidney and, at the same time, evaluate the opposite kidney for normal function. The scan is typically performed prior to scheduled unilateral nephrectomy of the diseased kidney to ensure that the nondiseased kidney has retained enough function to maintain life once the diseased kidney is removed. A GFR scan is not accurate in animals with significantly impaired renal function as demonstrated by severe azotemia because the kidneys may not be well visualized.

Image Acquisition

A dynamic acquisition is obtained at 6 seconds per frame for a total of 5 minutes (Figures 100-30 and 100-31). All images are made with the gamma camera centered over the dorsum of the patient's kidney region. The patient may be imaged while in right lateral recumbency (camera behind the patient) or in dorsal recumbency (camera underneath the patient). It is imperative that the patient not move during the 5-minute acquisition; therefore either a very cooperative patient (with skilled animal handlers) is needed, or mild sedation or general anesthesia is usually required. It is preferable not to administer tranquilizers or anesthetics because these agents will invariably affect the GFR quantification, rendering a less than optimal nonphysiologic measurement.

It is important that the radiopharmaceutical be administered in a bolus fashion, and it is preferable to inject through a preplaced patent catheter using a three-way stopcock apparatus and adequate sterile saline flush. To prevent the gamma camera from blushing with activity from the syringe and

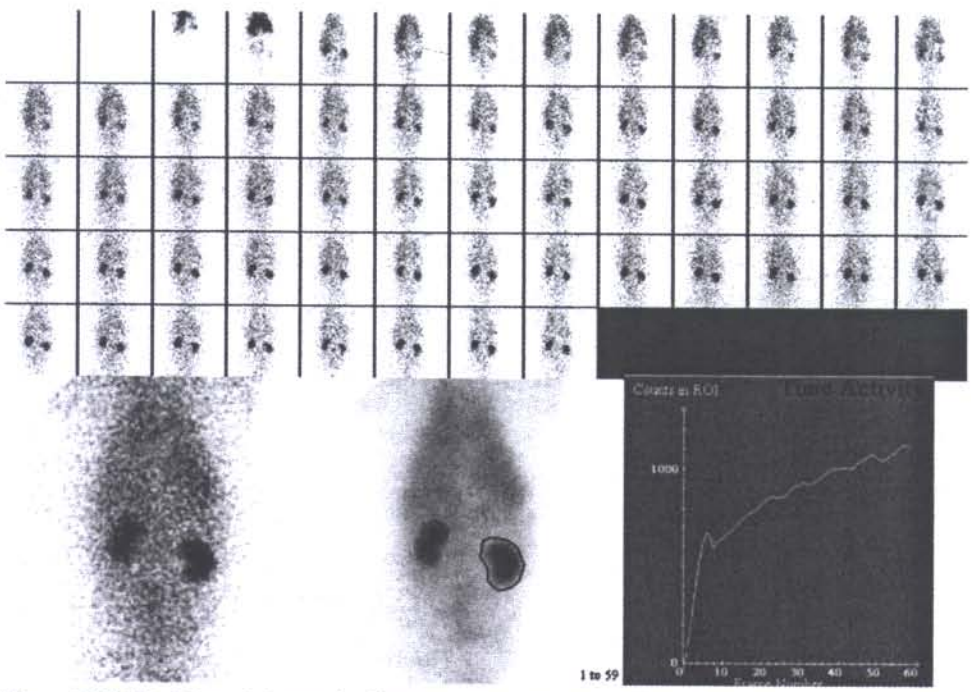

Figure 100-30 Normal glomerular filtration rate (GFR) scan. These dorsal images were obtained immediately after a bolus injection of ^{99m}Tc-DTPA at 6 seconds per frame. Dynamic, dorsal composite images with and without regions of interest (ROIs) drawn around the kidneys and time activity curves. Normal, intense, symmetrical uptake is seen within each kidney.

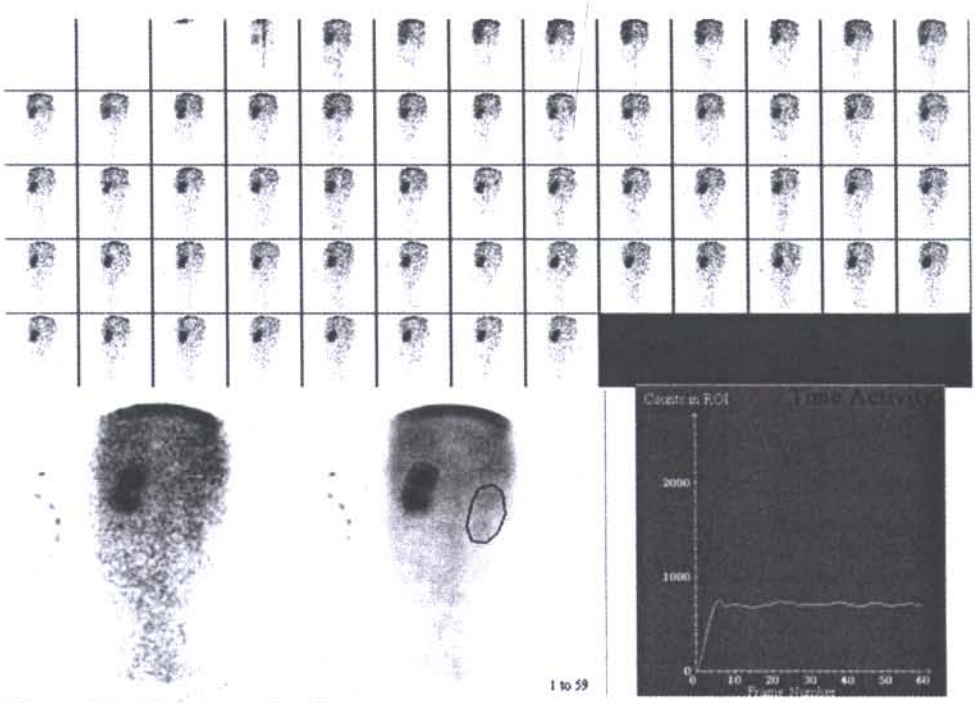

Figure 100-31 Glomerular filtration rate (GFR) scan with unilateral renal disease. Dynamic, dorsal composite images with and without regions of interest (ROIs) drawn around the kidneys and time activity curves show normal uptake in the right kidney and no uptake in the left kidney. The reader should note that the time activity curve of the left kidney and individual dynamic images show no evidence of normal excretion. This animal had severe left-sided hydronephrosis and mild hydronephrosis of the right kidney secondary to bilateral ureteroliths.

catheter itself during acquisition, a sterile intravenous extension tube can be used; however, care must be taken to ensure an adequate volume of fluid is available to flush the entire extension tubing. The bolus of activity should be injected as quickly as possible, preferably in less than 2 seconds. Immediately prior to injection, the acquisition should be started. By starting the acquisition computer just prior (4 to 6 seconds) to injection of the bolus, a "blank" frame will be obtained.

Within only seconds, activity will be seen first entering the right heart, lungs, left heart, and aorta; then a kidney blush will be seen. As the acquisition progresses, it is common to see activity within the urinary bladder. Ureters are rarely defined.

Interpretation and Analysis

At the end of the acquisition, a total of 50 individual images will be available for viewing, each representing a 6-second timed acquisition. These images should be examined subjectively and objectively using the computer's particular method of GFR analysis (visual inspection). The images can usually be run in a cine mode to create a movie appearance, which can be repeated over and over for evaluation.

Subjective analysis of the study should include rapid uptake of the radiopharmaceutical by both right and left kidneys. Cats will especially demonstrate rapid and intense uptake by the renal cortex. The kidneys should be inspected for size and shape, and the amount of uptake should be symmetrical. An initial intense blush is followed by further concentration of the Tc-DTPA within the kidneys until maximum concentration is seen (2 to 3 minutes), followed by gradual decrease in intensity as the kidneys excrete the activity into the ureters and bladder. During the scan, there will be a moderate amount of activity seen in the soft tissues, which should decrease to hardly noticeable amounts by the end of the scan. Activity within the urinary bladder is normal in the latter frames and should gradually increase over the time of the acquisition. Activity within a ureter is rarely seen; when present it often suggests hydroureter.

Calculation of GFR begins with summating all of the individual dynamic images into a single "composite" image. This image is then subjected to a spatial and temporal smoothing algorithm that helps define the boundaries of each kidney. Manual or automated ROIs for each kidney, as well as appropriate background ROIs for each kidney, are then placed. An ROI can also be drawn around the urinary bladder. Estimation of kidney depth performed with ultrasound or from an additional lateral view of the abdomen using the gamma camera can be used to correct for soft tissue attenuation of the technetium. Correction for kidney depth has been shown to increase the correlation between the calculated GFR and inulin clearance in the dog,[73,76] but not in the cat.[74] The amount of radiopharmaceutical within the summated kidney ROIs and background ROIs during a time period of 1 to 3 or 2 to 3 minutes postinjection is used to calculate the total GFR. Differential GFR is then determined by calculating the percent contribution of the total GFR by each kidney. Because most standard nuclear medicine software is designed for human use and the equation used to calculate GFR is different for dogs and cats, it is often necessary to export the appropriate numbers to another program, such as Microsoft Excel, for the results to be meaningful.

Besides the calculation of a total GFR and differential GFR, the time activity curves for each ROI should also be inspected. The normal kidney time activity curve should have a very sharp initial increase (which represents the initial arterial bolus of activity within each kidney), followed closely by a slight decrease in activity, then a longer "uptake" period (as the radiopharmaceutical is concentrated by the kidney), and finally a gradual and longer "washout" period (as the

radiopharmaceutical is excreted from the kidney into the collecting system). In normal animals, kidney activity should peak at approximately 2.5 to 3.5 minutes postinjection. A delay in the time to peak (with a normal bolus peak) is consistent with glomerular disease. Animals undergoing diuresis may demonstrate a shorter time to peak activity. Each kidney's time activity curve should be similar in activity and may closely superimpose each other. A delayed onset or blunted initial "bolus" peak is consistent with a fragmented bolus injection, vascular abnormality, or significant renal disease. A lack of concentration by either kidney signifies renal insufficiency. A lack or delay of the excretory phase (washout) is suggestive of obstructive urinary disease. The time activity curves for each background area should be flat and not change over time. If included, the urinary bladder ROI should start off at the *x*-axis and rise slowly during the entire acquisition.

For most animals the total GFR should be greater than 2.0 ml/minute/kg and be evenly distributed between each kidney (i.e., each kidney should have a differential GFR of 1.0 ml/minute/kg or greater). A total GFR value of 1.8 ml/minute/kg or greater is considered normal in older cats (values less than these imply some degree of renal insufficiency). Like most imaging procedures, an abnormal total GFR result is extremely nonspecific; in all but a few rare cases, the cause for the renal disease cannot be determined.

CHAPTER 101

Endoscopic and Cytologic Procedures for Evaluation of the Gastrointestinal Tract

Michael E. Matz

ENDOSCOPIC PROCEDURES

Gastrointestinal (GI) endoscopy is a minimally invasive, atraumatic technique that permits direct visualization of the mucosa of the esophagus, stomach, small bowel, and colon. GI endoscopy can provide valuable information when evaluating GI disorders. Diagnostically, it allows clinicians to obtain samples for cytologic and histologic examination with relative ease. Therapeutically, it can be used for the removal of foreign bodies, dilation of esophageal or colonic strictures, and placement of gastric or jejunal feeding tubes. These endoscopic procedures offer an alternative to surgical intervention. This section will focus on the technique involved in performing diagnostic upper GI endoscopy, proctoscopy (examination of the rectum), and colonoscopy.

ENDOSCOPIC EQUIPMENT

Both rigid and flexible endoscopes can be useful in GI endoscopy. Rigid endoscopes are available in several sizes. This type of endoscope is inexpensive and easy to use. Rigid endoscopes are most valuable for performing proctoscopy and colonoscopy. Poor visualization, limited maneuverability, and relatively short length compared with flexible endoscopes, limit the use of rigid endoscopes for other diagnostic procedures.

A number of flexible endoscopes of different makes, lengths, diameters, and functions are available for use in evaluating the GI tract. Fiberoptic endoscopes use fiber-optic bundles to deliver bright light to the tip of the endoscope and transmit the image to the eyepiece. The quality of the image is dependent on the number, size, and quality of the fibers. Numerous, small-diameter fibers produce a better image than larger, less numerous fibers. Video endoscopes replace the image fiber bundle with a computer chip camera that transmits an electronic signal to a processor where it is converted to a video image and displayed on a high-resolution monitor. Image quality is superior with video endoscopes.

Versatility is important because veterinary patients vary greatly. A flexible endoscope to be used for GI endoscopy in dogs and cats should possess the following characteristics: a working length of at least 100 cm (ideally 125 cm); an insertion tube diameter of less than 10 mm, optimally less than 8 mm; a minimum instrument channel diameter of 2.0 mm, with an ideal size being 2.8 mm; four-way distal tip deflection with at least 180 to 210 degrees in one direction and 90 to 100 degrees in the other three directions; automatic air-water insufflation; suction capabilities; a forward direction of view; an angle of view of 90 to 120 degrees; a depth of field of 3 to 100 mm; and comfortable handling. Light sources for the endoscope should be halogen or preferably xenon. An external vacuum source (portable or central) is necessary.

Additional instrumentation required for flexible diagnostic endoscopy include biopsy forceps and cytology brushes. The author prefers fenestrated ellipsoid biopsy forceps. For rigid endoscopes, alligator biopsy forceps (punchtype preferred) are necessary.

ENDOSCOPIC TECHNIQUE

Upper Gastrointestinal Endoscopy

Diagnostically, upper GI endoscopy is indicated for evaluation of dysphagia, persistent regurgitation, chronic vomiting, acute vomiting with hematemesis, melena, chronic small bowel diarrhea, and unexplained weight loss or anorexia.

It is essential for the animal to be fasted to prevent ingesta from interfering with the examination. In most cases an 8- to 12-hour fast is sufficient; however, a longer fast may be necessary if evidence of delayed gastric emptying exists. Upper GI endoscopy should not be performed within 24 hours of a

barium contrast study. This allows for clearing of residual barium that often adheres to mucosal surfaces even though radiographically it may appear that the barium has been cleared from the GI tract. Appropriate preparation is essential for maximizing examination efficiency and for ensuring patient safety.

General anesthesia with placement of a cuffed endotracheal tube is necessary for upper GI endoscopy. The choice of anesthetic regimen should be made with respect to the animal's general condition and suspected disease processes. Narcotics (morphine, meperidine, butorphanol) increase antral motility and may increase pyloric tone, potentially interfering with the passage of the endoscope into the duodenum. The animal should be positioned in left lateral recumbency with a mouth speculum placed to protect the endoscope.

The insertion tube of the endoscope is passed initially over the endotracheal tube and through the oropharynx and upper esophageal sphincter. Once the endoscope is in the esophagus, air is insufflated until the esophagus is adequately distended to visualize the lumen. The endoscope is centralized in the esophageal lumen and then slowly advanced toward the gastroesophageal junction. *The endoscope should only be advanced when the lumen is clearly visible.* It is important to examine the esophagus completely during the insertion of the endoscope because it may become traumatized during passage of the endoscope. Normal esophageal mucosa is smooth, pale, and glistening. Submucosal vessels are not normally visualized in dogs, but are easily observed in cats. Little or no fluid is normally found in the esophageal lumen. In the proximal esophagus, an impression of the trachea can be seen. Pulsations of the heart and aorta are visualized in the thoracic esophagus. In the distal one-third of the esophagus of cats, concentric circular rings are observed because of the presence of smooth muscle. The gastroesophageal sphincter (GES) is usually closed in the normal animal. The bright pink to red color of the gastric mucosa may be visible at the GES, creating an irregular rosette appearance. At the GES, a slight directional change is necessary to align the tip of the endoscope with the center of the sphincter. Insufflation of air, while gently advancing the endoscope, should result in passage into the stomach. When properly directed there should be minimal resistance to advancing the endoscope into the stomach.

The large lumen of the stomach means the endoscopist must develop and maintain a systematic approach to gastroscopy so that completeness and reproducibility are ensured. During initial examination of the stomach it is important to obtain at least a cursory view of the mucosa as the endoscope is advanced to avoid misinterpreting endoscope-induced trauma as an abnormality during endoscope withdrawal. Normal gastric mucosa is smooth, glistening, and pink. Submucosal vessels are not normally observed, except in the cardia. The presence of ingesta or fluid, ease of distensibility of the gastric wall during insufflation, and the appearance of the rugal folds should also be evaluated.

Upon entry into the stomach, the endoscope will lie along the greater curvature. The stomach will be collapsed and prominent longitudinal rugal folds will be visible. Air should be insufflated into the stomach only until spatial orientation is achieved. Care must be taken not to overinflate the stomach. Overdistension of the stomach can occur quickly in cats and small dogs because of their relatively small stomach size. The endoscope should continue to be advanced along the greater curvature until the junction between the antrum (characterized by the lack of rugal folds) and the body comes into view. A frontal view of this area is usually accomplished in dogs. In the cat, the antrum is often hidden behind the incisura angularis, a narrow shelf of tissue that separates the pyloric antrum from the lesser curvature of the gastric body. To enter the antrum the endoscope is advanced further along (dogs), or deflected off (cats), the greater curvature.

Once in the antrum, the endoscope can be slowly advanced toward the pylorus. The pylorus in most dogs and cats is readily visible. The appearance and location of the pylorus will vary. In general, the pylorus has clean margins and is not obscured by excessive folds. It may be closed or open. Passing the endoscope tip through the pylorus into the duodenum can be the most difficult part of upper GI endoscopy. It is most easily accomplished by gradually advancing the endoscope while keeping the pylorus aligned in the center of the field of view. Rapid and forceful advances of the endoscope should be avoided. If gastric distension is minimized the pylorus is usually in a more relaxed state, facilitating duodenal intubation. If the pylorus cannot be properly aligned, repositioning of the dog or cat (dorsal or right lateral recumbency) may help to improve alignment. Just past the pylorus the cranial duodenal flexure is encountered. To negotiate this sharp turn, the tip of the endoscope should be deflected downward and to the right while insufflating and gently advancing the endoscope. During this advancement the mucosa will be seen sliding by the viewing lens. Once the tip of the endoscope has successfully negotiated the flexure, centralization of the tip of the endoscope within the lumen will be possible. Normal intestinal mucosa is paler, more granular in texture, and more friable in nature than the gastric mucosa. The major duodenal papilla is observed on the medial wall of the duodenum in most dogs and in some cats. Careful examination may reveal the minor duodenal papilla in dogs. The papillae may be best visualized as the endoscope is slowly retracted back into the proximal duodenum because of their close proximity to the duodenal flexure. In dogs, Peyer's patches are often observed as shallow, pale craters on the lateral aspect of the nondistended descending duodenal wall. The endoscope should be advanced until it reaches its full working length, as long as only minimal resistance is encountered.

A more thorough evaluation of the duodenal and gastric mucosa is often best accomplished as the endoscope is withdrawn. Diagnostic procedures are also performed at this time. Once the endoscope has been retracted into the stomach, the pylorus, antrum, and incisura angularis are examined carefully. A frontal view of the angularis can usually be obtained while the endoscope is removed from the antrum. The endoscope is then withdrawn along the greater curvature and retroflexed 180 degrees to allow visualization of the lesser curvature, fundus, and cardia—the latter region being defined by the location of the entrance of the endoscope into the stomach and the presence of submucosal vessels. Torquing the endoscope at this point will provide complete (360 degrees) evaluation of this area. Once the proximal stomach has been thoroughly evaluated, the scope tip is straightened and the endoscope is slowly retracted. At this point, insufflation of the stomach should be sufficient to cause flattening of the rugal folds without causing overdistention, facilitating observation of the entire gastric mucosa. Before retraction of the endoscope into the esophagus, all air or residual fluid is suctioned from the gastric lumen. The esophagus should be carefully reexamined as the endoscope is removed.

Proctoscopy and Colonoscopy

Proctoscopy and colonoscopy are relatively easy to perform in dogs and cats because their large intestines are anatomically simple. For this reason, clinicians with an appreciation of normal and abnormal endoscopic anatomy can become proficient in performing proctoscopy and colonoscopy within a relatively short period of time.

Endoscopic examination of the rectum and colon can be accomplished with either a rigid or flexible endoscope. Rigid endoscopes limit visualization to the rectum and descending colon. Flexible endoscopes allow evaluation of the rectum, entire colon, cecum, and possibly the distal ileum.

Indications for proctoscopy and colonoscopy include chronic large bowel diarrhea, obstipation or tenesmus, dyschezia, or hematochezia that accompanies formed feces. Because most inflammatory diseases of the large intestine in the dog and cat are diffuse, their presence is usually detected in the descending colon, allowing rigid endoscopy to be a valuable procedure.

One of the keys to successful proctoscopy or colonoscopy is adequate patient preparation. Various protocols can be used depending on the extent of the examination to be performed, the availability of support staff to complete the necessary work, and the degree of patient cooperation. Proper preparation for colonoscopy requires complete evacuation of fecal material from the colon and production of a clear ileal effluent. Food should be withheld for a minimum of 24 to 36 hours before the procedure. If flexible endoscopy is to be used, use of an oral GI lavage solution is recommended, such as one containing polyethylene glycol as the main nonabsorbed solute (GOLYTELY®, NULYTELY®, COLYTE®). These are isosmotic solutions that result in a severe diarrhea with virtually no net absorption or secretion of electrolytes, bicarbonate, or water. This method has been shown to result in superior colonic preparation compared with multiple enemas in dogs. Disadvantages are that fairly large volumes of the colon electrolyte lavage solution need to be used, and administration via orogastric or nasoesophageal intubation is usually necessary. Although dose guidelines have not been firmly established for the dog and cat, two doses of a lavage solution are recommended at 30 mL/kg via orogastric (dog) or nasoesophageal (cat) tube 2 to 4 hours apart in the afternoon prior to the examination. In addition, a warm-water enema (20 mL/kg body weight) should be given after the first dose of lavage solution the morning before colonoscopy. The well-lubricated enema tube should be inserted a length equal to that from the anus to the last rib. Enemas should be avoided in animals with rectal pain.

For rigid endoscopy, patient preparation does not have to be as vigorous as the protocol outlined previously. Preparation may be limited to withholding food for an appropriate time (usually 36 to 48 hours) and administering multiple warm-water enemas 1 to 2 hours apart on the afternoon before the procedure. Enemas should be given until the water exiting the rectum is repeatedly clear. A final enema is given the next morning 2 to 4 hours before the procedure is begun.

These or similar protocols generally result in adequate rectal and colonic cleansing. It is essential that the rectum and colon be as clean as possible before endoscopy. Lesions may easily be missed if this is not accomplished.

General anesthesia is generally recommended for colonoscopy, although heavy sedation may be adequate for proctoscopy or rigid colonoscopy. Passage of a flexible endoscope into the transverse and ascending colon and cecum may cause painful stretching of mesenteric attachments.

Before performing endoscopy, a digital rectal examination should be done to rule out the possibility of anal and rectal lesions or perineal hernias. Insertion of a digit is also useful for straightening the rectal lumen, making it easier to insert the endoscope into the colon. Rigid endoscopy is usually performed with the animal in right lateral recumbency. Right lateral recumbency reduces gravitational flow of fluid and fecal material into the distal colon. The well-lubricated rigid endoscope is advanced into the rectum. Rigid endoscopes have a smooth obturator that facilitates advancement of the endoscope through the anal sphincter. The obturator is removed after entering the rectum and the hinged viewing lens is closed tightly over the end of the endoscope. Air is insufflated to distend the colon, and the endoscope is advanced under direct visualization until the entire length of the endoscope has been inserted. With a rigid endoscope, air insufflation is done manually with a bulb-pumping device. The normal colon should have a pale pink, smooth, glistening mucosa with visible submucosal blood vessels. Lymphoid follicles, seen as 2 to 3 mm plaques (often with umbilicated surfaces) are normally observed in the descending colon and cecum.

Flexible endoscopy is performed with the animal in left lateral recumbency to prevent compression of the area of the ileocolic valve by abdomial viscera. After the endoscope is inserted into the rectum, air is insufflated. It is often necessary, especially when small-diameter flexible scopes are used, to have an assistant apply digital pressure around the anal orifice to prevent insufflated air from escaping from the colon. Insufflation distends the colon and flattens out mucosal folds, which are most prominent in the rectum and distal descending colon. The endoscope tip is then centralized and advanced slowly. *The endoscope should only be advanced if the lumen is clearly in view.* At the junction of the descending and transverse colon, a flexure (splenic) will be observed. The tip of the endoscope should be deflected around the flexure and advanced slowly along the mucosa. The mucosa should be seen sliding freely across the viewing lens. After passing the flexure, the tip of the endoscope can again be centralized within the lumen of transverse colon. The transverse colon is short in the dog and cat. Another flexure (hepatic) will be encountered at the junction of the transverse and ascending colon. This flexure can be passed in a manner similar to the splenic flexure. In the cat, distinct flexures delineating the boundaries between the sections of the colon are generally not observed as clearly as in the dog. Upon entering the ascending colon, the ileocolic junction is visualized. The ileocolic sphincter often protrudes into the lumen. If the ileum is to be entered, the tip of the endoscope should be centralized within the lumen of the sphincter and the endoscope advanced using gentle pressure combined with air insufflation. If the scope cannot be advanced into the ileum, blind biopsy specimens can be obtained by passing the biopsy forceps through the ileocolic sphincter. Using this blind biopsy technique does, however, increase the risk of perforation. The cecocolic junction may be partially open or, if closed, appear as a flat sphincter. The cecum usually can be entered. In the dog, the scope should be advanced into this spiral structure (8 to 30 cm in length) until the blind end is reached. The cecum of the cat is comma shaped and short (2 to 4 cm) in length.

A more thorough evaluation of the colon should be performed as the scope is withdrawn. Diagnostic procedures are performed at this time. The endoscope should be slowly retracted while making necessary directional adjustments to ensure that the entire circumference of the colon is carefully evaluated. As the rectum is approached in dogs greater than 15 kg, the flexible endoscope should be retroflexed 180 degrees to allow better visualization of the terminal rectum.

DESCRIPTIVE ENDOSCOPIC TERMINOLOGY

The esophageal, gastric, duodenal, jejunal, and colonic mucosa should be described using the following: hyperemia, friability, granularity, and erosion or ulceration, degree of luminal narrowing, stricture and visibility of submucosal vessels. The presence of an intraluminal mass or foreign body should be noted. Mucosal hyperemia should be carefully interpreted because it can be affected by a number of factors, including anesthesia, warm-water enema, and mild trauma from the endoscope. The amount of insufflation can alter the appearance of the mucosa and should be considered during evaluation. With experience, the endoscopist will learn to distinguish normal from abnormal GI mucosa. A description of the position and size of any lesions should be recorded. Size can be estimated by comparing the lesion to an open biopsy forceps.

ENDOSCOPIC BIOPSY SAMPLES

Flexible endoscopic biopsy samples are small, 2 to 3 mm mucosal specimens obtained through the instrument channel of the endoscope. In view of the small size of these biopsy samples, multiple biopsies using sharp biopsy forceps and good technique are essential to provide diagnostic material. To obtain a biopsy sample with the flexible scope, the tip of the endoscope should be placed in close proximity to the intended biopsy site. If possible, the tip should be directed at a 90-degree angle to the mucosal surface to be biopsied. Removing the majority of luminal air will facilitate attaining a perpendicular orientation of the tip in narrower tubular lumens such as the small intestine. A biopsy forceps is placed into the biopsy channel and advanced until it protrudes from the endoscope tip and is clearly visible. The endoscopic assistant opens the forceps, and the endoscopist advances the forceps towards the mucosa. The forceps should be advanced with gentle pressure until resistance is met. The assistant then closes the forceps, and the endoscopist pulls the biopsy instrument back into the biopsy channel. This tears the mucosa, capturing a small tissue sample.

As previously noted, biopsy specimens are obtained while the endoscope is gradually withdrawn from the area of the GI tract being investigated. In instances where a focal mucosal lesion is identified, multiple directed biopsy specimens should be taken. In instances where the abnormality is diffuse or where no gross abnormalities are visualized, multiple biopsy specimens should be obtained from various anatomic sites. For upper GI endoscopy, these sites include the duodenum jejunum (minimum of 8 to 10 biopsies), and antrum/angularis/lesser curvature, greater curvature, and cardia of the stomach. For colonoscopy, these sites include the cecum ascending colon transverse colon and proximal, middle, and distal descending colon.

To obtain biopsy specimens with a rigid endoscope, the tip of the endoscope should be placed 1 to 2 cm from the area to be sampled. The viewing lens is then opened, allowing the colon to collapse as air moves out. The area to be sampled should be visible in the tip of the endoscope. Alligator biopsy forceps are advanced through the endoscope, opened, and the area to be biopsied gently grasped. Before the tissue is pinched off, the biopsy forceps should be gently moved back and forth. If only mucosa or submucosa has been grasped, the tissue should be freely movable and the biopsy cups can be clamped down to obtain the sample. However, if the grasped tissue remains firmly attached to the colonic wall, this indicates that the forceps has gathered muscular tunics and colonic perforation is possible. In this event the forceps should be opened and a new site at least 1 cm away selected. A total of four to five samples should be obtained from the descending colon while the endoscope is progressively withdrawn.

Endoscopic biopsy specimens are delicate and easily damaged. Biopsy specimens should be handled gently and not allowed to dry. Placing the biopsy specimens on some form of support minimizes tissue contraction and preserves orientation. Transfer of the biopsy specimen directly from the biopsy forceps onto a moistened (normal saline) histopathology cassette sponge is recommended. Teasing the biopsy specimen from the biopsy forceps with a needle may damage the tissue. The sponge is placed in a labeled cassette and immersed in 10% formalin.

CONTRAINDICATIONS

Other than anesthetic considerations, GI endoscopy has no absolute contraindications. Endoscopic procedures are discouraged in inadequately prepared animals and in animals with bleeding disorders. Food within the stomach increases the risk of aspiration.

COMPLICATIONS

Complications of GI endoscopy include perforation of the GI wall, with resultant mediastinitis, pleuritis, or peritonitis. Perforation also can result from forceful insertion of the endoscope or biopsy forceps. *The endoscope should only be advanced if the lumen is visible.* Underlying disease in the bowel wall may predispose to perforation. Perforation usually results in the immediate development of air-filled body cavities (e.g., pneumoabdomen).

Overdistension of the stomach will cause cardiopulmonary compromise by impeding venous return, limiting tidal volume, and inducing vagal stimulation. Vagovagal reflexes can be induced by excessive traction on the mesentery. Significant hemorrhage can occur after biopsy procedures, but is rare. Enteropathogenic bacteria may be transmitted by poorly disinfected endoscopes. Gastric dilatation and volvulus can occur because of the inadequate removal of insufflated air.

CYTOLOGIC PROCEDURES

Cytologic samples can be used for the diagnosis of inflammatory, infectious, and neoplastic disorders of the GI tract of dogs and cats. Appropriate samples can be obtained manually (fecal smear, rectal scraping) or endoscopically.

The clinician prepares fecal smears by obtaining a fleck of mucus or a sample of feces from the surface of a stool and smearing the sample thinly on a microscope slide. To obtain a rectal scraping for cytologic evaluation, a gloved finger or small curette is inserted into the rectum and scraped along the mucosal surface. The sample collected should be thinly smeared on a microscope slide. After staining with new methylene blue or Wright's stain, the fecal smears and rectal scrapings can then be evaluated for the presence of inflammatory cells, pathologic organisms (e.g., *Histoplasma capsulatum*, *Prototheca* spp., *Campylobacter jejuni*, *Clostridium perfringens*), and neoplastic cells.

Cytologic examination of exfoliative specimens obtained endoscopically can be a useful adjunct to mucosal biopsy for the diagnosis of GI inflammation and malignancy in dogs and cats. It can also be useful for identification of *Helicobacter* in the gastric mucosa. Cytologic preparations can be obtained by brush or touch cytologic techniques (or both). The basic technique of brush cytology involves advancing a single-use guarded brush through the instrument channel, extending the brush beyond its protective sheath, and vigorously brushing the area of interest to exfoliate cells. The brush is then retracted into its sheath and removed from the endoscope. Finally, the brush is extended from its sheath and gently rolled across a glass slide. Theoretically, brush cytology offers the advantage of allowing for sampling of a larger surface area than biopsy. The touch cytology technique involves the transfer of an endoscopic mucosal biopsy to a glass slide. The clinician then makes multiple cytologic imprints by placing a second slide on top of, and at right angles to, the first slide and applying gentle pressure. Proper cytologic evaluation of samples obtained using these techniques requires an experienced GI cytopathologist.

CHAPTER • 102

Rhinoscopy, Nasal Flushing, and Biopsy

Mark J. Acierno
Mary Anna Labato

INDICATIONS

Clinical signs of acute and chronic nasal disorders vary but often include an obstruction of one or both nasal passages and a discharge that can be clear, mucoid, or hemorrhagic. Some dogs and cats respond to empirical therapy; others take a progressive and insidious course. These pets benefit from further diagnostics.

Nasal flushing and rhinoscopy are a part of the diagnostic workup for nasal diseases. Radiographic imaging should precede any invasive diagnostic procedure. Historical questions of interest include the onset and duration of the condition, whether one or both nostrils are involved, and the clinical progression of the disorder. The physical examination should include both the general physical and a detailed examination of muzzle, nasal planum, and nares. Looking at the condensation that forms on a glass slide placed in front of the nares is a convenient way to assess airflow. Diagnostic imaging is important not only because it may reveal a characteristic lesion but also because it may also provide information that can be used to direct the efforts of the nasal flush and rhinoscopy. Although computed tomography (CT) and magnetic resonance imaging (MRI) are significantly more sensitive in detecting and characterizing internasal lesions, skull radiographs taken under general anesthesia are often helpful. When used together, the history, physical examination, blood work, and diagnostic imaging provide an important foundation.

ANATOMY

A basic understanding of nasal anatomy is essential if consistently rewarding diagnostic procedures are to be performed (Figure 102-1). The left and right nasal cavities are separated by the bony nasal septum. The vestibule, located just within the nostril, contains the cartilaginous alar fold. The rostral aspect of each cavity is then divided into four airways (dorsal, middle, ventral, and common meatus) by the simple dorsal nasal concha and the more complex scroll-like ventral nasal concha. These conchae are primarily composed of cartilage rostrally and become increasingly calcified caudally. Nasal conchae are covered with a ciliated pseudocolumnar mucosal lining that serves to warm, humidify, and filter air as it travels through the meatus. The caudal aspect of the nasal cavities is filled with ethmoid conchae. These delicate, mucosa-covered scroll-like structures arise from the ethmoid bone; they extend to the cribriform plate and up to the sinuses. The cribriform plate, which also arises from the ethmoid bone, separates the nasal cavities from the cranial vault. Although dogs and cats have a complex arrangement of sinuses, these are rarely visualized during endoscopic procedures. All inspired air leaves the nasal cavity by passing from the ventral meatus to the nasopharynx via the choanae. The choanae is dorsal to the hard palate and funnels air from the two nasal sinuses into the common nasopharynx. The nasopharyngeal space, which is delineated ventrally by the soft palate and dorsally by the vomer bone, directs the flow of air into the oropharynx and eventually the trachea.

NASAL FLUSH

The nasal flush is the least invasive method of obtaining diagnostic samples from the nasal cavity; however, this procedure has several limitations. Samples collected are obtained by infusing saline into the caudal aspect of the nasal cavity and collecting it as it leaves the nares. Therefore only cells and debris that are easily dislodged are collected. Many tumors

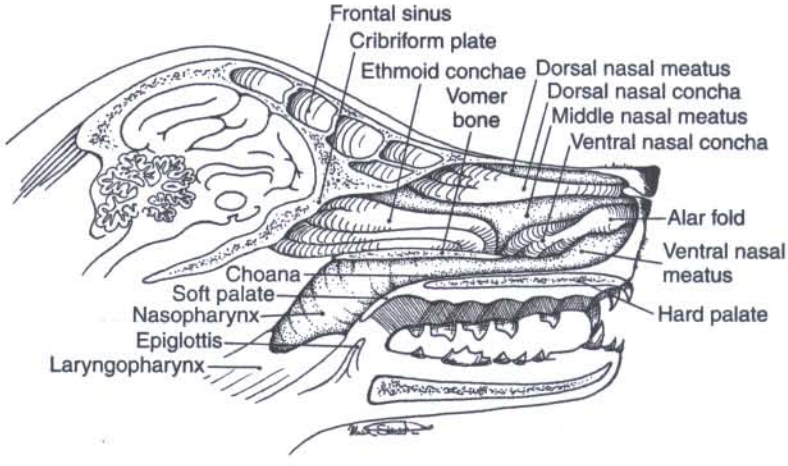

Figure 102-1 Nasal anatomy of canine. (Drawn by Mariah Steinwinter.)

will not exfoliate sufficient cells to permit diagnosis. In addition, no attempt is made to visualize the structures of the nasal cavity. This allows for gross abnormalities to escape detection. Lastly, although sterile saline is infused into the nasal cavity, it is collected as it flows out of the nares allowing for contamination by bacteria from outside the nasal cavity.

The anesthetized patient is placed in sternal recumbency with its nose pointed toward the floor. A cuffed endotracheal tube should always be used to prevent possible aspiration. A mouth gag is placed and a soft catheter (red rubber) is inserted into the nasopharynx so that its tip is pointed rostrally and the end of the catheter exits via the mouth. Sterile saline is then forcibly injected into the end of the catheter and fluid is collected as it leaves the nares. Depending on the size of the patient, 5 mL to 60 mL of infused saline should be sufficient to obtain samples for bacterial culture, fungal culture, and cytologic study. The flush can be repeated several times to improve diagnostic yield.

MODIFIED NASAL FLUSH

A second technique for nasal flushing has been described. Briefly, the tip of a polypropylene urinary catheter is cut to form a jagged edge. The distance from the nares to the eyes is measured and then marked on the catheter. This line estimates the distance from the nares to the cribriform plate; the catheter should never be advanced beyond this distance. The patient is then positioned as described previously and the catheter is inserted into the nares and advanced into the nasal cavity. While using the syringe to both flush saline into the nasal cavity and then suction the fluid back out, the sharpened catheter tip is used to scrape the nasal mucosa. Although this procedure has the theoretic advantage of active exfoliation of cells and larger samples, it is still performed blindly and has not been proven to provide greater diagnostic sensitivity. Some samples collected in this fashion may be suitable for histopathology.

RHINOSCOPY AND BIOPSY

A thorough examination of the upper respiratory tract requires direct visualization of each nasal cavity, nasopharynx, oropharynx, and larynx. The oropharynx and larynx can be examined in a sedated patient using only a laryngoscope, whereas visualization of the nasal cavities and nasopharynx requires general anesthesia and specialized equipment and techniques. Although no currently available endoscopic system will allow visualization of the entire nasal cavity and nasopharynx, the combined use of carefully selected rigid and flexible scopes will allow examination of most of the nasopharynx and nasal cavity.

Bacterial and fungal cultures should always be collected prior to rhinoscopy because the procedure is likely to introduce contamination. Once the patient is anesthetized, a nasal flush is performed and the sample submitted for culture. Alternatively, culture swabs are carefully inserted into the nasal cavity and then removed; contact with the external nares is avoided. Additional samples can also be retrieved during the rhinoscopy procedure if bacterial or fungal infection is suspected.

Examination of the nasopharynx is best achieved using a small flexible endoscope. Two commonly used instruments are the 5 mm bronchoscope and the 2.5 mm cystoscope. Although placement of the scope into the nasopharynx initially appears difficult, it is a skill that is easily mastered. The anesthetized patient is placed in sternal recumbency with the nose pointed slightly toward the floor. A cuffed endotracheal tube should always be used to prevent the aspiration of secretions, blood, or saline. In addition, a mouth gag is always used to prevent possible damage to the scope and facilitate proper scope placement. The scope is flexed to 180 degrees. Then, with the tip of the retroflexed scope parallel to the lower jaw, the scope is inserted into the oral cavity and advanced. Once past the caudal aspect of the soft palate, the scope is rotated so that the tip is pointing up and perpendicular to the lower jaw. By moving the scope slightly rostrally, the tip "hooks" the nasopharynx and proper placement of the scope is achieved.

Once inside the nasopharynx, a careful examination of the relevant structures can begin. It is important to remember that because the scope is flexed, the image will be inverted; therefore the soft palate will be viewed dorsally. The entire nasopharynx should be examined by moving the tip of the scope rostrally until the choanae can be clearly visualized. The nasopharynx and choanae should be assessed for texture, contour, and patency. The soft palate should be pink, smooth, and flexible, whereas the dorsal wall of the nasopharynx is smooth, dome shaped, and rigid. A cobblestone appearance to the mucosa may be evidence of lymphoid follicular hyperplasia (inflammation) or lymphoma. Fungal colonies will often appear as gray or yellow plaques. Large masses or polyps can protrude into the airway. Chronic inflammation, infectious diseases, or surgery all may result in scarring and stenosis of the nasopharynx, whereas a membranous obstruction of the choanae (atresia) can be caused by a congenital abnormality. Foreign material that has been vomited into the nasopharynx resulting in inflammation and obstruction may be visualized.

Any deviation from the normal anatomic structure should be investigated by biopsy and histopathology or culture. A biopsy instrument should not be passed through the scope's instrument channel when it is maximally flexed because the scope may sustain permanent damage. Therefore it is recommended that the scope be removed from the nasopharynx and straightened before the instrument is passed though the channel. The biopsy instrument should be positioned so that its forceps lie at the tip of the scope. Once in this position, the scope can be retroflexed and reinserted as described previously. This maneuver must be repeated for each biopsy sample.

Although the rostral most aspect of the nasal cavity can be examined by inserting a nasal speculum or flexible endoscope into the nares, a complete and through examination of the turbinates necessitates the use of a small-diameter rigid endoscope. One such instrument is the 2.7 mm universal telescope (Karl Storz Veterinary Endoscopy). When combined with a 4.0 × 5.5 mm oval cystoscopy cannula, this scope provides the user with a 16.5 cm working length and a 5 French (F) biopsy channel, which also allows for irrigation. The primary advantage of this system is that it allows direct visualization of a large portion of the nasal cavity and guided placement of biopsy forceps.

The anesthetized patient is placed in sternal recumbency with the nose pointed slightly toward the floor. The use of a cuffed endotracheal tube is essential to prevent aspiration. In addition, the placement of gauze sponges in the oropharynx may provide additional protection to the airway. Although the bleeding associated with rhinoscopy and biopsy can sometimes be a source of concern, instilling the nasal cavity with 0.25 to 0.5 mL of a dilute (1:10) mixture phenylepinephrine and lidocaine just prior to the procedures can be helpful in minimizing hemorrhage. The scope is inserted into the nasal cavity by lifting the flap of the nasal planum laterally and directing the scope over the alar fold. The scope can then be directed into the dorsal, middle, or ventral meatus. If the scope is equipped with a suitable channel, warm saline should be infused. This assists in visualizing the nasal structures by keeping the lenses free of blood, mucus, and debris. The scope is directed caudally to examine both the turbinates and

air-filled meatus; however, the clinician should never advance the tip of the scope past the level of the eyes. The preliminary diagnostic workup may provide important information in regards to the location of a nasal lesion, yet a through examination of the entire nasal cavity is always recommended so as not to miss more subtle lesions.

The turbinates should be examined for color, texture, and contour. They should be smooth, scroll-like, and covered with a shiny pink mucosa. Each meatus should be patent, free of debris, and contain minimal mucous. In addition, the air passages will gradually taper in the caudal aspect of the nasal cavity, and sudden widening or narrowing is evidence of a lytic or proliferative lesion. Abnormal endoscopic findings include increased mucus production, swelling of the turbinates, changes in the color or texture of the turbinates, foreign bodies, destruction or proliferation of the turbinates, fungal colonies, polyps, or tumors.

Increased mucus production, swelling of the turbinates, and changes in the appearance of the turbinates are nonspecific inflammatory findings that can be associated with allergic rhinitis, lymphoplasmacytic rhinitis, foreign bodies, bacterial infections, fungal infections, dental disease, and neoplasms. When a thorough endoscopic inspection fails to reveal a foreign body, mass, or fungal plaques, then biopsies of nasal mucosa should be submitted for histopathalogic examination and bacterial and fungal culture. It is important to remember that the source of the nonspecific inflammatory changes may be the result of dental disease. Therefore a thorough dental examination should always be performed while the patient is anesthetized.

Destruction of the turbinates is often associated with fungal rhinitis *(Aspergillus, Penicillium)*, bacterial rhinitis, viral rhinitis (cats), foreign bodies, and malignancies. Once again, if endoscopic examination does not reveal fungal colonies, a foreign body, or evidence of malignancy, then samples should be taken for histology and fungal and bacterial culture. As always, the teeth should be considered as a possible underlying cause of the turbinate destruction.

The appearance of masses in the nasal passage is variable but usually causes some degree of turbinate destruction, mucous production, and tissue proliferation, which obstructs the meatus. It is important to note that some fungal organisms, including *Rhinosporidium* and *Cryptococcosis*, can induce masslike formations rather than turbinate destruction. The appearance of any deviation in the normal appearance is sufficient reason to obtain a biopsy specimen and bacterial and fungal cultures.

CHAPTER • 103

Thoracic and Pericardial Taps and Drains

Lynette D'Urso

THORACOCENTESIS

Thoracic radiographs provide evidence that fluid or air exists within the pleural space. They show the location of the fluid and if pockets of fluid are present. If the patient is severely dyspneic and auscultation of the thorax indicates the presence of fluid or air, the clinician should proceed directly to thoracocentesis without taking radiographs. Care and good medical judgment are important factors in the decision to tap prior to radiography. For example, if a diaphragmatic hernia or solid mass was the origin of the pleural fluid then performance of thoracocentesis without initial diagnosis of the condition could lead to a puncture of an intestinal loop or the liver. Performing thoracic ultrasound prior to thoracocentesis is ideal due to the ease and rapidity at which it can be performed to identify fluid location.

Thoracocentesis is the technique used to remove air or fluid from the pleural space. Cytologic and chemical analysis of the pleural fluid assists in understanding the etiology and significance of abnormal fluid collection.

Materials required to perform thoracocentesis may include a butterfly catheter or 20-, 18-, 16-gauge needle or over-the-needle catheter, a three-way stopcock, an extension set, a large syringe (35 or 60 mL), tubes for fluid collection (EDTA and plain tubes), and slides for cytologic preparation.

The site for thoracocentesis varies with the individual patient and the amount and location of fluid or air. The seventh or eighth intercostal space is appropriate for a moderate to large quantity of fluid usually at the midthoracic level for fluid or more dorsally to remove air. In cats, an appropriate location is at the cranial right second to third or third to fourth intercostal space. The insertion site should avoid the caudal aspect of the ribs and therefore the intercostal vessels. If performance of thoracocentesis is ventral, the vessels along the sternum must be avoided. Similarly one must avoid the crura of the diaphragm and the liver, which lies just adjacent and caudal to the diaphragm.

A sterile three-way valve and 3- or 6-cc syringe are attached to the needle or tubing of the catheter. An extension set may also be used from the needle to the three-way valve to compensate for patient movement. The needle is advanced through the thoracic wall while gentle traction is maintained on the syringe. Once fluid is observed in the tubing, the needle is held in place or the needle angled so that it lies parallel to the chest wall. The first sample collected should be saved for analysis. Once a sample is collected a large (35- or 60-cc) syringe is attached and as much fluid as possible is drawn off. Holding the needle along the thoracic wall will decrease the chance of lung tissue laceration. The needle should be withdrawn if there is excessive patient movement or coughing to avoid a lung laceration. Fibrin clots may clog the end of the needle during the procedure. The needle may need to be moved to different locations or fluid occasionally injected into the pleural space through the needle to remove the clots.

An over-the-needle catheter may be used to avoid potential complications of lung laceration. Once inserted into the pleural space, the catheter is advanced and the needle removed. The extension set and stopcock are immediately attached.

If repeated thoracocentesis is necessary, the catheter can be sutured in place; however, caution must be exercised. The patient must be properly restrained to avoid tampering with the catheter and the needle must be properly capped to avoid iatrogenic pneumothorax, as well as making sure it is very securely sutured in place. Too large an amount of fluid removal and/or removing fluid too quickly can lead to reexpansion lung injury. Removal of less fluid may be safer and will quickly help to stabilize the patient.

Following thoracocentesis, radiographs or ultrasound can be performed to assess the quantity of fluid remaining or to identify iatrogenic pneumothorax.

PERICARDIOCENTESIS

Pericardiocentesis confirms the suspicion of pericardial fluid and provides diagnostic and therapeutic benefit by relieving decreased cardiac function (cardiac tamponade).

Materials required for pericardiocentesis include 6-, 12-, 60-mL syringes; +/– three-way stopcock and IV fluid extension line; 16-gauge, 3¼-inch, or 5-inch over-the-needle Angiocath catheter; sterile gloves; lidocaine for local anesthesia; a scalpel blade; and tubes for collection and culture of fluid.

The most important consideration is a strong clinical suspicion of fluid collection in the pericardial sac. Physical examination findings include increased venous pressure, decreased heart sounds, and decreased peripheral blood pressure. Signs of right-sided heart failure may be observed (ascites and peripheral venous distension). Radiographs of the thorax aid in supporting the diagnosis if rounding of the entire cardiac silhouette is observed on both lateral and dorsoventral views. The heart appears globoid rather than elliptic in shape. The pericardial sac can become distended so that it contacts the thoracic wall. Ultrasound provides a definitive diagnosis of pericardial effusion and cardiac tamponade (see Chapter 205).

The suspicion of pericardial fluid is supported on ECG by a generalized decrease in electrical amplitude of the complexes or electrical alternans. If pericardial fluid has been confirmed by ultrasound there are no contraindications to the procedure except for a bleeding diathesis or ruptured left atrium leading to continual bleeding into the pericardial space.

Complications of pericardiocentesis could include puncture of the ventricular wall, which could induce an arrhythmia, puncture of a coronary blood vessel, or epicardial laceration.

Sedation can be used if necessary but acepromazine should be avoided to prevent exacerbation of preexisting hypotension. Most pericardiocenteses are performed without sedation and often with use of only lidocaine at the site of skin and thoracic wall puncture. The patient should be gently restrained either standing or in sternal or left lateral recumbency. ECG monitoring of the heart rate and rhythm during the procedure is recommended but not essential.

A wide area of the right ventral hemithorax is surgically prepared from the third to the eighth intercostal space (ICS) to avoid trauma to the lung by entering the pleural triangle where there is no lung tissue. One milliliter of lidocaine is infiltrated into the skin and down to the parietal pleura at the site of entry (costochondral junction over the fifth or sixth ICS). A stab incision is made through the skin to permit needle entry. A 6- or 12-cc syringe is attached to the end of an angiocatheter and it is advanced into the thorax through the incision cranial to the rib (the intercostal vessels caudal to each rib are avoided) while maintaining gentle traction on the syringe plunger. The needle and syringe are held perpendicular to the chest wall and directed medially and slightly dorsally (Figure 103-1). A small "pop" may be felt when passing through the pericardium. When fluid appears in the syringe, a small amount for evaluation is collected and the catheter is advanced into the thorax all the way to the hub while the stylet is held steady (Figures 103-2 and 103-3). The stylet is removed and a 60-cc syringe is attached to the angiocatheter. Negative pressure is not present within the pericardial sac and usually pericardial fluid continues to pulsate out of the catheter. If the catheter rubs on the myocardium, ventricular premature contractions (VPCs) may be observed; the needle should be withdrawn slightly.

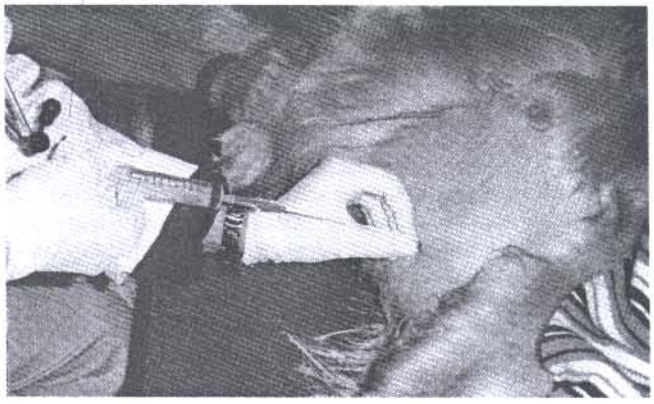

Figure 103-1 Placement of the angiocatheter at the sixth intercostal space at an angle perpendicular to the chest wall to perform a pericardiocentesis. Gentle suction is applied to the end of the catheter with a 12-cc syringe while the needle is advanced into the thorax and pericardial sac.

If pericardial fluid is bloody it should be monitored for signs of clotting (Figure 103-4). If clotting is observed then acute bleeding from a ruptured vessel or the tapping of blood directly from within the heart is suspected and the catheter removed. Comparing clotting time and hematocrit of peripheral blood often assists in determination of the fluid type.

The amount of fluid removed should be recorded. Depending on severity and duration of the condition 1000 cc or more may be obtained from the pericardial sac of a large dog. The fluid sample should be submitted in a plain tube and a tube containing an anticoagulant for cytology and chemical analysis. A sample may be considered for culture.

Following the procedure a thoracic radiograph or ultrasound should be performed to determine if the fluid is reaccumulating or if total fluid withdrawal has been accomplished. When ultrasound availability is not present, a pneumopericardial study should be considered.

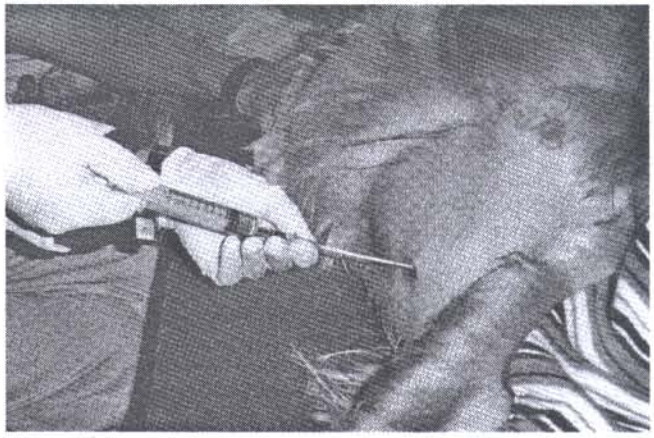

Figure 103-2 Pericardial fluid is first observed within the syringe. Advancing the needle is discontinued here.

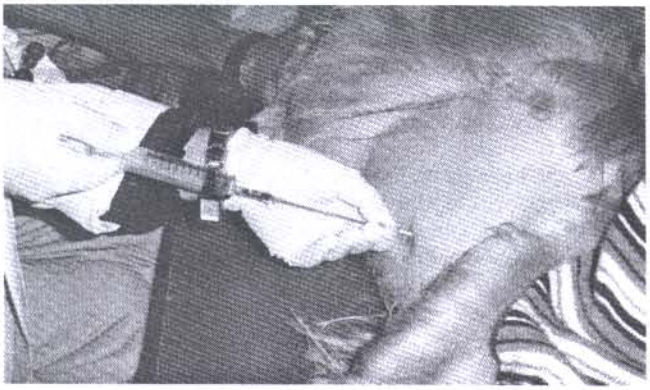

Figure 103-3 The catheter is advanced with one hand in one smooth motion while the other hand holds the stylet steady and prevents it from injuring the epicardium.

CHEST TUBE PLACEMENT

Temporary indwelling chest tubes are indicated for conditions requiring repeated thoracocentesis such as pneumothorax, tension pneumothorax, pyothorax, chylothorax, postoperative thoracotomy, or pleurodesis.

Appropriately sized tubes selected according to weight and tube size should comfortably fit in the intercostal space (Table 103-1). As a guide, the inside diameter of the chest tube should be the same size as the main stem bronchus on radiographs if the fluid is viscous or contains clots. A smaller tube (12 French) can be used to evacuate a pneumothorax.

Types of tubes used include silicone rubber (does not easily occlude but difficult to place without a stylet), red rubber (irritating and non-radiopaque), and polyvinylchloride (commercially available).

Commercially available chest tubes have fenestrations (holes) preplaced. Additional holes can be made that encompass less than 30% of the tube circumference so as to not weaken it. To make such a hole the tube is prebent and a tiny amount at the angle of the tube is cut. The hole size will be approximately four times as large as the piece removed so the cut should be conservative. All holes must be within the portion of the tube placed within the thorax.

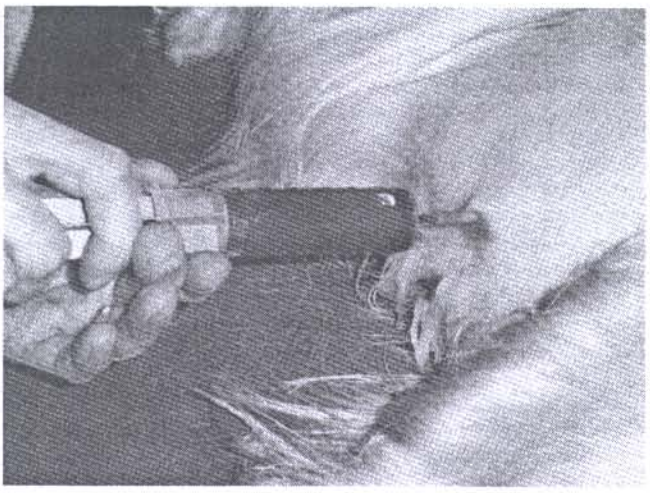

Figure 103-4 A 60-cc syringe is attached to the catheter and gentle traction is applied until all fluid has been removed. Appearance of the pericardial fluid is often bloody as seen here. This part of the procedure is no longer sterile.

Table • 103-1

Recommended Tube Sizes for Cats and Dogs

WEIGHT	TUBE SIZE (FRENCH)
<7 kg	14-16
dogs 7-15 kg	18-22
dogs 16-30 kg	22-28
dogs >30 kg	28-36

The clinical condition of the patient must be assessed prior to restraint or sedation for tube placement. The desired length of tube is premeasured from the tenth intercostal space (ICS) to the ipsilateral elbow.

Iatrogenic pneumothorax, laceration of a lung lobe or vessel, and tube migration within the thoracic cavity are potential complications to be considered with chest tube placement. Additional considerations include pain, lung or pleural irritation, and the presence of ventricular premature contractions with cardiac-induced pleural effusion.

The patient is gently restrained in lateral recumbency with the side for the tube placement facing up or is maintained sternally. Hair is clipped from shoulder to last rib and to the dorsal and ventral midline. Surgical preparation or cleaning of the skin follows. The tube is placed approximately mid-thorax at the seventh ICS. If air is suspected the tube is placed at the junction of upper third and lower two thirds of the chest wall. If fluid is to be removed, the tube is placed at the junction of the lower third and upper two thirds of the chest wall.

A local infiltrative block is performed directly at the site of tube placement or an intercostal or line block along the seventh ICS. There are two different techniques for incisions:

1. Incision is made using a blade over the tenth ICS (previously locally anesthetized). The tip of trocar is placed through skin incision and it is advanced subcutaneously cranially to the seventh ICS.
2. A gloved assistant pulls skin cranially starting just behind the elbow. A blade is used to incise the skin over the seventh ICS. The subcutaneous and intercostal muscles can be incised with the blade or dissected with Mayo scissors. The trocar is inserted through the full incision.

The trocar is placed in a vertical position perpendicular with the thoracic wall and the tip directed toward the opposite elbow. With one hand the trocar is held securely 2 to 3 cm above the skin to avoid penetration of the thoracic cavity too deeply. The palm of the other hand is placed on the head of the stylet and firm consistent pressure is applied to penetrate the trocar into the pleural space in a single motion. Once the pleura is penetrated, the trocar is angled so that it is parallel with the ribs and directed dorsally to remove air or ventrally for fluid. The stylet is pulled back very slightly and the tube and stylet advanced to the desired length. The tube is clamped with the handle portion of a hemostat as the stylet is removed to prevent pneumothorax. The skin is released and it will migrate caudally and form a tunnel to seal the hole just created. A tube adaptor and a 3-way stopcock with ports closed are attached to the tube.

A purse-string suture is used at the skin incision in addition to a Chinese finger trap or Roman sandal suture pattern to secure the tube to the chest wall. Alternatively, a "butterfly" is

made out of 1-inch white tape around the tube just distal to the skin incision and suture the wings to the skin.

A thoracic radiograph confirms tube placement. Antibiotic ointment and sterile gauze are placed over the insertion site followed by a comfortable chest bandage. The bandage and skin incision should be checked at least several times daily. All connections must be secure with no leaks.

The tube can be removed when there is less than 2 mL/kg/day of fluid accumulation. One continuous rapid motion is used to remove the drain. Sedation is not necessary. Overwrap with a thoracic circumferential bandage for 1 to 2 days.

An E-collar or other method of preventing access to the tube must be utilized at ALL times. Initially the tube should be monitored and evacuated every 1 to 2 hours, more often if the patient becomes tachypneic or dyspneic. A large (35- or 60-cc) syringe can be used to provide intermittent suction in small dogs and cats, whereas continual suction may be required in large dogs. One additional consideration is that some patients may have a complete mediastinum due to pathology within the thorax. This may require chest tube placement on both sides of the thorax to completely remove fluid or air.

CHAPTER • 104

Transtracheal Wash and Bronchoscopy

Brian C. Norman

Transtracheal wash and bronchoscopy are diagnostic procedures used in the diagnosis of bronchopulmonary airway disease. The transtracheal wash is used to obtain tracheobronchial cells and secretions for cytology and microbiologic evaluation. The bronchoscope is a more specific procedure that allows visualization of the trachea and airways while obtaining samples. The choice of procedure should be based on stability of the patient, diffuseness of disease, and operator skill level.

TRANSTRACHEAL WASH

A transtracheal wash can be performed in animals with a diffuse disease that cannot undergo prolonged sedation. The ventral portion of the patient's neck is clipped and aseptically prepared. The patient is then placed in sternal recumbency with an assistant holding the head and pointing the nose up. Sedation with Propofol (Diprivan) or a short-acting barbiturate anesthetic is preferred. In dogs, a 16-gauge through-the-needle jugular catheter is inserted between proximal tracheal rings or the cricothyroid membrane and advanced down the airway. In cats, an open-end polypropylene urinary catheter or 5 F red rubber catheter can be placed through a sterile endotracheal tube. The catheter is slowly advanced down the trachea. Warm sterile saline is infused through the catheter: 5 mL is infused for cats and small dogs up to a maximum of 20 mL in large dogs. After 5 to 10 seconds, the operator attempts to retrieve the sample by applying gentle negative pressure several times with the syringe. Generally, 50% of the original volume will be retrieved. Several drops of the sample should be placed on a culture swab for culture and sensitivity, and the remainder should be placed in a sterile tube or container for cytology.

Pneumomediastinum and subcutaneous emphysema are complications of this procedure that may need to be addressed.

BRONCHOSCOPY

Bronchoscopy is best performed with a flexible fiber-optic bronchoscope. The patient is anesthetized with Propofol® and maintained on a drip or gaseous anesthesia. In larger animals, an endotracheal tube may be placed and the bronchoscope can go through the tube. In smaller animals, the bronchoscope is too large and the animals cannot be intubated during the procedure. After the animal is lightly anesthetized, the bronchoscope is inserted through the arytenoids and into the trachea. Inspection of the trachea should include the appearance of the mucosa, the amount of secretions, and any evidence of collapse. The carina should then be identified, and each lung lobe should be systematically examined. (Figures 104-1 and 104-2). The operator must note the presence of mucus plugs, foreign bodies, dynamic collapse of airways, masses or nodules, and parasites.

The bronchoscope offers several options to sample the airways. The first method uses a bronchoscope brush. The brush is covered by plastic that can be pulled back once the brush is in its desired location. With the bronchoscope in the desired location, a small sampling brush is passed through the sampling channel. When the brush is visualized, the brush is extended and gently scraped against the airway. The brush is then pulled back into its casing and removed from the scope. The brush can be cultured and then gently rubbed on a glass slide for cytology.

The second sampling method uses a biopsy instrument. In a similar method, the bronchoscope is placed in the desired location and then the biopsy instrument is inserted into the sampling port. The bronchoscope is then used to guide the instrument to the desired location and the biopsy is taken. The sample can be submitted for culture and histopathology.

The third sampling method is bronchial or bronchoalveolar lavage. This is performed after all lobes have been inspected. The bronchoscope is directed into the desired lung and then advanced until it is wedged or is occluding the airway. The clinician should instill 10 to 30 mL of warm sterile saline into the sampling port, and (5 to 10 seconds later) aspirate the sample using a syringe. Approximately 40% to 50% of the sample should be retrieved. It is helpful if the patient is not heavily sedated. The lightly sedated animal will cough, producing a better sample. This procedure can be repeated several times. Several drops of the sample should be cultured, and the rest should be placed in sterile tubes for cytologic evaluation.

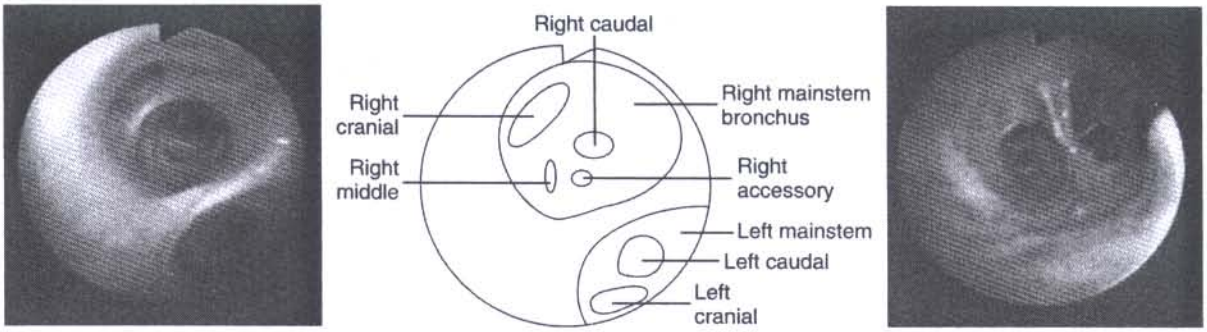

Figure 104-1 Diagram of normal bronchoscopic image of the division of the carina, demonstrating the position of the right and left main stem bronchi.

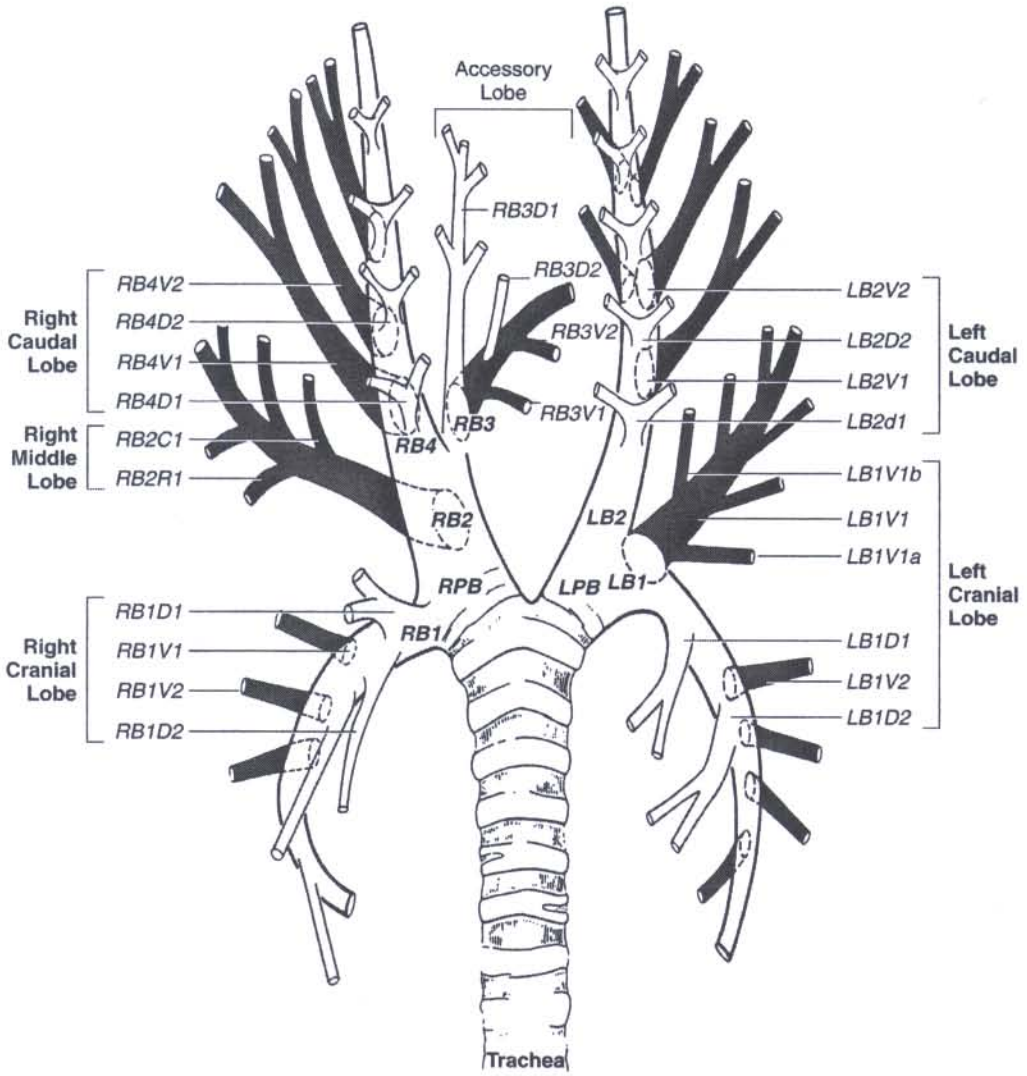

Figure 104-2 Diagram of normal bronchial anatomy in dogs. Each lobar bronchus is subdivided into segmental bronchi: *V1*, first ventral segmental bronchus; *V2*, second ventral segmental bronchus; *D1*, first dorsal segmental bronchus; *D2*, second dorsal segmental bronchus; *C1*, first caudal segmental bronchus; and *R1*, first rostral segmental bronchus. Segmental bronchi are subdivided into subsegmental bronchi: *V1a*, first subsegmental bronchus; *V1b*, second subsegmental bronchus. *LB1*, Lobar bronchus of left cranial lung lobe; *LB2*, lobar bronchus of left caudal lung lobe; *LPB*, left main stem bronchus; *RB1*, lobar bronchus of right cranial lung lobe; *RB2*, lobar bronchus of right middle lung lobe; *RB3*, lobar bronchus of accessory lobe; *RB4*, lobar bronchus of right caudal lung lobe; *RPB*, right main stem bronchus. (From Amis TC, McKiernan BC: Systematic identification of endobronchial anatomy during bronchoscopy in the dog, *Am J Vet Res* 47:2649, 1986.)

CHAPTER • 105

Unblocking the Urethra of the Male Cat

Mary H. Bowles

The male cat may have an obstructed urethra due to inflammation, spasms, trauma, congenital defects, urethral or periurethral masses, foreign bodies, uroliths, and urethral plugs. The length and narrow diameter of the urethra predisposes these cats to obstruction. The urethral plug is the most frequent cause of obstruction.

Cats with feline lower urinary tract disease often display similar clinical signs regardless of the cause or the presence or absence of obstruction. Dysuria, hematuria, and frequent attempts to urinate are common but not exclusive signs of urethral obstruction. However, when these signs are combined with vocalization, licking the prepuce or penis, or systemic evidence of illness (e.g., depression, loss of appetite), it is likely that the animal has a urethral obstruction. Palpation of a distended bladder that is difficult to express is a key feature of urethral obstruction.

When urethral obstruction is suspected, a thorough assessment of the cat's physical condition is indicated prior to catheterization, especially if the cat is systemically ill. In addition to establishing further evidence of urethral obstruction by bladder palpation and inspection of the distal penis, special attention should be paid to the cardiac status because hyperkalemia-related arrhythmias may be present that affect the treatment plan. Quick assessment tests (QUATS) (e.g., blood urea nitrogen [BUN], glucose, packed cell volume [PCV]) are indicated in any cat prior to catheterization to evaluate both anesthetic risk and overall condition. Appropriate blood samples should be saved for subsequent complete blood count (CBC) and biochemistry profile evaluation, especially in systemically ill cats. Bladder decompression by cystocentesis provides optimum samples for urinalysis and culture, alleviates distress, and may facilitate flushing obstructive material back into the bladder when necessary. Urethral catheterization usually requires general anesthesia unless the cat is moribund. Anesthetic agents requiring renal excretion should be used with caution.

UNBLOCKING TECHNIQUE AND INDWELLING CATHETER PLACEMENT

The cat should be placed in lateral recumbency. The clinician should then clip the hair in the perineal area and surgically scrub the prepuce and tip of the penis, taking care to avoid undue trauma to the penis. The tail and hindlimbs should be drawn forward toward the head to provide better exposure of the preputial area. Using sterile technique, the prepuce should be pushed back toward the body, exposing the distal end of the penis. Because urethral plugs often lodge near the external urethral orifice, the exposed distal penis should be gently massaged to loosen any obstructing material present and extrude it from the urethra. The lubricated tip of an open-ended tomcat catheter (3.5 F polypropylene, 4.5 to 5.5 inches in length) or a Minnesota olive-tipped feline urethral catheter (22 G × ½- to 1½-inch E-JAY International, Inc., Glendora, Calif.) is then inserted into the external urethral orifice, extending the penis caudally and dorsally until it is parallel to the spine to facilitate advancement of the catheter (Figure 105-1). Once the obstruction has been reached, the clinician should attach a syringe (≥ 20 mL) filled with saline or lactated Ringer's solution to the catheter either directly or by an intravenous extension set. A liberal amount of flushing solution is then injected into the urethral lumen, allowing fluid to run back out of the urethral orifice. The clinician should periodically attempt to cautiously advance the catheter toward the bladder, noting evidence of relief of obstruction, such as debris emerging from the orifice or a decrease in reflux of flushing solution. Applying moderate pressure to the bladder wall and occasionally repeating gentle massage of the extruded penis between flushings may facilitate dislodgement of a urethral plug or urolith.

If the previously described technique does not result in relief of obstruction, the clinician should continue to flush while manually occluding the urethra around the catheter tip, attempting to dilate the urethral lumen and force the obstructive material back into the bladder. As pressure builds up in the obstructed urethra, the clinician should try to carefully advance the catheter toward the bladder. To prevent iatrogenic damage to the urethra, excessive force should be avoided when advancing the catheter and when injecting flushing solution from the syringe into the manually occluded urethra.

If the urethra is successfully unblocked, a catheter should be inserted into the bladder lumen and the majority of urine aspirated from the bladder, saving a portion for urinalysis +/– culture if not obtained previously by cystocentesis. The bladder should be flushed repeatedly with saline or lactated Ringer's solution until aspiration of the flushing solution appears relatively free of blood and particulate material. If a urethral plug or urolith was obtained during the unblocking procedure, it should be saved for analysis. Urethral plugs can be examined cytologically, and uroliths can be submitted for quantitative analysis +/– culture.

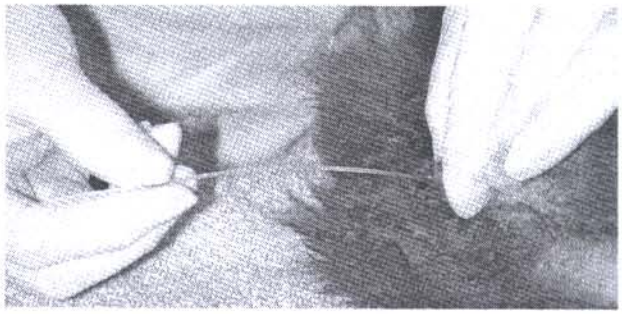

Figure 105-1 Proper positioning of the feline penis for urethral catheterization with a 3.5 F polypropylene catheter. The penis is extended caudally and dorsally while the tail and hind limbs are drawn forward toward the head.

If the unblocking techniques previously described are unsuccessful, the bladder can be serially decompressed by cystocentesis or a cystostomy tube can be placed for temporary urine diversion. These procedures provide relief while the cat receives supportive therapy and has diagnostic imaging performed to further define the source and location of obstruction; they also allow for alternative treatment plans to be developed.

Monitor urination for at least 24 hours after relief of obstruction. Express the bladder manually at least three times daily if the cat is not voiding regularly or a large amount of urine is retained in the bladder after voiding. Place an indwelling catheter immediately after the unblocking procedure if a strong urine stream is not present on expression, the cat is systemically ill, excessive hematuria exists, or relief of obstruction was difficult. An indwelling catheter may be placed up to several hours later if the patient reobstructs or has difficulty urinating due to an atonic bladder. Ideally, a 5 French (F) (the 3.5 F. size may be used but becomes obstructed more easily) red-rubber (polyvinyl) or Foley catheter should be used because these catheters are more pliable than the polypropylene variety and less likely to cause injury to the urethral and bladder mucosa. Placement may require the use of a wire guide due to the increased pliability. The application of a generous amount of lubricant is often required to facilitate passage, especially for the balloon portion of the Foley catheter. To minimize bacterial contamination after insertion into the bladder lumen, the clinician should attach the indwelling catheter to a sterile, closed urine collection system available as a commercial product (Cook Urological, Spence, Ind.) or constructed from a recently emptied intravenous (IV) fluid bag attached to a sterile IV administration set. The clinician can reduce tension placed on the indwelling catheter by the collection system by using elastic wrap and suture to attach the apparatus to the cat (Figure 105-2). Indwelling catheters should be removed as soon as possible, generally within 1 to 3 days after placement. Although indwelling catheters predispose the cat to urinary tract infection, antibiotic therapy is not recommended unless evidence of urinary tract or systemic infection exists.

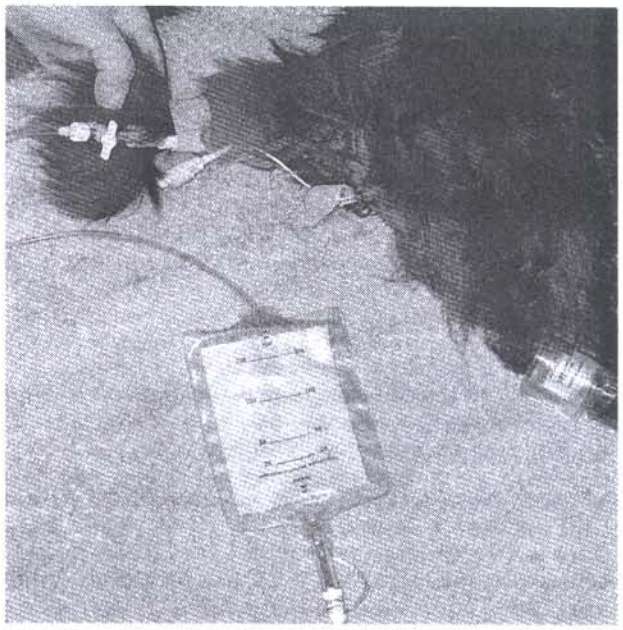

Figure 105-2 Indwelling 5 F. Foley urethral catheter attached to a sterile, closed urine collection system. Elastic wrap attaches the urine collection system to the tail, and an elastic wrap flange is loosely sutured in the preputial area to reduce the tension on the urethral catheter and help keep it in place.

CHAPTER • 106

Venous and Arterial Puncture

Harold Davis

VENIPUNCTURE

The most commonly used veins for venipuncture are the cephalic (dog and cat), lateral saphenous (dog), medial saphenous (cat), and jugular (dog and cat). The ear veins (dog and cat), sublingual veins (dog and cat), and abdominal veins (dogs) have also been used. Any visible vein is an option for venipuncture.

The most important aspects of any venipuncture technique are the proper restraint of the animal and proper distention and immobilization of the vessel. These objectives are most easily accomplished when the procedure is done as a two-person project. The phlebotomist should only attempt the venipuncture when the vessel can be clearly delineated. Blind venipuncture attempts, in the hopes of accidentally "skewering" the vein, are doomed to failure and create unnecessary patient discomfort. If the phlebotomist is unable to locate the vessel (by visual inspection or digital palpation), the manner in which the vessel is distended and immobilized must be changed.

Awake animals need to be restrained for any of these procedures, but excessive restraint should be avoided because it may incite more resistance from the animal than the venipuncture procedure itself. All venipunctures (and arterial punctures) must be done aseptically. The hair should be clipped and the skin prepared with antiseptic solutions as if for surgery.

CEPHALIC VEIN VENIPUNCTURE

The dog or cat may be positioned in sternal or lateral recumbency. The restrainer leans over the top of the animal and grasps the leg of interest at the elbow. The other hand or arm

can be used to restrain the animal's head if the animal is awake, to prevent an aggressive response to the skin puncture. If the animal is in sternal recumbency, the restrainer should lean on his or her elbow to help prevent the animal from withdrawing its leg at some critical time during the procedure. The thumb or forefinger is wrapped around the leg at the level of the elbow. Pressure at this point occludes the cephalic vein. The skin is then rotated outward to roll the vein to the top (anterior) of the leg.

The phlebotomist grasps the leg with one hand at the level of the metacarpus and further extends the leg. In loose-skinned animals, it may be necessary to flex the carpus. The objective is to tether the vein between the two points of traction (at the elbow and at the carpus) so that the vein is both distended and does not roll from side to side. It should not be necessary for the phlebotomist to use his or her thumb to help immobilize the vein; this may only serve to collapse the vein, making venipuncture more difficult.

The needle is directed, as much as possible, along the longitudinal axis of the vein. The needle is inserted through the skin with the bevel facing up. It is not necessary to achieve both skin and vein puncture in the first movement. The skin puncture is the painful part, and animals will often move in response to it. Once the animal has settled down, the needle can be directed into the vein. If blood does not spontaneously flow into the hub of the needle, the phlebotomist should gently aspirate to determine if the needle is or is not in the vein. If it is not in the vein, the needle should be advanced a bit further and the process repeated. The needle can be advanced to its full length. If at this point the venipuncture has not been successful, the needle will have to be withdrawn to its subcutaneous position (it should not be removed entirely, because another skin puncture will then be necessary). It is most important to withdraw the needle slowly, while gently aspirating. The deep wall of the vein may have been inadvertently penetrated, and the lumen will thereby be found as the needle is withdrawn.

Once the blood sample is taken or the drug is administered, the needle is withdrawn from the vein and digital pressure applied over the venipuncture site for at least 30 seconds. The site should be monitored for bleeding or hematoma formation for an additional several minutes.

Lateral Saphenous Venipuncture

Dogs are usually positioned in lateral recumbency for this procedure (Figure 106-1, *A*). The restrainer grasps the upper leg at the stifle. The other hand or arm can be used to restrain the animal's forelegs and head if the animal is awake. Circumferential pressure is applied at the stifle to occlude and distend the vein. The phlebotomist grasps the leg with one hand at the level of the metatarsus. In loose-skinned animals it may be necessary to extend the leg and flex the tarsus to better tether and immobilize the vein. It should not be necessary for the phlebotomist to use his or her thumb to help immobilize the vein. The venipuncture is performed as described previously.

Medial Saphenous Venipuncture

Cats are usually positioned in lateral recumbency for this procedure. The restrainer grasps the lower leg at the stifle while reflecting the upper leg caudally with the forearm. The other

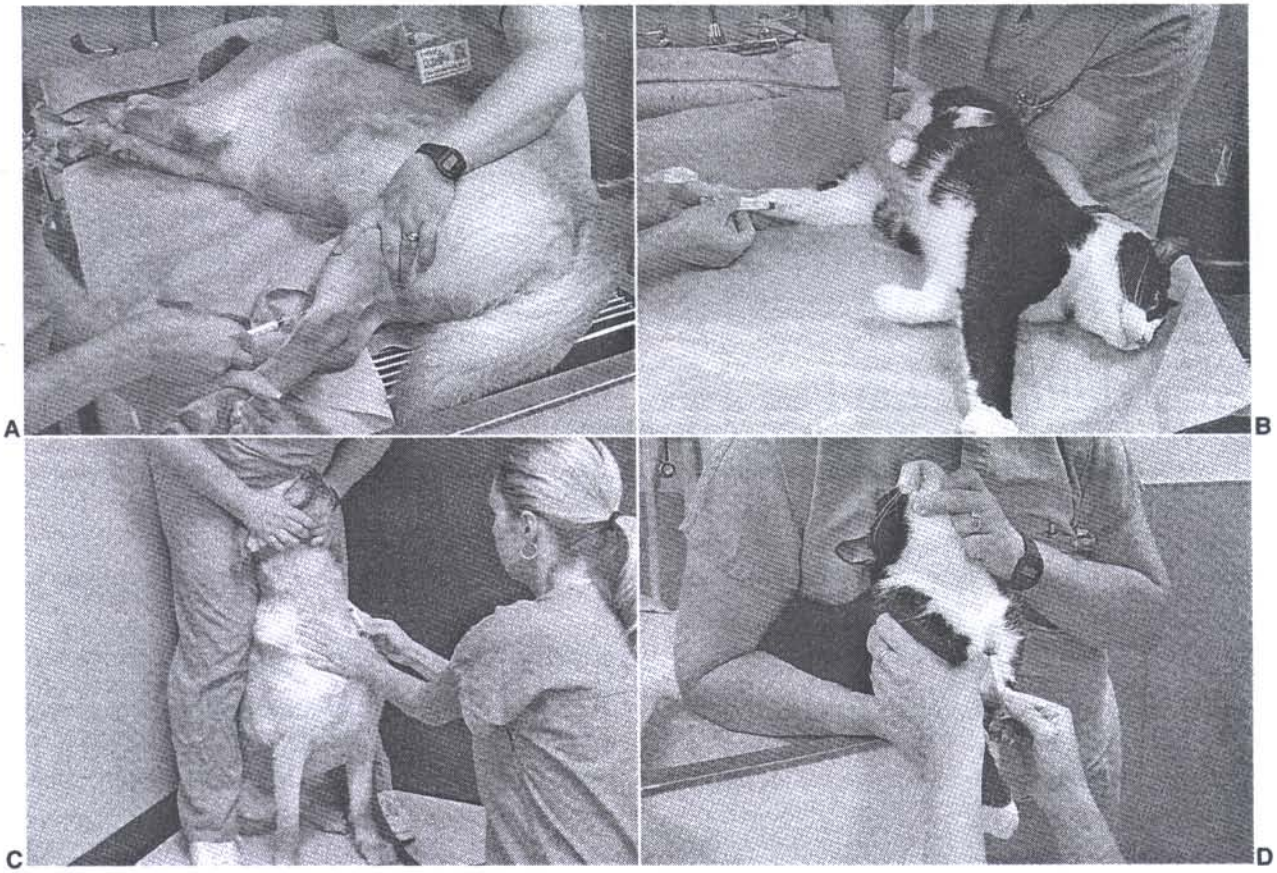

Figure 106-1 The various positions used for dog and cat venipuncture. **A,** Dog positioned for venipuncture of the lateral saphenous vein. **B,** Cat positioned for venipuncture of the medial saphenous vein. **C,** Dog positioned for venipuncture of the jugular vein. **D,** Cat positioned for venipuncture of the jugular vein.

hand or arm can be used to restrain the animal's forelegs and head if the animal is awake. Circumferential pressure is applied at the stifle to occlude and distend the vein. Alternatively, in the cat, the phlebotomist should grasp it by the scruff of the neck and place in lateral recumbency (Fig 106-1, *B*). The upper hind leg is abducted and flexed to expose the medial surface of the bottom leg. Applying pressure with the edge of the hand that abducts and extends the upper leg distends the vein. The phlebotomist grasps the leg with one hand at the level of the metatarsus. In loose-skinned animals it may be necessary to extend the leg and flex the tarsus to better tether and immobilize the vein. It should not be necessary for the phlebotomist to use his or her thumb to help immobilize the vein. The venipuncture is performed as described previously.

Jugular Venipuncture

Dogs and cats may be positioned in sternal or lateral recumbency for this procedure. In sternal positioning, one convenient technique includes backing the animal into a corner, between the legs of the holder (Fig 106-1, *C*). Alternatively, the dog or cat can be restrained on a table in sternal recumbency (Fig. 106-1, *D*). One hand grasps the legs at the carpel joint and stretches the legs over the edge of the table. In any position the head will need to be extended. Either the restrainer or the phlebotomist occludes the vein by applying occlusive pressure at the thoracic inlet. Care must be taken not to compress the trachea or impair breathing. Vein distention and immobilization can be maximized by pressing into the thoracic inlet in a caudal direction and by further extending the head. Extensive longitudinal traction, however, can collapse the vein. With optimal positioning, the vein is easy to palpate (or visualize) and does not roll much from side to side. In sternal positioning, the venipuncture is usually done in a cephalad direction; in lateral positioning the venipuncture is generally done is a caudal direction. The venipuncture is performed as described previously.

Arterial Puncture

The dorsal metatarsal (pedal) and femoral arteries are most commonly used for arterial blood sampling. The dorsal metatarsal is smaller but the interstitial connective tissues around it are tight (compared with the femoral artery), which facilitates vessel positioning and minimizes postpuncture hematoma formation. The radial, brachial, aural, and sublingual arteries have also been used.

Arterial puncture is usually done with the animal in lateral recumbency; however, it can be accomplished when the animal is standing if it resents the lateral recumbent positioning. The pulse is palpated with one or two fingers of one hand. The needle is inserted through the skin but not into the artery. Once the animal settles down from the skin puncture, the needle is aligned with the longitudinal axis of the artery (bevel up). The tip of the needle and the artery are simultaneously palpated with the one finger, and the needle inserted into the artery. Blood should spontaneously flow into the hub of the needle in an animal with normal blood pressure; however, gentle aspiration on the plunger may be required in animals with low blood pressure or when small needles are used. If the arterial puncture is unsuccessful, the needle can be inserted a bit further. As for venipuncture, when the needle is withdrawn, it should be done slowly and with gentle aspiration applied to the plunger in case the deep wall of the artery was inadvertently punctured during needle introduction. The needle is withdrawn to its subcutaneous position and the arterial puncture is reattempted.

Once the sample collection is complete, the clinicians should withdraw the needle and apply digital pressure over the puncture site for at least 1 minute; then the animal should be monitored for bleeding or hematoma formation for another 4 minutes. If blood gas measurements cannot be done immediately, the sample should be stored in ice water to minimize in vitro metabolic changes in the measured parameters.

CHAPTER 107

Skin Scrapings and Skin Biopsies

Sonya V. Bettenay
Ralf S. Mueller

GETTING THE MOST FROM SKIN SCRAPINGS

Skin scrapings in veterinary dermatology are used to identify ectoparasites or to evaluate cells and organisms from the skin surface cytologically. The focus of this chapter is obtaining skin scrapings to diagnose cutaneous ectoparasites.

Superficial Skin Scrapings

Indication

Superficial skin scrapings are taken to detect mites living on the skin surface, such as *Cheyletiella* spp. or *Otodectes cynotis*, or to identify mites burrowing in the stratum corneum, such as *Sarcoptes scabiei* or *Notoedres cati*. All these mites can cause pruritus (which is seen least commonly in cheyletiellosis). Particularly in any severely pruritic small animal, where itching began suddenly or where other animals or humans in the household are affected (or both occur), scabies should be suspected. The preferred anatomic sites vary with the ectoparasite. Scabies most commonly affects the elbows, ear margins, hocks, and ventrum. *Notoedres cati* in cats most commonly affects the face. In both dog and cat, the dorsum is most commonly affected with *Cheyletiella* mites, which typically cause scaling. Superficial skin scrapings should thus be performed in any scaly or pruritic dog or cat.

Procedure

Mineral oil or pyrethrin eardrops should be put on the scalpel blade *and* affected skin. The authors select nonexcoriated sites, preferably in scaly or papular areas. It is important to scrape a large area. In hairy dogs with suspected scabies, it is recommended to clip the hair first. It is important not to remove the surface scale or crust that may be present, should

such clipping be necessary. *Sarcoptes* mites are located superficially within the epidermis and may be dislodged with such cleansing. Clipping is contraindicated in animals with possible cheyletiellosis. Mineral oil is applied to the affected skin, gently scraped off the surface, and translocated onto a microscope glass slide. Scrapings are done in the direction of hair growth. The oil on the skin will facilitate gathering of debris and increase the chance of positive results. When evaluating a sample microscopically for ectoparasites, a cover slip is applied to distribute debris evenly. This minimizes the chance of missing mites covered by debris and enables a rapid yet thorough scanning at low magnification without the need for continuous adjustment of focus. The condenser of the microscope should be lowered for easy identification of parasites.

Interpretation

For scabies or cheyletiellosis, one mite or egg is diagnostic and adequate for initiating miticidal therapy. In canine scabies, 50% of affected dogs may be negative on several scrapings and trial therapy may be needed. Occasionally, a short-bodied *Demodex* mite may be found on superficial skin scrapings. These short-bodied mites are supposed to live in the epidermis rather than the follicles, and their detection should trigger deep skin scrapings because they may occur in combination with a proliferation of follicular *Demodex* mites.

Deep Skin Scrapings

Indication

Deep skin scrapings are performed to detect *Demodex* mites. In the dog, *Demodex canis* lives in the hair follicle; a longer-bodied *Demodex* mite is suspected to live in the sebaceous glands. Papules, pustules, and crusts characterize canine demodicosis. Comedones, scales, and alopecia also may be seen. Demodicosis is on the list of differential diagnoses in almost any dog presented with skin disease. A deep skin scraping is one of the most common diagnostic procedures performed in veterinary dermatology. Demodicosis in the cat is less common, usually affects the head, and typically occurs secondary to systemic disease.

Procedure

A small area of affected skin (1 to 2 cm^2) is scraped in the direction of hair growth until capillary bleeding is observed. A blade covered with mineral oil should be used. Follicular papules or pustules are particularly suited for scraping. Because *Demodex* mites live in the hair follicles, it is useful to squeeze the skin prior to and during the scraping in an attempt to push the mites out from the depths of the follicles. A survey conducted by summer dermatology students revealed a 50% higher mite count when the skin was squeezed prior to scraping. Paws and faces are difficult to scrape, and skin biopsies may be needed in some of these dogs to confirm the diagnosis. Old English sheepdogs, Scottish terriers, and especially Shar Peis with demodicosis are anecdotally reported to be negative on scrapings and may have to be biopsied for diagnosis. Although not documented, it is thought that these breeds have more tortuous and deep hair follicles. Trichograms (hair plucks) provide an alternative test in these situations. Hairs are plucked with a hemostat and placed in mineral oil on a glass slide for examination. Approximately half of all dogs with demodicosis will show positive trichograms; a negative result does not rule out the disease, and the clinician must initiate further testing.

Interpretation

Although *Demodex canis* is a normal part of cutaneous fauna (and thus an occasional mite can be found on skin scrapings of normal dogs), one should never see more than one *Demodex* mite on a dog not affected by demodicosis. If only one mite is found, further scrapings or a biopsy are recommended. When evaluating deep skin scrapings, it is important to assess and to note in the record the site of scraping and the relative numbers of adults, larvae, nymphs, and eggs per low-power field (LPF). In subsequent visits, assessment of response to therapy relies on the comparison of such numbers. It is recommended that repeat scrapes at the same sites take place monthly when monitoring.

GETTING THE MOST FROM A SKIN BIOPSY

Skin biopsies are recommended as useful in textbooks and by dermatologists, yet the results are often "inconclusive." The manner in which a biopsy sample is obtained can significantly influence the end results.

Lesions have "lives," disease is a dynamic process, and the biopsy section is like a single frame taken from a roll of movie film. If clinicians set the "film" on a developing lesion, it would display many different appearances throughout its evolution. Because a single biopsy reveals only one "snapshot," the clues as to the cause of the disease may simply not be present at that point in time. *Taking multiple samples* from well-chosen clinical sites exhibiting a variety of lesions will potentially help to avoid inconclusive results. In a pustular disease, erythematous macules develop into papules, then pustules, and finally crusts and erosions. Sampling every single one of these stages and then several of the most exciting lesions, the pustules, will give the pathologist the widest range of lesion development and hence the best chance to come up with some helpful comments.

Selection of the Site

Site selection requires careful examination of the entire animal for the most representative range of lesions. With the exception of a solitary nodule, multiple tissue samples are taken. Pustules or vesicles are fragile lesions, that have to be handled with great care to prevent rupture.

Depigmenting lesions should be biopsied *in an area of active depigmentation* (i.e., gray color) rather than the final stage (i.e., white). Once the pigment has been lost from the epidermis, active disease is probably absent; a biopsy of a depigmented area should be expected to reveal loss of melanocytes and pigment but not necessarily the reason for the depigmentation.

Alopecia should be biopsied *in the center of the most alopecic area*, as well as in junctional and normal areas. The clinician should remember that the glabrous (nonhaired) areas of the body normally contain fewer hair follicle units and smaller sebaceous glands; therefore if possible, these areas should be avoided if diseases with follicular pathology are on the list of differential diagnoses.

Ulcerated areas should also be avoided, unless they are sampled *in addition* to other areas or unless one is looking for a deep dermal, vascular, or pannicular pathologic disease.

Adjacent normal skin should be sampled where possible. In a bacterial folliculitis and furunculosis with a possible underlying allergy or endocrinopathy, the presence of a lymphocytic infiltrate consistent with hypersensitivity or follicular atrophy seen with hormonal diseases can be completely obliterated by the inflammation of a severe secondary pyoderma so that only a diagnosis of deep infection can be made. Clues in regard to the primary diagnosis may be present only in adjacent skin.

Preparation of the Site

Surgical preparation of the site should not be performed at all. Crusts should be left on the skin. If they are accidentally dislodged, they should still be placed in the formalin. It may be helpful to wrap them inside a piece of lens-cleaning tissue paper prior to placement in the formalin container to prevent

accidental loss. Crusts may contain microorganisms, inflammatory or acantholytic cells (epidermal cells that have become detached from their neighbors and "rounded up"), which will help establish a diagnosis. Infection as a result of this lack of surgical preparation is almost never seen.

Helping the Laboratory Technician to Orient the Sample

After formalin fixation, it is impossible even for the most experienced technician to recognize most lesions because the sample appears as gray amorphous tissue. Drawing a line in direction of the hair growth on the skin prior to biopsy using a waterproof pen will help the technician to orient the tissue appropriately (Figure 107-1).

Surgical Technique

The overlying hair should be clipped and gently removed. If crusts are present, scissors may be less traumatic to use than electric clippers. No aseptic preparation is performed (except when excising solitary nodules). If manual restraint or sedation is planned, then the subcutaneous injection of 1 or 2 mL of Xylocaine without adrenaline will usually provide adequate local anesthesia. The needle entry point should be kept outside the proposed biopsy area to avoid disruption to the tissue in the biopsy. The clinician should draw a line in the direction from nose to tail to enable easy relocation of the site and to aid laboratory orientation. General anesthesia is indicated for facial or paw biopsies.

Wedge versus Punch Biopsy

The punch biopsy is quick, relatively atraumatic, and usually used with suspected infectious, inflammatory, and endocrine dermatoses. Disposable biopsy punches are readily available in 4, 6, and 8 mm diameter sizes (8 mm punches are routinely used). However, in small dogs and cats, 6 mm punches may be used (4 mm punches are reserved for biopsies of footpads, nasal planum, mucocutaneous junctions, or eyelids).

Punch Biopsy Sampling

The clinician should hold the punch at a vertical angle to the surface of the skin, firmly brace the surrounding skin, and rotate the punch in one direction with continuous pressure.

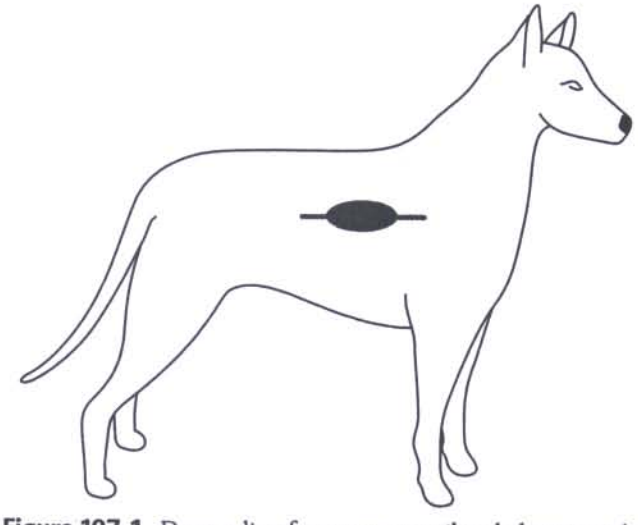

Figure 107-1 Draw a line from nose to tail to help orient the laboratory technician. This technique has revolutionized the interpretation of follicular pathology. The clinician should not draw over fragile lesions like pustules, which may rupture with pressure.

When the skin no longer tries to "turn" with the rotation of the punch, a sufficient depth has been reached to free the dermis from its underlying attachment. The punch is then removed, and any blood is carefully blotted. The tissue is gently grasped at the base—which should be the panniculus—and the subcutaneous attachments severed. Fine instruments (e.g., iris scissors, forceps) should be used. Under no circumstances should the dermis or epidermis be grasped with forceps because this leads to "crush artifact." Crushed tissue may be misinterpreted as scarring at best; at worst it renders the sample worthless. The specimen should be placed in formalin immediately.

Note: The punch technique is not suitable for biopsy of the skin when lesions of the panniculus or deep dermis are suspected.

The wedge biopsy is used as an excisional technique when removing solitary nodules and fragile lesions such as vesicles or as an incisional technique when complete excision is not possible or desirable. Biopsies of deeper tissues such as in suspected cases of panniculitis cannot be adequately taken using a punch and must be taken with a wedge technique. Finally, when an area of skin exhibits a range of changes radiating from the center to the edge of a lesion, a wedge may be preferable—a punch should not be used in the margin of a lesion (Figure 107-2). Ulcers are best sampled with a wedge biopsy extending from the center of the ulcer to adjacent normal tissue.

Excisional and Incisional Sampling

Tissue is surgically excised and closed routinely. The tissue is rolled on gauze to gently blot the blood from its surface. The clinician should use a minimum volume of formalin of (approximately) ten times the volume of the sample. Nodules should be sectioned into 1 cm thick pieces to allow adequate penetration of the formalin into the center of the lesion. They should not be sectioned through completely but should be left attached at the base (fat tissue side), so they are held together in the original piece. Cytology from the impression of the freshly excised surface is a valuable adjunctive test.

When Should a Skin Biopsy Be Performed?

A skin biopsy should be performed for the following reasons:

- When lesions appear unusual to the clinician
- When lesions fail to respond to empiric therapy
- When nodular lesions are present
- When neoplasia is a differential diagnosis

Interpretation—Brief Comments

One of the major reasons to perform a skin biopsy is to rule out other diagnoses. "I think this is an allergy but..." In this

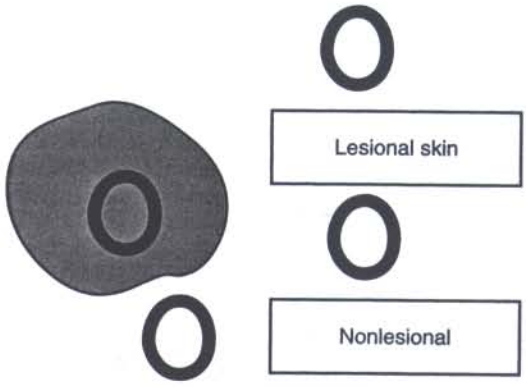

Figure 107-2 Rule of thumb: The clinician should include 100% lesional or nonlesional skin when sampling with a punch biopsy.

situation the biopsy report of "chronic hyperplastic dermatitis with mononuclear perivascular infiltrate," although not confirming allergy, has at least ruled out the common infectious agents and unusual dermatoses. A supportive pathologic diagnosis interpreted in conjunction with the clinical impressions may be just as useful as a confirmatory diagnosis.

The skin has only a limited number of ways to react to the infections, parasites, and allergens. Therefore many conditions share the same microscopic changes. Most dermatoses are diagnosed using a combination of the signalment, clinical presentation (distribution, type of lesions), history (in particular previous response to therapy), and *supportive* histopathologic changes.

Differential Diagnosis List and Submission of Biopsy Samples

A differential diagnosis list is important to any clinical case, but it is essential in dermatology. If the list of clinical differentials fails to correlate with the histopathology, a further review of the sections is undertaken. If the submission clearly states that a deep infectious process is suspected, then special stains may be done to rule out infectious organisms. If an immune-mediated dermatosis is the major differential diagnosis and convincing supportive evidence is not seen on the first section, then recuts may reveal this. When the pathologist is supplied with sufficient clinical information, he or she will likely initiate further examinations (rather than waiting until prompted by a phone call).

To obtain a better skin biopsy result, the clinician should:

1. Not prepare the skin surface.
2. Thoroughly look for a representative range of lesions.
3. Select multiple samples (six is a good rule of thumb) that represent the range of lesions from normal to most severely affected.
4. If possible, include a normal sample collected from haired skin of the dorsum or flank, not the ventrum.
5. Draw an orientation line in the direction from the nose to the tail tip.
6. Use 6 to 8 mm punches or an excisional biopsy except on noses and paws.
7. Handle the biopsy specimen carefully; treat it like tissue paper even when excising.
8. Give the pathologist a complete history, signalment, and physical-findings report, with a list of at least 4 differential diagnoses.
9. Choose a pathologist with an active interest in dermatopathology or a dermatologist with advanced dermatopathology training.

CHAPTER 108

Inhalation Therapy for Airway Disease

Patricia M. Dowling

The latest approach to the management of inflammatory airway disease is inhalation therapy using metered dose inhalers (MDIs). With inhalation therapy, high drug concentrations are delivered directly to the lungs and systemic side effects are avoided or minimized. The onset of action for inhaled bronchodilators and anti-inflammatory drugs is substantially shorter than for oral or parenteral formulations. Nebulizers have been used for a long time in veterinary patients, but the overall efficiency of drug delivery is low, and the equipment is cumbersome and inconvenient for owners. Administration of medications with an MDI is now commonplace in the treatment of human asthma and appears beneficial in the management of veterinary patients as well.

Human MDIs are designed for actuation during a slow, deep inhalation for optimal lung delivery. This is obviously impossible to control in infants and animals. The addition of a spacer enables the MDI to be used in young children and small animals. Spacers decrease the amount of drug deposited in the oropharynx (up to 80% of the actuated dose with the MDI alone), thereby substantially reducing systemic drug absorption and other potential side effects, such as yeast overgrowth (thrush), coughing, and dysphonia.

The drugs currently available in MDI formulations include $beta_2$ agonists, glucocorticoids, ipratropium bromide, cromolyn sodium, and nedocromil. Each product delivers a set amount of drug per actuation (puff). In the United States, MDIs are labeled according to the amount of drug delivered at the mouthpiece, whereas in Canada and the European Union, they are labeled according to the amount of drug delivered from the valve. The U.S. system is used in this chapter.

For client convenience, MDIs are color coded to aid identification. (For a pictorial guide to MDIs, see the website www.peds.arizona.edu/allergyimmunology/southwest/devices/inhalers-asthma/mdikeyhtml.htm.) Even in human medicine, the relative potencies, risks of adverse effects, and optimal dose of the different inhaled asthma medications are still unclear. The results of clinical use in asthmatic cats and dogs with chronic bronchitis have been promising but anecdotal, and clinical trials are needed to determine the most efficacious therapies.

$BETA_2$ AGONISTS

Albuterol

Albuterol is available in the United States under the trade names Ventolin (GlaxoSmithKline, Research Triangle Park, North Carolina) and Proventil (Schering Corp., Kenilworth, New Jersey). It is marketed as salbutamol in Canada and the European Union. Albuterol is a short-acting $beta_2$ agonist that is the medication of choice for treating acute exacerbations of bronchoconstriction. It relaxes smooth muscle and increases airflow within 5 minutes of administration. Albuterol's effects last 3 to 6 hours. Although effective for symptomatic relief of bronchoconstriction, albuterol does not control inflammation. Monotherapy may exacerbate airway disease and increases morbidity and mortality in human asthmatics. Tolerance may

develop with chronic therapy from down-regulation of $beta_2$ receptors. The Proventil MDI is dark blue, and the Proventil MDI is light orange. Each actuation delivers 90 µg of albuterol.

Salmeterol

Salmeterol (Serevent [GlaxoSmithKline]) is a long-acting $beta_2$ agonist. Its onset of action is slow (15 to 30 minutes), but its duration of action is long (over 12 hours). It is not recommended for use in acute bronchoconstriction, but it improves symptom control when used daily in addition to glucocorticoids, more than would simply increasing the glucocorticoid dose. The salmeterol MDI is green, and each actuation delivers 21 µg.

Glucocorticoids

Inhaled glucocorticoids are the most potent inhaled anti-inflammatory drugs currently available. In human beings, early intervention with inhaled glucocorticoids improves asthma control and normalizes lung function and may prevent irreversible airway damage. Improvement after inhaled administration of glucocorticoids can occur within 24 hours of beginning treatment, although maximum benefit may not be achieved for 1 to 2 weeks or longer after starting treatment. When glucocorticoids are discontinued, asthma stability may persist for several days or longer. The potential risk of adverse side effects of glucocorticoids is well balanced by their efficacy in chronic management of inflammation. Oral candidiasis (thrush), dysphonia, and reflex cough and bronchospasm are the most common adverse effects in humans; all of these effects are reduced by the use of a spacer. The risks of systemic side effects, such as suppression of the hypothalamic-pituitary axis, are less than with oral prednisone or prednisolone therapy. Inhaled glucocorticoid formulations include fluticasone (Flovent [GlaxoSmithKline]); beclomethasone (Beclovent [GlaxoSmithKline] and Vanceril [Schering Corp.]); budesonide (Pulmicort [AstraZeneca, Wilmington, Delaware]); and Proventil [Schering Corp.]); and triamcinolone (Azmacort [Aventis Pharmaceuticals, Bridgewater, New Jersey]). Currently, fluticasone is considered the most potent glucocorticoid formulation with the longest duration of action. Because of its large molecular size, systemic absorption is minimal. Fluticasone MDIs are orange. Fluticasone is available in three sizes; each actuation delivers 44, 110, or 220 µg.

ANTICHOLINERGIC DRUGS

Ipratropium bromide (Atrovent [Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut]) is a quaternary derivative of atropine that lacks its adverse side effects. In asthmatic humans, ipratropium bromide is used as an additional reliever medication to reverse bronchoconstriction when inhaled short-acting $beta_2$ agonists do not give enough relief. Its anticholinergic action also decreases mucous secretions. In an experimental model of feline asthma, long-term antigen sensitization caused an augmented muscarinic receptor response to acetylcholine. Modulation of muscarinic receptors with anticholinergic drugs may be useful for treatment of asthmatic cats. Currently, there are no published reports of the use of ipratropium in the cat; however the drug has shown efficacy in horses. It is not well absorbed after inhalation and therefore does not cause systemic cholinergic effects. The Atrovent MDI is encased in a clear holder with a white mouthpiece and green cap; it delivers 18 µg per actuation.

MAST CELL STABILIZERS

Cromolyn sodium (Intal [Aventis Pharmaceuticals]) and nedocromil sodium (Tilade [Aventis Pharmaceuticals]) are chloride channel blockers that modulate mast cell mediator release and eosinophil recruitment. Cromolyn and nedocromil both have strong human safety profiles, but nedocromil has a broader spectrum of efficacy. In human beings, the clinical response to either of these drugs is less predictable than the response to glucocorticoids, therefore cromolyn and nedocromil are usually used as adjunctive therapy to treatment with bronchodilators and glucocorticoids. Currently, there are no published reports of the use of cromolyn or nedocromil in asthmatic cats or dogs with bronchitis; however, pretreatment with nedocromil aerosols attenuated viral-induced airway inflammation in beagle puppies. Because of the sensitivity of the cat to serotonin released from degranulating mast cells, these drugs should be further investigated in asthmatic cats. The cromolyn MDI is white and delivers 800 µg per actuation. The nedocromil MDI is also white and delivers 1.75 mg per actuation.

SPACERS

Human MDIs (OptiChamber [Respironics HealthScan Asthma and Allergy Products, Cedar Grove, New Jersey] and Aerochamber [Forest Pharmaceuticals]) may be modified for use in dogs and cats. Also, recently a small animal–specific spacer has become available (AeroKat [Trudell Medical International, London, Ontario, Canada]). The OptiChamber must be modified with a suitable face mask, such as the type used to "mask" cats for anesthesia. The Aerochamber is available with a variety of face masks intended for infants, children, and adults that will conform to a variety of veterinary patients. The Aerochamber is color coded according to the type of face mask (orange for infants, yellow for children, blue for adults). Both the OptiChamber and the Aerochamber are equipped with one-way valve leaflets that allow the owner to actuate the inhaler away from the cat or dog and then apply the spacer. The AeroKat spacer is valveless, therefore actuation must occur with the mask applied. The device fits cats and most small dogs. Human spacers can be purchased at most pharmacies.

TECHNIQUE FOR USING MDIs AND SPACERS IN DOGS AND CATS

The steps for using the MDI are as follows:

1. Prime the MDI prior to first use or if it has not been used recently, because the initial actuation contains higher drug concentrations than subsequent actuations.
2. Immediately before each use, shake the inhaler.
3. Remove the cap from the mouthpiece and insert the mouthpiece into the spacer.
4. Keep track of the number of actuations administered. Some manufacturers include a "check off" list in the patient directions. For daily maintenance medications, divide the number of actuations per canister (printed on the canister) by the number of puffs to be taken each day to calculate how many days the device will last and when the MDI should be replaced. The widely used method of immersing the inhaler in water to see if it floats is inaccurate. Discard the canister after the labeled number of actuations.
5. If using the AeroKat spacer, position the inhaler over the animal's face prior to actuation. If using a valved MDI, the device can be actuated before placing the mask on the animal's face (Figure 108-1).
6. Press down firmly and fully on the top of the metal canister with the index finger. Hold the mask in place over the animal's face for 5 to 10 seconds. Wait 30 to 60 seconds and then shake the inhaler again. Repeat these steps for each inhalation as prescribed by the veterinarian.

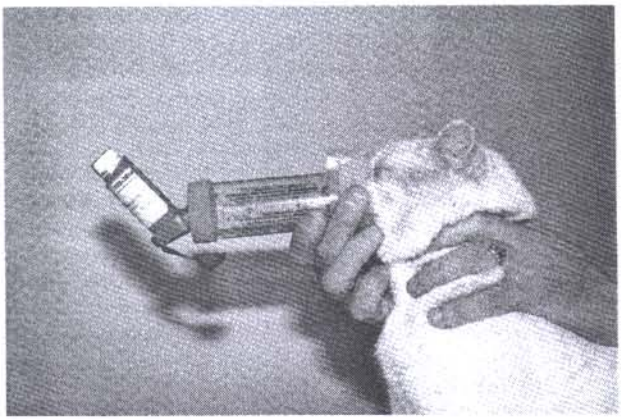

Figure 108-1 Albuterol MDI can be actuated into the Aerochamber prior to placing the mask over a cat's nose and mouth.

NOTE: When a $beta_2$ agonist is used in conjunction with a glucocorticoid or anticholinergic drug, it should be administered 5 minutes before the glucocorticoid or anticholinergic drug. The resulting bronchodilation results in increased deposition of the glucocorticoid or anticholinergic drug in the smaller airways.

7. Replace the mouthpiece cap after each use and make sure to clean the inhaler thoroughly and frequently. Remove the metal canister and clean the plastic case and cap by rinsing thoroughly in warm, running water at least once a day. (Do not immerse metal canisters containing cromolyn or nedocromil.) After thoroughly drying the plastic case and cap, gently replace the canister in the case with a twisting motion and replace the cap.
8. The manufacturer's recommendations for care of the spacer should be followed. Typically, the spacer only needs to be soaked weekly in a diluted dishwashing solution and air dried. It is not necessary to rinse the device, because the soap helps disperse aerosol particles that come in contact with the spacer's surface.

SUGGESTED TREATMENT REGIMENS

Dyspnea

For emergency management of dyspnea, two to four puffs of albuterol should be given every 20 minutes until clinical signs resolve. Additional therapy may include oxygen administration and an intravenous dose of a rapid-acting glucocorticoid.

Feline Asthma and Chronic Canine Bronchitis

The current recommended chronic therapy for feline asthma and chronic canine bronchitis is salmeterol, the long-acting bronchodilator, at a dosage of one puff (21 µg) twice a day and 220 µg of fluticasone twice a day. For initial therapy of moderately affected animals, a 5-day course of oral prednisone (1 mg/kg) may be helpful. Severely affected animals may require 1 mg/kg of prednisone every other day. Adjunctive therapy with ipratropium or nedocromil or cromolyn may be useful in some patients. Therapy must be individualized for the patient.

SECTION IV

Critical Care

CHAPTER 109

Acid-Base, Oximetry, and Blood Gas Emergencies

Marie E. Kerl

Acid-base and oxygenation disorders occur commonly in emergency and critical care medicine as a response to respiratory or metabolic abnormality from trauma, intoxication, or naturally occurring disease. Technologic advances in point of care testing have made laboratory assessment of these disorders accurate, practical, and affordable in the veterinary emergency setting. A working knowledge of acid-base and respiratory physiology and pathophysiology, as well as appropriate therapies, is imperative for achieving successful patient outcomes.

Testing of blood gas samples may be performed with arterial or venous blood. Arterial blood must be used to assess oxygenation. Acid-base parameters other than partial pressure of oxygen (PO_2) may be evaluated using either arterial or mixed venous samples. In most emergent patients, venous blood is easier to obtain. Samples should be drawn into syringes that are coated with 1:1000 heparin to prevent clot formation. Immediately after sample acquisition, the syringe should be made airtight to prevent contamination with room air, which could alter gas measurements. The sample should be analyzed within 15 minutes or placed on ice.

BASIC ACID-BASE PHYSIOLOGY

The following is a brief description of traditional acid-base physiology; in-depth discussion is beyond the scope of this publication. For further information, the reader is referred to the Suggested Readings.

An *acid* is a hydrogen ion (H^+) (i.e., proton) donor, and a *base* is a proton acceptor. Acids typically are represented by the notation HA, which signifies a hydrogen ion and any negatively charged particle. When placed in solution, HA dissociates into H^+ (acid) and A^- (base). Hydrogen ions are nonvolatile or fixed acids produced by normal metabolism of proteins and phospholipids and are renally excreted. A base combines with an acid to lower the amount of acid in solution, or to buffer the solution.

Carbon dioxide (CO_2) is a volatile acid, or fat-soluble gas, that can combine with water in the presence of carbonic anhydrase to form carbonic acid (H_2CO_3). Carbon dioxide is formed during normal carbohydrate and fat metabolism and is excreted via the respiratory system. These two sources of acid (H^+ and CO_2) are interrelated, as is shown in the carbonic acid equation:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2$$

This equation can go either direction, depending on the availability of substrate on either side of the formula. The enzyme carbonic anhydrase catalyzes this reaction, and any cell containing carbonic anhydrase is capable of this reaction.

By definition, *pH* is the negative log of the hydrogen ion concentration. A gain of H^+, or acid gain, results in a decrease in blood pH (acidemia), whereas a loss of H^+ results in an increased pH (alkalemia). Acid can be gained systemically from abnormal renal elimination of a naturally occurring compound or from ingestion of an exogenous acid source. Changes in CO_2 influence the H^+ concentration, as evidenced by the carbonic acid equation. As CO_2 is eliminated by increasing alveolar ventilation, carbonic acid dissociates to form more CO_2, and H^+ and bicarbonate (HCO_3^-) combine in turn to form carbonic acid. This effectively lowers the H^+ concentration and increases pH. Conversely, as CO_2 increases from ventilation impairment, pH decreases.

Buffers act to bind H^+ to prevent large fluctuations in pH. A variety of buffer systems exist in the body, including nonbicarbonate buffers (proteins and phosphates), which are primarily intracellular, and HCO_3^-, which is the primary extracellular buffer. Bicarbonate is an effective buffer system because it exists in relatively large concentrations compared with other buffers, and it participates in the carbonic acid formula to produce CO_2 gas, which can be eliminated through ventilation. The HCO_3^- buffer system, therefore, is considered an *open system*, which can continue to buffer as long as the respiratory system is functional. When HCO_3^- is lost excessively from the urinary or gastrointestinal system, CO_2 and H_2O combine to form carbonic acid, which dissociates to increase H^+ and cause acidemia.

ACID-BASE DISORDERS

According to the Henderson-Hasselbalch equation, which is

$$pH = 6.1 + \log \{HCO_3^-/0.03PCO_2\}$$

pH can be characterized by changes in HCO_3^- and partial pressure of carbon dioxide (PCO_2). Because a predictable change in HCO_3^- occurs with gain or loss of H^+ ions, HCO_3^- can be used to correctly identify acid base abnormalities arising from metabolic disorders. Acidemia or alkalemia resulting from a respiratory disorder should show an increase or a decrease in PCO_2. Respiratory acidosis results in an increase in PCO_2, and respiratory alkalosis causes a decrease in PCO_2. In metabolic acidosis, an H^+ increase shifts the carbonic acid equation to cause a decrease in HCO_3^-; and in metabolic alkalosis, an H^+ decrease has the opposite effect on HCO_3^-. Blood gas analyzers typically measure pH and PCO_2 and calculate HCO_3^-.

This equation can also be used to predict how compensatory mechanisms engage to reduce the degree of change in the pH. When metabolic acidosis develops, the respiratory system is stimulated to increase the respiratory rate to eliminate CO_2 from the lungs and create respiratory alkalosis. Likewise, with a primary respiratory disorder, the opposite metabolic disorder is generated. The respiratory system provides rapid compensation, changing within minutes of onset of a metabolic disorder. Metabolic compensation occurs more slowly, becoming maximally effective in days. With either system, compensatory mechanisms should slow down as the pH improves, and compensation should never completely normalize the pH.

Base excess, which is expressed in milliequivalents per liter (mEq/L), is a value in which the amount of base above or below the normal buffer base is calculated, taking into account the expected change in HCO_3^- secondary to acute changes in PCO_2. The general rule of thumb is that the

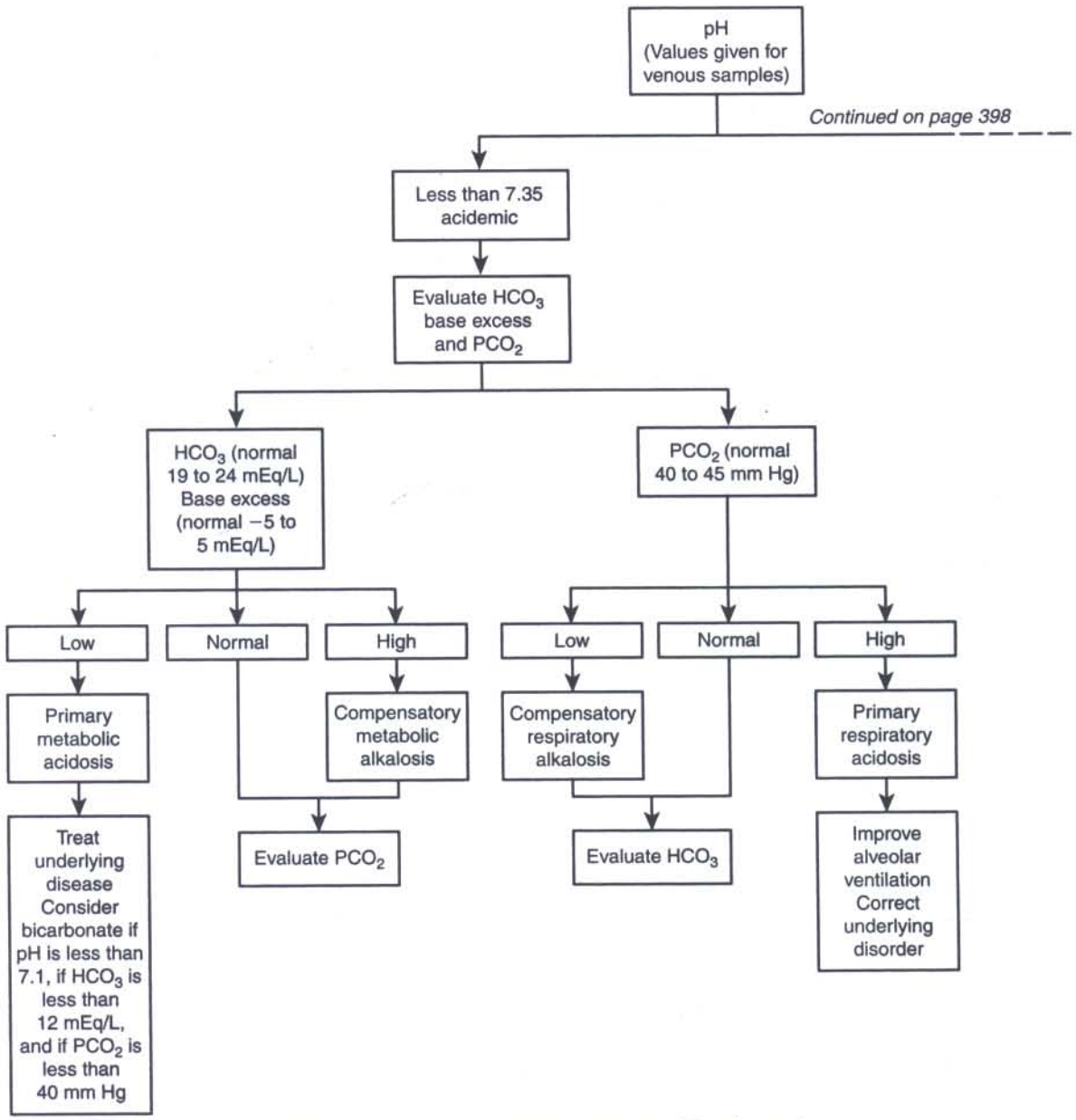

Figure 109-1 Algorithm for interpretation of blood gas values.

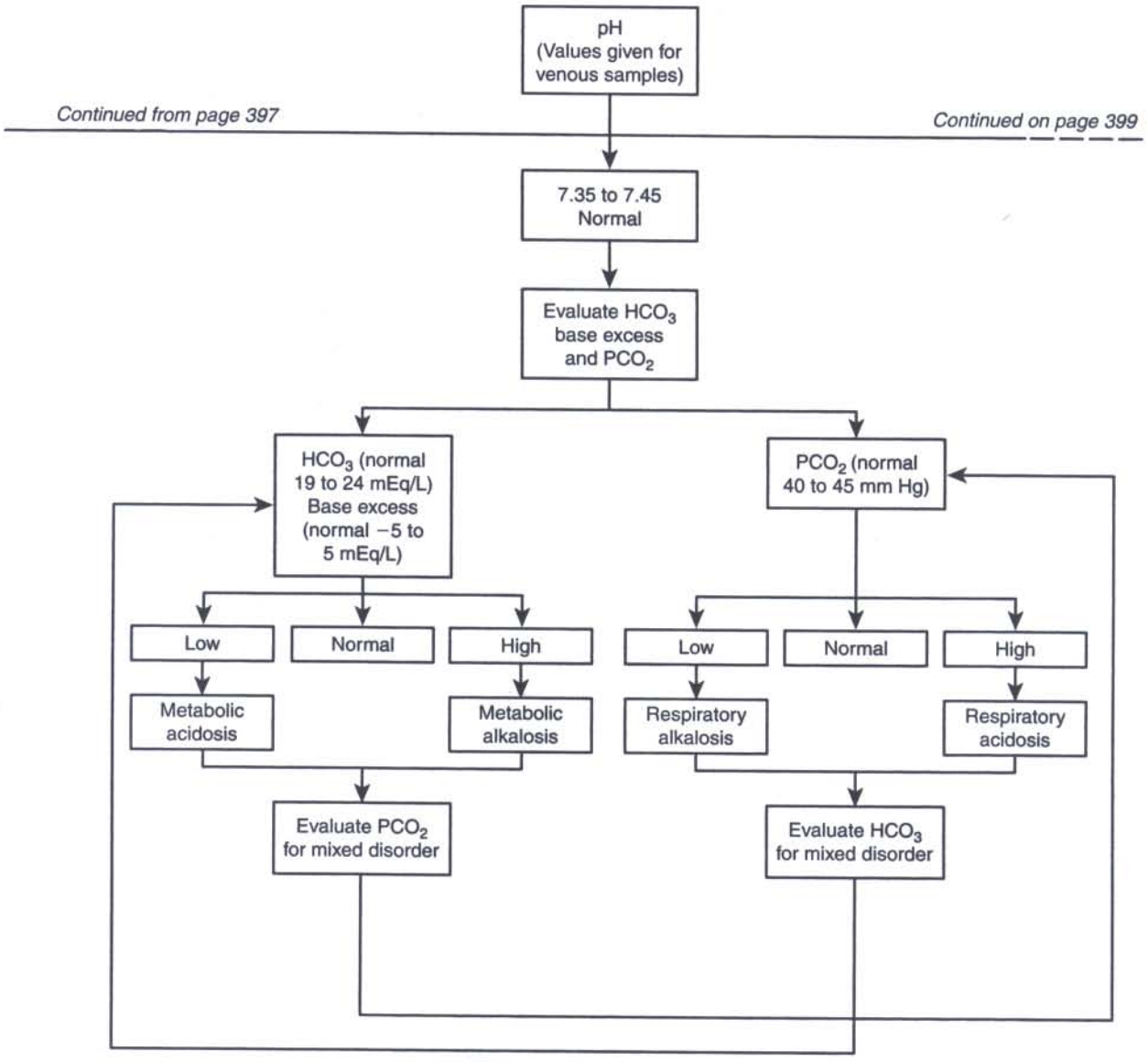

Figure 109-1 Cont'd

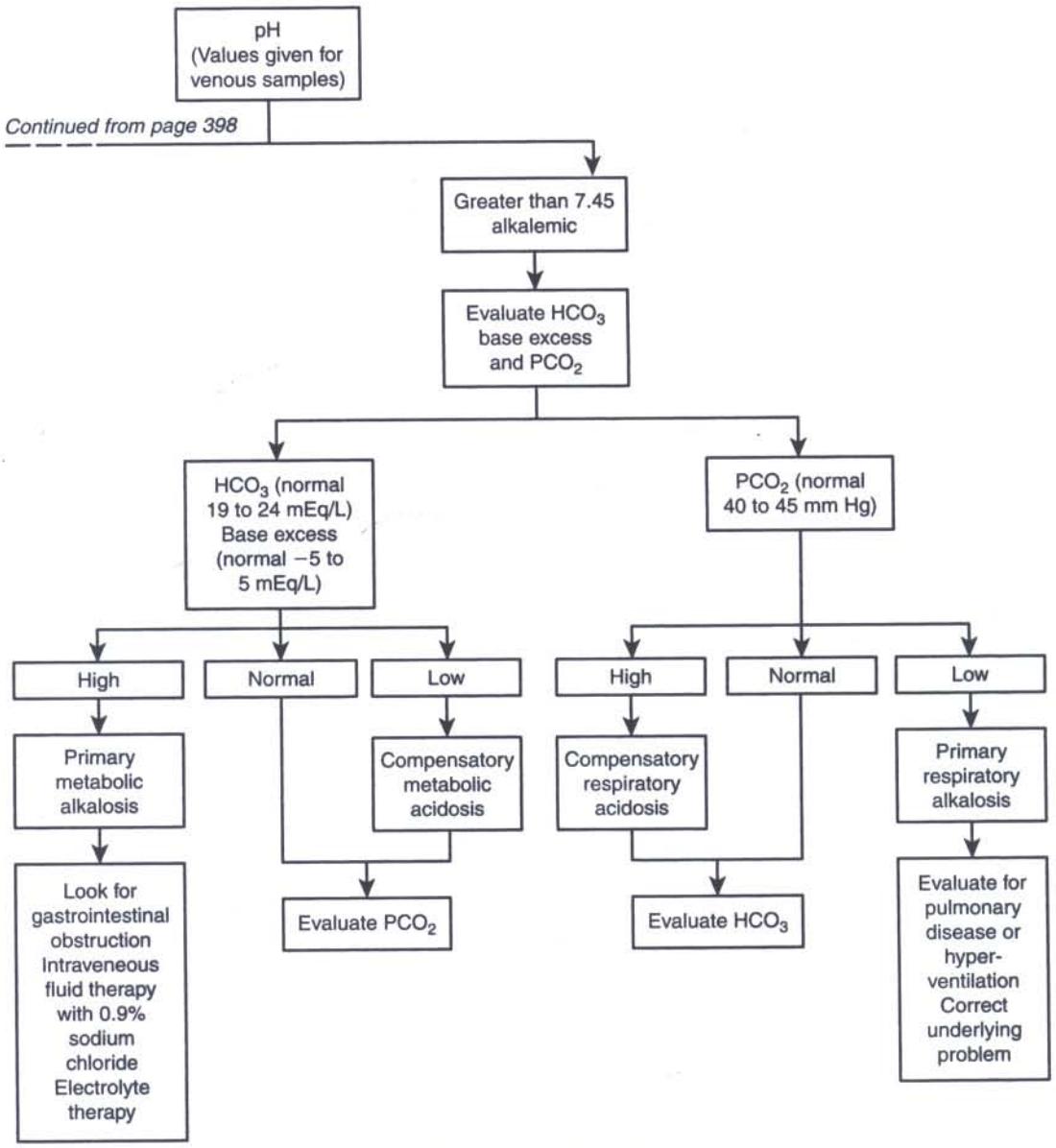

Figure 109-1 Cont'd

HCO_3^- concentration rises about 1 to 2 mEq/L for each acute 10 mm Hg increase in $PaCO_2$ above 40 to a maximum increase of 4 mEq/L, and that the HCO_3^- concentration falls 1 to 2 mEq for each acute 10 mm Hg decrease in $PaCO_2$ below 40, to a maximum decrease of 6 mEq/L. Some authors refer to a negative base excess as a base deficit.

By convention, a simple acid-base disorder is limited to the primary disorder and the appropriate compensatory response. A mixed disorder is one in which at least two separate abnormalities occur simultaneously. Normal values at sea level for venous blood gas interpretation are pH, 7.35 to 7.45; PCO_2, 40 to 45 mm Hg; and HCO_3^-, 19 to 24 mEq/L. Base excess normally should be –5 to 5 mEq/L.

Respiratory acidosis results from an increase of CO_2 in the blood (hypercapnia). Hypercapnia can be caused by anything that prevents normal gas exchange in the lungs, including impaired pulmonary circulation, reduced respiratory rate, circulation of blood to nonventilated portions of the lung, or impairment of gas diffusion. Diffusion impairment is the least likely cause of hypercapnia, because CO_2 is approximately 20 times more diffusible than oxygen. Disorders in which respiratory acidosis occurs include circulatory failure from cardiopulmonary arrest, central nervous system disease, respiratory muscle failure, physical impairment of ventilation (e.g., pleural space disease, pain, thoracic wall disease, external constriction), or primary pulmonary disease (e.g., alveolar flooding, interstitial disease, pulmonary thromboembolism). Iatrogenic respiratory acidosis results from inadequate ventilatory monitoring and assistance under general anesthesia. Clinical signs of hypercapnia are consistent with the underlying disorder. Situations that might cause respiratory acidosis must be anticipated and diagnosed with appropriate monitoring.

Treatment for respiratory acidosis involves correcting the underlying disorder by increasing alveolar ventilation. Chronic respiratory acidosis should be corrected slowly. Sodium bicarbonate should not be administered, because this drug exacerbates hypercapnia. Increasing the inspired oxygen concentration may be lifesaving; however, with severe hypercapnia, stimulation for respiration becomes driven by hypoxia. Resolution of the hypoxia may result in decreased voluntary respiration. The hypoxic drive for respiration remains adequate below a dissolved oxygen content of arterial blood (PaO_2) of 60 mm Hg.

Respiratory alkalosis results from an increase in the ventilatory rate, resulting in elimination of more CO_2 than is produced by normal metabolic function. Hypocapnia develops, and alkalemia ensues. Causes of respiratory alkalosis include hypoxemia caused by pulmonary or circulatory abnormalities, primary pulmonary diseases that stimulate ventilation independent of hypercarbia, central nervous system disorders, and iatrogenic tachypnea with assisted ventilation. Most disorders of respiratory alkalosis result in hyperventilation. Chronic respiratory alkalosis is usually well compensated

Treatment for respiratory alkalosis should be directed at normalizing the underlying disorder. Clinical signs are minimal, and no other therapy should be needed if the first treatment goal can be achieved.

Metabolic acidosis results most commonly from a gain of H^+ through ingestion of an acid into the body, increased production of an endogenous acid, or failure of elimination of an acid load at the renal tubular cells. Metabolic acidosis can also be caused by a loss of HCO_3^- buffering ability. Differentiating these two types of metabolic acidosis can assist diagnosis of the underlying cause.

When acid accumulates in the circulation, H^+ combines with HCO_3^- to buffer the acid load. When the acid dissociates, the anion remains in solution. Because electroneutrality must be maintained, another anion in circulation must decrease correspondingly. Anion gap (AG) is a formula that was created to classify disorders that cause metabolic acidosis. Anion gap, which is calculated from four common cations and anions from a serum chemistry profile, states:

$$AG = [Na^+ + K^+] - [Cl^- + HCO_3^-]$$

In normal animals, AG is 16 ± 4. Elevated anion gap metabolic acidosis is caused by a gain of acid, whereas normal anion gap metabolic acidosis (hyperchloremic metabolic acidosis) is caused by loss of bicarbonate buffers or a failure to excrete H^+ ions, with a corresponding increase in chloride to maintain electroneutrality. Causes of anion gap metabolic acidosis include ethylene glycol intoxication, uremia, tissue hypoxia, diabetic ketoacidosis, salicylate intoxication, and other unusual intoxications (e.g., drugs, alcohol). Hyperchloremic metabolic acidosis is less common and is caused by renal tubular acidosis (failure of the renal bicarbonate buffer system) or by severe diarrhea and loss of intestinal bicarbonate, or it occurs iatrogenically after administration of an alkali-free chloride containing solution for intravenous volume replacement.

Clinical signs associated with metabolic acidosis include lethargy, decreased cardiac output, decreased blood pressure, and decreased hepatic and renal blood flow. These signs may be referable to the acidemia or to the underlying cause of the acid-base disorder. Compensatory mechanisms would cause an increase in the respiratory rate to eliminate CO_2 generated by carbonic acid formation.

Treatment should be aimed at correcting the underlying disorder by improving tissue perfusion with intravenous fluid therapy; eliminating ingested toxin; and correcting metabolic, renal, or gastrointestinal disease. With severe metabolic acidosis (pH of 7.1 and HCO_3^- <12 mEq/L), sodium bicarbonate may be administered judiciously according to the following formula:

$$\text{Bicarbonate dose} = (0.3)(\text{Body weight [kg]})(\text{Base deficit})$$

Half of this dose should be administered slowly intravenously over 6 hours, and the acid-base status should be re-evaluated prior to continuation of therapy. Chronic metabolic acidosis should be corrected slowly to avoid undesired side effects, including hyperosmolality, hypernatremia, hypokalemia, hypocalcemic tetany from a shift of calcium from the ionized to the protein-bound form, and iatrogenic metabolic alkalosis.

Metabolic alkalosis is generated by loss of chloride in excess of extracellular fluid volume, which occurs as a result of upper gastrointestinal (GI) fluid loss or sequestration or of administration of a thiazide diuretic, causing chloride wasting. Rarely, metabolic alkalosis may be caused by overzealous administration of sodium bicarbonate or another organic anion or by hyperaldosteronism, causing sodium retention in excess of chloride. The most commonly associated clinical disease in small animal practice is gastric obstruction, with loss of chloride-containing gastric fluid. Renal compensation prevents an acid-base disorder until hypovolemia causes aldosterone release. Aldosterone increases renal uptake of sodium. During normal renal function, sodium is reabsorbed with bicarbonate or chloride or is exchanged for potassium. Gastric fluid has high chloride and potassium concentrations, and when these are depleted, sodium can be reabsorbed only with bicarbonate.

Clinical signs associated with metabolic alkalosis depend on the predisposing disorder. Muscle twitching and seizures have been reported. Signs associated with concurrent potassium depletion may include weakness, cardiac arrhythmias, renal dysfunction, and gastrointestinal motility disturbances.

Treatment of metabolic alkalosis is directed at resolving the predisposing disorder. Intravenous 0.9% sodium chloride (0.9% NaCl) should be initiated to restore intravenous volume. Fluids should not contain buffer. If vomiting is the underlying cause, use of drug therapy to minimize gastric hydrochloric acid (HCl) excretion may be warranted. Intravenous potassium therapy should be used to treat the hypokalemia frequently encountered with metabolic alkalosis.

OXYGENATION

Hypoxemia may be seen as a result of a low concentration of inspired oxygen, hypoventilation, diffusion impairment, dead space ventilation, or pulmonary shunting. Two methods are available to assess oxygenation in the emergency setting: measurement of PaO_2 and measurement of peripheral oxygen saturation (SpO_2) by pulse oximetry. A pulse oximeter is a noninvasive device that calculates hemoglobin oxygen saturation by measuring differences in absorption of two wavelengths of light (red and infrared) by oxygenated and deoxygenated hemoglobin. The measured light absorption values are applied to a preset nomogram, and a value for SpO_2 is determined. If tissue perfusion is adequate, SpO_2 approximates arterial hemoglobin saturation (SaO_2).

The advantage of oximetry as a monitoring tool is that it provides continuous, noninvasive determination of hemoglobin oxygen saturation. Technical aspects that help ensure accuracy include placing the probe on nonpigmented, moist skin with adequate perfusion (usually the tongue, the buccal, vaginal, or preputial mucosa, or the ear pinna), avoiding probe movement and light pollution, and monitoring the pulse rate to ensure accurate pulse signal transmittance. In poorly perfused tissues, the SpO_2 may be falsely low compared with the SaO_2. If inaccuracy of oximetry is suspected, the arterial blood gas PaO_2 may be obtained to evaluate oxygenation. In patients with alterations of hemoglobin concentration causing increased carboxyhemoglobin or methemoglobin, oximetry may be normal despite severe patient abnormality. Oximetry does not evaluate the PCO_2 and cannot be used to determine appropriate ventilation.

The hemoglobin saturation of oxygen and PaO_2 both contribute to arterial oxygen content (CaO_2) according to the following formula:

$$CaO_2\ (mL\ O_2/dL) = \{SaO_2\ (\%) \times Hemoglobin\ (g/dL) \times 1.34\ (mL\ O_2/g)\} + \{PaO_2\ (mm\ Hg) \times 0.003\ (mL\ O_2/dL/mm\ Hg)\}$$

Increasing the PaO_2 by increasing the inspired oxygen concentration has a minimal effect, whereas increasing the SaO_2 has a greater potential effect. In an anemic patient, increasing the arterial oxygen content would best be accomplished by increasing hemoglobin.

By the oxyhemoglobin dissociation curve, an SaO_2 of 90% corresponds to a PaO_2 of 60 mm Hg. This value is clinically important in that precipitous declines occur below these values, and small decreases in either parameter may have tremendous clinical consequences. The goal of treatment for hypoxemia is to maintain the SpO_2 above 90% through supplemental oxygen therapy. Methods of increasing the inspired oxygen content include use of an oxygen chamber, tent or mask administration, placement of an indwelling nasal oxygen catheter, or mechanical ventilation with an increased fraction of inspired oxygen.

CHAPTER 110

Acute Abdomen

Dez Hughes

The term *acute abdomen* is often used to refer to animals that have a rapid onset of abdominal pain; however, not all life-threatening intra-abdominal problems are painful. Furthermore, depressed mentation, including chemical sedation, may reduce response to painful stimuli. A more encompassing definition for the acute abdomen is any situation involving an acute onset of clinical signs referable to intra-abdominal pathology. Because this is a potentially life-threatening clinical syndrome rather than a definitive diagnosis, the underlying cause must be rapidly identified. Many causes (Box 110-1) require emergency surgery, and these animals must be promptly identified to allow definitive treatment to optimize the chances of survival. Because acute abdomen has so many potential causes, it is important to prioritize the list of diagnostic differentials based on pertinent findings from the history, physical examination, and initial diagnostic testing. Diagnosis and successful treatment of the dog or cat with an acute abdomen is one of the greatest challenges in emergency and critical care.

SIGNALMENT AND HISTORY

A full history should be obtained for all animals suspected of having an acute abdomen; however, with critically ill patients, this may have to be delayed to allow initial evaluation and stabilization. The history may occasionally be extremely suggestive of the underlying cause; for example, bitches with dystocia, witnessed ingestion of a foreign body, or protracted dysuria and pollakiuria with urethral obstruction. More commonly, however, the owner reports vague, nonspecific signs such depression, anorexia, lethargy, vomiting, and diarrhea. The only premonitory sign in some severe cases is acute collapse. Most dogs with a complete intestinal obstruction or pancreatitis exhibit profuse and frequent vomiting; however, diarrhea may or may not be present, and the severity of clinical signs can vary. Any sick, intact female should be evaluated for pyometra, regardless of whether the classic signs of anorexia, lethargy, vomiting, polyuria, polydipsia, and vaginal discharge are present. Any older intact male with hypoperfusion or caudal abdominal pain could have prostate gland disease. Dogs with prostatic disease may also exhibit hindlimb stiffness or an abnormal hindlimb gait, in addition to hematuria, pollakiuria, or dyschezia. A history of trauma raises the possibility of hemoabdomen or rupture of the urinary or biliary tracts. Any prior medical therapy by a veterinarian or by the owner should also be determined. For example, an old dog receiving nonsteroidal anti-inflammatory agents may be at risk of developing gastric ulceration, hemorrhage, or perforation.

Box • 110-1

Causes of Acute Abdomen

Gastrointestinal Tract
Necrosis/rupture/ulceration/perforation
Surgical wound dehiscence
Intestinal obstruction/intussusception
Gastric dilatation ± volvulus
Gastroenteritis (parvoviral; bacterial, toxic, hemorrhagic gastroenteritis [HGE] origin)
Mesenteric torsion
Duodenocolic ligament entrapment
Pancreatitis
Mesenteric thrombosis/embolism
Obstipation
Portal venous thrombosis
Colitis

Urogenital Tract
Pyometra/uterine rupture
Prostatitis/prostatic abscess
Dystocia
Cystic calculi
Urethral obstruction or rupture
Uroabdomen
Pyelonephritis
Renal abscess
Vaginal rupture
Testicular torsion

Hepatobiliary System
Necrotizing cholecystitis
Liver lobe torsion
Hepatic abscess
Bile peritonitis
Acute hepatitis/cholangiohepatitis
Biliary obstruction

Other Causes
Hemoabdomen (usually parenchymatous organ rupture)
Retroperitoneal hemorrhage
Neoplasia
Penetrating wounds/crush injury
Evisceration
Surgical contamination
Strangulated hernia
Splenic torsion
Splenic abscess
Pansteatitis

Conditions That May Mimic Acute Abdomen
Spinal disease with pain
Lead poisoning
Hypoadrenocorticism

Some extra-abdominal conditions may mimic signs of an acute abdomen, the most common being thoracolumbar intervertebral disk disease. Owners occasionally incorrectly assume that their animal has abdominal pain because the pet vocalizes when picked up beneath the abdomen. The clinician must always maintain a high index of suspicion that an acute onset of pain, especially in a chondrodystrophoid breed, may be spinal in origin. Even on physical examination, it can sometimes be difficult to differentiate between spinal and abdominal pain. The veterinarian must take care, especially with smaller animals, to avoid placing the thumbs along the spine when palpating the abdomen.

MAJOR BODY SYSTEM EVALUATION

Major body system evaluation initially is performed to identify and prioritize life-threatening problems of the cardiovascular, respiratory, and neurologic systems. Life-threatening problems should be addressed without delay while performing the initial examination. Hypovolemia may be mild, moderate, or severe. Animals with an inflammatory process and adequate circulating blood volume may demonstrate the classic signs of hyperdynamic systemic inflammatory response syndrome (SIRS), such as injected mucous membranes, strong pulses of short duration, fast capillary refill time (CRT), moderate tachycardia, and pyrexia. With severe hypovolemia, tachycardia is often severe (170 to 200 beats per minute in a dog), femoral pulses are weak, and the CRT is prolonged. Despite severe hypovolemia, dogs with peritonitis can have injected rather than pale mucous membranes, and this discrepancy in clinical perfusion parameters should prompt a search for an underlying cause of SIRS. Although a dog with an acute abdomen may exhibit tachypnea due to pain, animals that have been vomiting should always be evaluated for aspiration pneumonia.

When tympanic gaseous abdominal distension is present in a large breed dog, gastric dilatation and volvulus is the most likely diagnosis. Although pneumoperitoneum can occasionally cause abdominal distension, it is usually not tympanic. Dogs with a large volume of abdominal effusion may have an abdominal fluid "wave." However, smaller amounts of effusion may not be palpable, especially if the dog is recumbent. A fluid wave may also be detectable due to intra-abdominal fat, hepatomegaly, or fluid contained within a tubular viscus. Abdominal distension is not always noticeable in an animal with intra-abdominal fluid. For example, a dog with acute hemoabdomen after being hit by a car would likely be in severe hypovolemic shock before the slightest hint of abdominal distension would be noticed.

Bacterial peritonitis and pancreatitis almost always cause abdominal pain or discomfort in dogs, even in animals with severe hypoperfusion. When an animal in hypovolemic shock is rousable only by abdominal palpation, a diagnosis of peritonitis should be aggressively pursued.

Pyometra is not usually painful, and abdominal pain in conjunction with pyometra raises the likelihood of septic peritonitis. Pain appears to be an inconsistent finding with uroabdomen (acute uroabdomen tends to be more painful than chronic uroabdomen). Significant pain associated with a uroabdomen should prompt evaluation for septic peritonitis.

Occasionally dogs with cranial abdominal pain adopt the "prayer position"; however, this is the exception, not the rule. As a generalization, focal pain other than in the right cranial quadrant, or focal pain associated with the intestines, is often associated with a surgical lesion. The majority of animals with bile peritonitis are icteric unless the biliary tract rupture is recent.

A rectal examination should be performed in all animals with acute abdomen, but especially in older intact male dogs. When prostatomegaly has caused the prostate gland to descend over the pelvic brim, simultaneous abdominal and rectal palpation may be necessary to achieve a complete prostatic examination.

STABILIZATION

In a hemodynamically unstable patient, aggressive intravenous fluid therapy is often necessary. In many animals with peritonitis, especially septic peritonitis, hypoperfusion is due both to maldistribution (abnormally dilated arterioles) and to hypovolemia. Crystalloid infusion rates of 60 to 90 mL/kg/hour in the dog and 40 to 60 mL/kg/hour in the cat are often necessary. It is best to place two intravenous catheters to achieve this rate and to provide an alternative in case one catheter becomes dislodged or blood products are required. Fluid resuscitation with blood products or synthetic colloids (e.g., hydroxyethyl starch or dextran 70) may be more effective in animals with systemic and intra-abdominal vasculitis. Major body systems and perfusion parameters (mucous membrane color, CRT, pulse rate and quality, heart rate, and urine output) should be continually assessed during fluid resuscitation to ensure an appropriate response. Failure to respond adequately to intravenous fluids usually indicates the presence of sepsis or ongoing hemorrhage. In severely affected animals with sepsis, continuous-rate infusions of catecholamines may be required to maintain adequate blood pressure.

Broad-spectrum, bactericidal, intravenous antibiotics should be started as soon as a diagnosis suggests the possibility of leakage or translocation of gastrointestinal bacteria. Antibiotics with activity against gram-positive and gram-negative aerobes and anaerobes should be used. In septic peritonitis, intravenous administration has shown a trend toward improved survival compared with intramuscular or intraperitoneal routes. The most frequent isolates from cases of bacterial peritonitis are *Escherichia coli*, clostridia, and enterococci. Appropriate antibiotic combinations for these bacteria include ampicillin combined with cefoxitin, enrofloxacin, or amikacin; however, the use of amikacin often is contraindicated in animals with hypovolemia, dehydration, and pyrexia. Metronidazole may be added for additional anaerobic coverage.

Corticosteroids have long been advocated in the treatment of sepsis, but because of equivocal clinical evidence, their use appears to be declining. They are potent inhibitors of transcription of interleukin-1 and interleukin-6 and tumor necrosis factor alpha; however, much of the evidence demonstrating a benefit from corticosteroids involves administration prior to the infectious insult.

Interestingly, improved survival has been shown in experimental studies of septic peritonitis when dogs are treated with heparin, ostensibly due to improved bacterial clearance from the abdomen or to reduction of disseminated intravascular coagulation.

Novel therapies include prophylactic use of recombinant human granulocyte colony-stimulating factor, which has a protective effect in bacterial peritonitis and results in better survival than antibiotics alone. Encapsulation of antibiotics in liposomes may prolong the drug's half-life and improve reticuloendothelial targeting, and better survival has been demonstrated in fecal peritonitis models compared with conventional methods of antibiotic delivery.

Most animals with hemoabdomen have suffered abdominal trauma or rupture of an intra-abdominal mass. To minimize ongoing hemorrhage, an abdominal pressure bandage should be applied prior to aggressive fluid resuscitation. As the majority of intra-abdominal hemorrhage is due to venous rather than arterial bleeding, the abdominal wrap need provide pressure only in excess of venous blood pressure (0 to 5 mm Hg), which can be achieved by a firm but not excessively tight bandage. In general, padding beneath the wrap should be avoided because it allows the bandage to move caudally rather than provide compression in the cranial abdomen, where it is most effective.

DIAGNOSTIC EVALUATION

Blood should be obtained for analysis when the intravenous catheter is placed. As a minimum, packed cell volume (PCV), refractometric total solids, glucose, and serum electrolytes should be evaluated. Parameters must be re-evaluated frequently in animals receiving aggressive intravenous fluid support. A low total solids concentration with a normal PCV should prompt a search for hemorrhage or severe vasculitis. Animals with septic peritonitis often have panhypoproteinemia, presumably due to exudation of protein into the peritoneal cavity. In the absence of hemorrhage or liver or kidney disease, an abnormally low serum total solids concentration in a dehydrated and hypoperfused animal should raise the possibility of severe vasculitis, most commonly bacterial peritonitis. Hypoglycemia should prompt a search for sepsis and pancreatic or hepatic neoplasia.

If in-house hematology and blood chemistry analysis are available, a complete blood count, serum biochemical analysis, urine analysis, and coagulation screen should also be obtained prior to fluid resuscitation. Depending on the severity and chronicity of the underlying condition, the neutrophil count may be increased, normal, or low, and a left shift may or may not be present. Most puppies with parvoviral enteritis have severe neutropenia. Serum chemistry changes can provide helpful information. For example, bile peritonitis often results in increased serum alkaline phosphatase, alanine transaminase, and total bilirubin concentrations. Unless it is peracute or the animal is still voiding urine, uroperitoneum is usually associated with an increase in blood urea nitrogen, creatinine, and potassium.

The main aim of the initial diagnostic evaluation of the animal with an acute abdomen is rapid identification of the patient that needs immediate surgery. If available, immediate abdominal ultrasound to detect abdominal effusion, followed by cytologic fluid analysis, is the fastest way to diagnose septic peritonitis. In early cases of peritonitis, even with bowel rupture, little or no abdominal effusion may be present; in other words, the absence of abdominal effusion does not rule out peritonitis. Nevertheless, most animals with peritonitis have an abdominal effusion.

Abdominal ultrasonography may also identify the cause of the acute abdomen. Abscesses in parenchymal organs, pyometra, pancreatitis, abdominal masses, and abnormalities of organ blood flow, such as in splenic torsion, can all be detected by trained personnel. The accuracy of ultrasonography in detecting or ruling out gastrointestinal obstruction can vary, and caution should be exercised in the interpretation of ultrasound findings.

If ultrasound is not available, abdominal radiographs should be obtained as soon as the animal has been stabilized. Abdominal radiographs are superior to abdominal ultrasound in detecting intestinal obstruction or foreign material in the gastrointestinal tract. Abdominal radiographs may also demonstrate free gas and/or loss of intra-abdominal detail suggestive of fluid or increased soft tissue in the peritoneal cavity. Free gas may result from rupture of a hollow viscus, gas-forming bacteria, abdominocentesis, recent abdominal surgery, or penetrating injuries; however, many animals with penetrating abdominal injuries do not have free gas in the abdomen. Pneumoperitoneum can complicate radiographic and ultrasonographic evaluation of the postoperative abdomen. After experimental injection of air, radiographic evidence of intraperitoneal gas may persist for up to 18 days in dogs.

Abdominocentesis, with or without ultrasound guidance, is a quick, easy, and safe method for detecting and retrieving abdominal fluid. Contraindications to abdominocentesis are few but include coagulopathy, organomegaly, and distension of

an abdominal viscus. If these conditions are a possibility, abdominal radiographs should be obtained prior to abdominocentesis or the tap should be performed with ultrasound guidance. Penetration of the gastrointestinal tract during abdominocentesis is unusual unless the viscus is dilated or adherent to the abdominal wall. Abdominocentesis may be performed by means of a single centesis, a four-quadrant approach, or diagnostic peritoneal lavage (DPL).

Prior to abdominocentesis, the site is clipped and prepared using standard aseptic technique. Closed needle abdominocentesis is performed using a 20- or 22-gauge hypodermic needle attached to a syringe. Initially, the ventral aspect of the right cranial quadrant is used (where fluid pools by gravity and diaphragmatic movement) to minimize the chance of splenic puncture. If blood is aspirated, the needle should be withdrawn and the blood observed to see if it clots. Blood from a vessel or organ clots, whereas blood from the abdominal cavity does not in all but the most peracute cases of hemoabdomen. Free air is not usually seen on radiographs after a closed abdominocentesis.

Diagnostic peritoneal lavage may be sensitive in detecting intra-abdominal pathology. The conventional method of DPL usually requires sedation and uses a peritoneal dialysis catheter with the animal in either lateral or dorsal recumbency. However, an over-the-needle catheter can be placed into the abdomen just caudal to the umbilicus and 10 to 20 mL/kg of tsotonic crystalloid solution infused. This procedure should not require sedation. The catheter is then removed, and the abdomen is gently palpated. Thirty minutes later, a single or four-quadrant abdominocentesis is performed. Because DPL introduces free fluid into the abdomen and because it is not uncommon to retrieve only a small portion of the infused fluid, abdominal radiographs and ultrasound scans should be obtained prior to lavage.

Biochemical, cytologic, and microbiologic analysis of abdominal fluid is extremely useful in the diagnosis of the underlying cause. Initially the appearance of the fluid should be noted, followed by determination of the PCV, refractometric total solids concentration, and cytologic results to classify the fluid as a transudate, modified transudate, or exudate. Toxic degenerate neutrophils with intracellular and extracellular bacteria are indicative of bacterial peritonitis and warrant surgical exploration once the animal is hemodynamically stable. Rupture of the gastrointestinal tract is more likely if multiple bacterial species are seen and very likely if plant fibers are present. Occasionally bacteria are not seen with bacterial peritonitis, and in these dogs and cats, differentiation from severe pancreatitis can be difficult. Both are associated with high numbers of degenerate neutrophils in the effusion.

The abdominal fluid amylase and lipase concentrations may be helpful in detecting pancreatitis; however, it is vital to appreciate that more than half the cases of septic peritonitis may have concurrent pancreatitis, therefore a diagnosis of pancreatitis does not preclude the presence of bacterial peritonitis. An abdominal effusion glucose concentration of less than 50 mg/dL is often indicative of bacterial peritonitis.

With uroabdomen, abdominal fluid almost always shows higher blood urea nitrogen (BUN), creatinine, and potassium concentrations than does serum; however, the difference can be relatively minor. Creatinine equilibrates more slowly with the intravascular space and can therefore more be more useful. To enable comparison of serum and abdominal fluid, samples must be obtained within minutes of each other. If a bolus of intravenous fluids is administered after the abdominal fluid sample is obtained, the serum levels can be diluted, and ascites of another cause may be misdiagnosed as uroabdomen.

When uroperitoneum is suspected, retrograde contrast urethrocystography and/or excretory urography should be performed to confirm the site of leakage. The most common causes of bile peritonitis are rupture of the biliary tract secondary to trauma or necrotizing cholecystitis. A green abdominal effusion is usually present, which sometimes contains dark green, brown, or black particulate matter. The bilirubin concentration should be higher in the effusion than in serum.

CHAPTER 111

Cardiac Emergencies

Kirstie A. Barrett

The management of cardiac emergencies can be very rewarding if a prompt diagnosis is made and if the proper treatment is instituted without delay. Sometimes patients are not stable enough to handle extensive diagnostics, and treatment decisions must be made quickly. In such cases, an insightful history and physical examination are critically important, because the choice of further diagnostics may be limited.

Cardiac emergencies commonly seen in veterinary patients are arrhythmias, acute congestive heart failure, pericardial effusion, and arterial thromboembolism. Other cardiac emergencies or potential cardiac emergencies, described elsewhere in detail, include cardiopulmonary resuscitation (CPR), shock, syncope, hypertension, and hypotension.

ARRHYTHMIAS

Arrhythmias, which occur in a high percentage of critical patients, represent a disturbance in the rate, regularity, or site of cardiac electrical impulse formation. Their clinical significance is a result of a heart rate that is either too slow or too rapid, depressing cardiac output and potentially leading to heart failure or circulatory collapse. Cardiac arrhythmias are particularly ominous if they have the potential to deteriorate into an electrically unstable form, causing or exacerbating circulatory failure or cardiac arrest.

A correct electrocardiographic (ECG) diagnosis is essential to appropriate management and therapy and should always be interpreted in the context of the patient's history and current

clinical status. Identification and correction of precipitating factors (e.g., cardiopulmonary disease, metabolic derangements, acid-base and electrolyte imbalances, current drug therapy) are equally essential to successful management of cardiac arrhythmias and to the clinician's decision on whether to initiate antiarrhythmic therapy.

Arrhythmias that cause clinical signs generally warrant therapy. Clinical signs that reflect decreased cardiac output may be acute or progressive and include weakness, exercise intolerance, syncope, collapse, ataxia, pulse abnormalities, congestive heart failure, and sudden death.

Arrhythmias present during cardiopulmonary arrest (CPA) include asystole (complete absence of QRS-T complexes), ventricular fibrillation (chaotic depolarization of the ventricles characterized by a lack of QRS-T complexes with unorganized fibrillation waves), and electromechanical dissociation (little or no myocardial contractile activity with a normal ECG tracing). All these arrhythmias require immediate intervention using standard CPR recommendations. Other potentially lethal arrhythmias include continuous (sustained) or intermittent (paroxysmal) ventricular tachycardia, ventricular flutter, paroxysmal or sustained supraventricular tachycardia, sick sinus syndrome (SSS), complete or high-grade second-degree atrioventricular block, and sinus standstill. Sinus bradycardia frequently precedes CPA in critically ill patients. Antiarrhythmic therapy should be initiated if treatment of the underlying disorder does not improve the arrhythmia; if hemodynamic impairment is identified; or if the risk of sudden death exists. Identification of the above arrhythmias and treatment options are discussed in detail elsewhere (see Chapter 202).

HEART FAILURE

Heart failure is a clinical syndrome caused by cardiac disease that results in systolic or diastolic cardiac dysfunction or both. Systolic failure describes decreased myocardial performance and diastolic failure results from abnormal filling of the ventricles during diastole.

Decompensated heart failure manifests either as congestion/edema (backward heart failure) or circulatory failure (low-output, forward heart failure). Right-sided congestive heart failure results in systemic venous congestion and may manifest as jugular distention, subcutaneous edema, hepatic congestion, ascites, and/or pleural effusion. Left-sided congestive heart failure presents as pulmonary edema.

Because the clinical signs of left-sided congestive heart failure can mimic those of pulmonary disease, it is important to determine accurately which condition is truly present. The signalment, history, and response to treatment can be helpful in making this distinction. The single most useful test for confirming congestive heart failure is a thoracic radiograph. However, the potential stress of any diagnostics must be seriously considered, because the anxiety associated with even minimal handling of a severely dyspneic animal can be life-threatening.

The goal of medical therapy in congestive heart failure is to improve cardiac output by increasing contractility, decreasing afterload, or normalizing a cardiac dysrhythmia. It is equally important to relieve clinical signs by reducing abnormal fluid accumulation. Furosemide is the diuretic of choice for relieving acute pulmonary edema and normalizing cardiac filling pressures. High doses of furosemide (up to 4 mg/kg given intravenously or intramuscularly every 2 hours) may be used initially to induce diuresis. Intravenous furosemide acts within 5 minutes, peaks within 30 minutes, and dissipates after 2 to 3 hours. Use of the intravenous route is preferred, but this must be weighed against the potential stress of administration.

Intramuscular administration of furosemide is an alternative. The dose is highly variable and depends on the response desired. The dose and frequency should be reduced as a clinical response (diuresis, respiratory rate reduction, and respiratory character improvement) is achieved. Cats tend to be more sensitive to furosemide than dogs and respond to lower doses (2 mg/kg).

In addition to the diuretic, a low dose of morphine (0.05 to 0.1 mg/kg given subcutaneously or intramuscularly) can reduce the anxiety associated with pulmonary edema and provide mild venodilatation.* The dose is repeated up to four times a day, as necessary, to achieve the desired effect. The primary adverse consequence of using morphine is respiratory depression, therefore it must be used with caution in hypoxic animals. Acepromazine (0.05 to 0.1 mg/kg given subcutaneously) is an anxiolytic that does not depress respiration. Acepromazine is an alpha-adrenergic blocker that decreases peripheral vascular resistance, which may also be beneficial.

Nitroglycerin, a venodilator, may further reduce congestion, although information in the veterinary literature is merely anecdotal. Nitroglycerin paste can be applied to the inner surface of the pinna of the ear (¼ to 1 inch every 6 hours in the dog; ⅛ to ¼ inch every 6 hours in the cat). Nitroglycerin is typically used for only 48 hours due to the drug tolerance that develops.

Hydralazine, a potent arteriolar dilator, can be used in the emergency management of a normotensive congestive heart failure patient (0.5 to 2.0 mg/kg given orally). Nitroprusside is both a potent venodilator and a potent arteriolar dilator for use in severe, refractory congestive heart failure (1 to 2 µg/kg/minute given intravenously initially). Continual blood pressure monitoring is essential with nitroprusside. Dobutamine (2.5 to 10 µg/kg/minute, intravenously), which is primarily a $beta_1$ agonist, is used to improve cardiac output by increasing contractility in hypotensive patients with refractory congestive heart failure. Digoxin is especially beneficial in the emergency treatment of congestive heart failure when supraventricular tachycardia or atrial fibrillation is present.

Strict cage rest and prevention of stress are critically important to the management of a congestive heart failure patient. Additional measures that may benefit the patient are thoracocentesis and oxygen therapy. Cats with congestive heart failure often present with both pulmonary edema and pleural effusion. When congestive heart failure results in pleural effusion of significant quantity and the animal is dyspneic, thoracocentesis often results in prompt and dramatic improvement (the technique is described elsewhere in this text).

Dogs and cats with severe pulmonary edema are hypoxic due to the decreased ability of oxygen to diffuse from the alveoli into the pulmonary capillaries. Supplemental oxygen increases this pressure gradient, resulting in an increase in arterial oxygen tension. Therefore it is of critical importance that patients with severe edema have supplemental oxygen. This can be achieved using an oxygen cage (40% oxygen) adjusted to maintain a normal temperature (20° to 22°C [68° to 72°F]) and appropriate humidity (45% to 55%). Oxygen cages are generally better tolerated and less stressful than other means of administration. In a larger dog, oxygen can be administered through a nasal cannula. An oxygen mask is an alternative but should not be used if the animal is struggling against the mask.

Endotracheal intubation may be required in animals with extreme respiratory distress and fulminant pulmonary edema to provide controlled ventilation and 100% oxygen administration. In addition, copious amounts of pulmonary edema may be removed physically by suction or postural drainage. Intravenous fluids are rarely indicated in the treatment of

*Notably, morphine can cause agitation and aggression in cats.

acute, cardiogenic pulmonary edema because they often exacerbate the edema.

PERICARDIAL EFFUSION

Pericardial effusion is an abnormal accumulation of fluid in the pericardial sac. The hemodynamic effects of pericardial effusion depend on the rate and volume of the fluid accumulation and the compliance of the pericardium itself. If the effusion develops slowly, the pericardium will expand and the intracardiac pressure will not increase enough to compromise cardiac filling. In contrast, acute cardiac tamponade is characterized by rapid accumulation of fluid in the pericardial space, leading to a rise in intrapericardial pressure. The results are restriction of ventricular filling, decreased cardiac output, and arterial hypotension. Clinical signs of right-sided congestive heart failure or reduced cardiac output predominate and include anorexia, lethargy, syncope, dyspnea, weakness, exercise intolerance, and abdominal distention (hepatomegaly, ascites). Common physical examination findings are muffled heart sounds, jugular venous distension, sinus tachycardia, and weak femoral pulses. Pulsus paradoxus (an exaggerated decline greater than 10 mm Hg in systemic arterial pressure during inspiration) is a valuable clinical sign that may also be appreciated in cardiac tamponade.

Although thoracic radiography typically demonstrates an enlarged, globoid cardiac silhouette, echocardiography is the most sensitive and specific noninvasive means of diagnosing pericardial effusion. The therapeutic goal for patients with pericardial effusion is to reduce the intrapericardial pressure quickly. Pericardiocentesis is the treatment of choice for initial stabilization of dogs and cats with pericardial effusion and cardiac tamponade (the technique is described in Chapter 205). Attempts to lower venous pressures with medical therapy (i.e., diuretics) should be avoided because the patient's cardiac preload depends on these elevated pressures. The result can be a significantly reduced cardiac output, manifested as hypotension or syncope or both.

ARTERIAL THROMBOEMBOLISM

Arterial thromboembolism is a common sequela to all types of feline myocardial disease (hypertrophic cardiomyopathy, dilated cardiomyopathy, and restrictive cardiomyopathy); it is uncommon in the setting of a structurally normal or mildly abnormal heart. Arterial thromboembolism results in significant morbidity and mortality. Systemic thromboembolism is rarely reported in the dog and is usually associated with neoplasia, sepsis, Cushing's disease, protein-losing nephropathy, or other hypercoagulable states. Distal aortic embolization (saddle thrombus at the distal aortic trifurcation) occurs in more than 90% of feline cases. Corresponding clinical signs may occur with embolization of other organs, such as the lungs (respiratory distress), kidneys (acute renal failure), brain (central nervous system signs), gastrointestinal tract (bowel ischemia), and right (more commonly than left) brachial artery (pain and paresis).

A distal aortic embolism presents as peracute paresis or paralysis with vocalization due to intense pain. The clinical consequences depend on the site, extent, and duration of the embolization, as well as the degree of functional collateral circulation. The *four Ps* characterize the clinical signs of changes observed in the extremities: paralysis, pain, pulselessness (lack of palpable femoral pulses), and pallor (cold, pale distal extremities and pads). Absence of bleeding from a cut nail on the affected limb may also be seen. Ten to 12 hours after the embolization, the anterior tibial and gastrocnemius muscles often become firm as a result of ischemic myopathy. In most cases these muscles become softer after 24 to 72 hours. Respiratory distress is commonly associated with systemic thromboembolism in cats because most have concurrent congestive heart failure. Acute aortic blockade by the thromboembolus increases afterload to the left ventricle. The clinician must differentiate the respiratory changes seen with congestive heart failure from those seen with pain.

A variety of therapeutic measures can be used to offset the consequences of a thromboembolism. These range from attempts to limit thrombus growth or formation and pain control to supportive care and treatment of accompanying congestive heart failure.

Although heparin has no effect on established thrombi, it is commonly administered in hopes of limiting thrombus growth.* Heparin can be administered at an initial dose of 220 U/kg given intravenously, followed by a maintenance dose of 70 to 200 U/kg given subcutaneously every 6 hours. Thrombolytic agents such as streptokinase, urokinase, and tissue plasminogen activator (t-PA) are used extensively in humans and infrequently in cats. These agents are expensive, have not been studied extensively, and are associated with high mortality and poor outcomes. Risks of bleeding complications, death from reperfusion syndrome (hyperkalemia, metabolic acidosis), and rethrombosis are common.

During the initial stages of the disease, most cats experience intense pain. The pain subsides as sensory nervous function is lost. Common choices for pain control include oxymorphone (0.05 to 0.15 mg/kg given intramuscularly or intravenously every 6 hours), butorphanol (0.1 mg/kg given intravenously or 0.02 to 0.4 mg/kg given intramuscularly or subcutaneously every 4 hours), and/or acepromazine (0.05 to 0.1 mg/kg given intravenously). Euthanasia should be considered as an option when severe, unrelenting pain is present.

General supportive care consists of maintaining hydration and normal electrolyte status, massaging firm muscles, expressing the bladder as necessary, and preventing self-mutilation. Management of concomitant congestive heart failure is discussed above.

*Heparin has never been proven to limit thrombus growth.

CHAPTER 112

Cardiopulmonary Arrest and Resuscitation

Nishi Dhupa

Cardiopulmonary arrest is defined as the cessation of effective ventilation and circulation. Resuscitative efforts should be aimed at patients with potentially reversible disease. The ultimate goals of cardiopulmonary resuscitation (CPR) are to maintain adequate tissue oxygenation and thereby preserve organ viability during the low-flow "arrest" state, to rapidly restore a spontaneous and effective cardiac rhythm, and to protect cardiovascular and neurologic function following resuscitation in order to improve the chances of survival as well as the return of acceptable cerebral and motor functions.

CPR may be divided into three phases. Basic life support (BLS) is the provision of artificial ventilation, oxygenation, and circulation in order to maintain vital organ perfusion. Advanced life support (ALS) involves the recognition and treatment of the arrest rhythm and other modalities to resuscitate the patient. Prolonged life support (PLS) covers post-resuscitative care. Guidelines for veterinary CPR are extrapolated from human medicine. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation has recently reviewed and updated its guidelines on CPR.[1] Methods that improve coronary perfusion pressure are being prioritized in an effort to improve resuscitation rates and outcomes.

RECOGNITION OF CARDIOPULMONARY ARREST

Incipient cardiopulmonary arrest (CPA) may be recognized by bradycardia or other cardiac arrhythmias, slow or irregular respirations, mental obtundation, hypotension, and hypothermia. In dogs and cats, the most common "arrest rhythms" are asystole and pulseless electrical activity (PEA) (otherwise known as electromechanical dissociation); a lower percentage display ventricular fibrillation (VF). CPR must begin immediately in the unresponsive, breathless, and pulseless patient. The chances of recovery from CPA are increased in cases of respiratory arrest alone, anesthetic overdose, upper airway obstruction, trauma or hemorrhage, vagally mediated arrest, electrolyte abnormalities, or upper airway obstruction. Patients with terminal or multisystemic disease will have a poorer prognosis.

BASIC LIFE SUPPORT

BLS should be initiated as rapidly as possible after the recognition of CPA. Traditionally BLS has been carried out according to the "ABC" mnemonic (airway, breathing, circulation). The first step is to secure the airway through endotracheal intubation. If pulmonary edema fluid discharges through the endotracheal tube, postural drainage, with the head hanging below the body, and suction will aid in clearing of the airway. Once intubated, positive pressure ventilation should be initiated at 15 to 25 breaths per minute using a rebreathing (AMBU) bag attached to high flow oxygen. The chest should be observed and ausculted to verify appropriate ventilation.

The goal of circulatory support during CPR is to maximize cerebral and myocardial oxygenation in order to achieve a rapid return of spontaneous circulation (ROSC) and long-term neurologic recovery. Ventilation with 100% oxygen ensures maximal saturation of hemoglobin and improves arterial oxygen content. Cerebral perfusion depends on cardiac output and cerebral vascular resistance; perfusion pressure is determined by the difference between mean arterial pressure and intracranial pressure. Myocardial perfusion is determined by the difference between aortic diastolic and right atrial pressure. Various compressive and therapeutic strategies are used to maximize these perfusion pressures.

First, during closed-chest CPR, rapid chest compressions are initiated at a rate of 80 to 100 per minute. In smaller patients, compressions are performed directly over the heart, with the patient in lateral recumbency, in order to maximize forward blood flow. In larger patients, greater increases in intrathoracic pressure can be achieved by performing chest compressions over the point of the sternum, with the patient in dorsal recumbency. The optimal compression: relaxation ratio of 50:50 allows for diastolic filling of the heart and maximizes myocardial perfusion.

Alternating abdominal compressions may be used to improve cardiac preload and cardiac output. Greater intrathoracic pressure changes can also be achieved during simultaneous compression-ventilation. In hypovolemic patients, aggressive fluid therapy is essential to restore circulating blood volume. The effectiveness of chest compressions and adjunctive strategies must be evaluated through palpation of femoral pulses, detection of orbital vessel blood flow through Doppler ultrasound applied to the cornea, and end-tidal carbon dioxide measurement (a higher value following chest compression is indicative of improved pulmonary perfusion and gas exchange).

Open chest CPR, with direct cardiac massage, is indicated in patients with conditions that interfere with the generation of intrathoracic pressure, which is necessary for forward blood flow. These include pneumothorax, diaphragmatic hernia, flail chest, severe obesity, pericardial effusion, very large animals, and severe hypotension. Although this modality is superior in terms of generation of blood flow, it is an invasive procedure, associated with increased morbidity and intensive after-care.

Recently, the "CAB" mnemonic has been suggested as an alternative to "ABC." This has some application in human patients in whom primary cardiac arrest is more common. In veterinary patients, in whom respiratory and vagally mediated arrests are common and hypoxia, hypercarbia and acidosis often precede cardiac arrest, the "ABC" approach, with its emphasis on early oxygenation, is still valid.

ADVANCED LIFE SUPPORT

ALS is initiated once effective artificial ventilation and circulation have been established. ALS consists of techniques to augment artificial circulation and encourage ROSC through

arrhythmia recognition (using electrocardiography) and treatment with drugs and defibrillation. First, any anesthetic, analgesic, or sedative agents must be discontinued or reversed to minimize cardiorespiratory depression (Table 112-1). The most common arrest rhythms are treated as follows: asystole is treated with atropine and epinephrine; pulseless electrical activity with atropine and epinephrine; and ventricular fibrillation with electrical defibrillation (see Table 112-1). Emergency drugs are administered through either the central venous (preferred), endotracheal, or intraosseous route (see Table 112-1). Intratracheal administration is achieved by a doubling of the intravenous dose, dilution to 5 to 6 mL in saline, and administration at the level of the carina via a 5- to 8-French red rubber tube.

Atropine is a vagolytic agent that is indicated in the treatment of sinus bradycardia, asystole, or PEA (all seen in up to 70% of small animal CPA) due to the role of the parasympathetic nervous system in these arrhythmias (see Table 112-1).

Epinephrine is an adrenergic vasopressor that is the current drug of choice for asystole, PEA, and refractory VF. Its alpha-adrenergic activity results in increased aortic diastolic pressure and improved myocardial perfusion, thus encouraging ROSC. The beta effects (inotropy, chronotropy) may increase myocardial work and oxygen demand, with the potential for tachyarrythmias and myocardial dysfunction following ROSC.

Several newer drugs are undergoing extensive study and may have value in CPR protocols. Vasopressin (Pitressin, Monarch Pharmaceuticals, Bristol, TN) is a potent nonadrenergic vasopressor, acting through direct stimulation of vasopressin (V1) receptors in vascular smooth muscle. Its advantages over epinephrine include the fact that the vasoconstrictive effects are not blunted in the presence of acidosis and, following ROSC, there is no increase in myocardial oxygen demand. In human CPA protocols, vasopressin is now being considered an alternative to epinephrine in refractory VF; it has also been used in asystole and PEA.[1] The single use of vasopressin, at a dose of 0.8 μ/kg IV, has been proposed for similar arrhythmias in veterinary CPR.[2] However, there is little data to support a strong recommendation at this time.

Aminophylline is an adenosine antagonist that has recently been used in human CPR in an effort to counteract the negative chronotropic effect, inhibition of catecholamine receptors, and vasodilation caused by endogenous vasodilators such as adenosine during CPA. Aminophylline can decrease defibrillation threshold and may be useful in refractory VF. More extensive studies into the use of this drug are underway.

Amiodarone is a newer antiarrhythmic agent that has been included in human CPR guidelines for use in ventricular arrhythmias refractory to lidocaine or procainamide, as well as for treatment of refractory VF.[1] To date, there is no data on its use in small animal CPR.

Aggressive fluid therapy during CPR can increase preload and interfere with cerebral and myocardial perfusion. However, as CPA progresses, increasing fluid volumes are required in order to maintain an effective circulating blood volume in the presence of systemic vasodilation. Fluid choice is dependant on volume status; colloids may augment isotonic crystalloid administration in hypovolemic patients.

Electrical defibrillation is the treatment of choice for VF, with the goal of conversion to asystole (with subsequent epinephrine administration) or a perfusing rhythm. In known VF, defibrillation may be carried out prior to the ABCs. Electrical countershocks are applied across the chest wall using hand-held defibrillator paddles coated with electrode gel, with the animal in dorsal recumbency. The initial electrical shock should be in the range of 3 to 5 J/kg. Two or three shocks are delivered in rapid succession, with increasing energy (5 to 10 J/kg) being applied if necessary. For internal defibrillation, during open chest CPR, an initial dose of 0.5 to 1 J/kg is used. The ECG is evaluated and countershocks are discontinued when VF converts.

PROLONGED LIFE SUPPORT

Successful resuscitation is characterized by the return of a perfusing rhythm and effective respirations. A large percentage of successfully resuscitated patients will suffer a second

Table • 112-1

Drugs Used in Cardiopulmonary Resuscitation

DRUG	DOSAGE AND ROUTE	INDICATIONS
Amiodarone	5-10 mg/kg IV	Refractory VF
Atipamezole	0.1-0.2 mg/kg IV	α_2 adrenergic reversal
Atropine	0.04 mg/kg IV, IT, IO	Bradycardia, asystole
Calcium gluconate	50 mg/kg IV, IO	Hypocalcemia, hyperkalemia
Diltiazem	0.05-2 mg/kg IV 1-10 μg/kg/min IV	Supraventricular arrhythmia after ROSC
Dobutamine	5-10 μg/kg/min IV	Reduced cardiac output after ROSC
Dopamine	5-10 μg/kg/min IV	Hypotension after ROSC
Epinephrine	0.02-0.2 mg/kg IV, IT, IO;	Asystole. Repeat q 3-5 min
Flumazenil	0.02 mg/kg IV, IT, IO	Benzodiazepine reversal
Lidocaine	2-4 mg/kg (dogs), 0.5 mg/kg (cats), IV, IT, IO followed by 50 μg/kg/min IV	Hemodynamically unstable ventricular arrhythmias after ROSC
Magnesium sulfate	30 mg/kg IV, IO	Hypomagnesemic patients; polymorphous ventricular tachycardia
Mannitol	0.25-1 g/kg IV, IO	Cerebral edema
Naloxone	0.01-0.04 mg/kg IV, IT, IO	Opioid reversal
Sodium bicarbonate	0.5-1 mEq/kg IV, IO (NOT IT)	10 minutes into CPA; earlier if pre-existing acidosis; hyperkalemia
Vasopressin	0.8 μ/kg IV,IO	Asystole, refractory VF

IV, Intravenous; *IT*, intratracheal; *IO*, intraosseous; *VF*, ventricular fibrillation; *ROSC*, return of spontaneous circulation.

arrest within a few hours. This is due to multiorgan failure secondary to hypoxic damage during low-flow CPA and CPR.

Aggressive monitoring and supportive care is required to optimize cardiac output, blood pressure, and vital organ function. Cardiovascular support is provided through appropriate fluid therapy, vasopressor or inotropic support, and the control of hemodynamically unstable arrhythmias (see Table 112-1). Stable and perfusing ventricular escape rhythms should not be suppressed with drug therapy. Ventilatory support may be essential for some hours following resuscitation, in order to maximize oxygenation and to prevent hypercarbia (and associated cerebral vasodilation). Neurologic recovery is also maximized by maintainance of mean arterial pressure (and therefore cerebral perfusion pressure) as well as by treatment for hypoxia-induced cerebral edema with Mannitol (see Table 112-1). Hyperglycemia has been associated with worse neurologic outcomes; for this reason, corticosteroids are not currently used in post-arrest protocols.

Good prognostic signs include the rapid recovery of upper airway function (coughing) and ocular reflexes, and rapid return of consciousness following cardiac arrest. The presence of prolonged unconsciousness, the absence of the oculocephalic (doll's eye) reflex, or any deterioration in neurologic status, following ROSC, suggests progressive cerebral ischemia and indicates a poor outcome. Blindness is a common but often reversible sequela to CPA.

CHAPTER 113

Traumatic Brain Injury

Rebecca S. Syring

Traumatic brain injury (TBI) is an important cause of morbidity and mortality in veterinary medicine. The severity of brain injury after head trauma can be quite variable, with neurologic signs ranging from relatively minor deficits to life-threatening impairments. An understanding of the pathophysiologic changes that occur after TBI and the appropriate diagnostic and therapeutic interventions for the animal with head injury can help the clinician optimize the outcome.

PATHOPHYSIOLOGY OF BRAIN INJURY

TBI can be caused by blunt or penetrating trauma. Blunt force to the head is the most common category of TBI. With blunt trauma, the kinetic energy from the impact is diffusely dissipated across the surface of the body. Head injury may be overtly obvious in these dogs and cats or may be overshadowed by more severe injuries elsewhere in the body. Although less common, penetrating injuries to the head, such as gunshot, stab, or bite wounds, are more likely to result in isolated trauma to the brain, because the kinetic energy from the trauma is focally dissipated along the penetrating tract.

Primary versus Secondary Injury

Two phases have been described as following TBI: primary and secondary injury. *Primary injury* refers to pathologic changes that take place when the injury is sustained. Examples of primary injury include direct axonal damage, such as compression or laceration from forces applied to the skull during impact or displaced skull fractures, and vascular disruption, including focal hematomas or diffuse parenchymal hemorrhage. Primary injury is complete at the time of trauma and, with the exception of surgical evacuation for focal hematomas or decompression of depressed fractures, little can be done to alter its course.

Secondary injury refers to a variety of pathologic processes that occur after the primary insult and that result in progressive neuronal damage not only at the initial site of trauma but extending to the brain globally. Because the brain has high metabolic requirements, decreased cerebral oxygen delivery or hypoglycemia can rapidly result in adenosine triphosphate (ATP) depletion, cell membrane pump failure, and loss of ion homeostasis. This can lead to excitotoxicity, oxidative stress, cytotoxic and vasogenic cerebral edema, inflammatory mediator release, activation of the coagulation cascade, vasospasm, and cell death. With anaerobic metabolism, hyperglycemia has been documented to exacerbate neurologic damage by increasing lactic acid accumulation in the brain, resulting in neuronal and glial cell death. These are just a few examples of types of secondary injury that occur after TBI. Because secondary injury occurs after the initial insult and is progressive in nature, medical intervention should focus on preventing the development or limiting the side effects of this type of injury. Two factors that have a significant impact on the perpetuation of secondary injury are systemic hypoxia and hypotension, both of which can be easily recognized and treated clinically.

Intracranial Pressure and Cerebral Perfusion Pressure

In the healthy brain, pressure autoregulation ensures that cerebral blood flow (CBF) is maintained within an acceptable range over a wide spectrum of systemic mean arterial blood pressures (50 to 150 mm Hg). In response to changes in blood pressure, parallel changes in cerebral vascular resistance occur to maintain blood flow to the brain. Above and below these values, cerebral blood flow is directly proportional to systemic blood pressure. This protective mechanism is often impaired (either globally or regionally) in animals with TBI, at which time cerebral blood flow becomes linearly dependent on systemic blood pressure.

Intracranial pressure (ICP) is defined as the pressure exerted between the skull and its intracranial contents. The components of ICP are the volume of blood, brain tissue, and cerebral spinal fluid (CSF) within the cranial vault. In dogs and cats with TBI, brain volume increases with hemorrhage or edema. The body attempts to maintain ICP with a compensatory decrease in the production of CSF or shunting of CSF

into the cisterna magna or by arterial vasoconstriction to lower the blood volume. ICP increases when intracranial volume exceeds the system's capability for compensatory decreases in the other components. The normal ICP for cats and dogs is 5 to 10 mm Hg.

Cerebral perfusion pressure (CPP) is considered the primary determinant of cerebral blood flow in animals with TBI. With intracranial hypertension, CPP is equal to the systemic mean arterial blood pressure (MAP) less intracranial pressure:

$$CPP = MAP - ICP$$

Maintaining CPP above a minimum value of 70 mm Hg is recommended in order to optimize oxygen and nutrient delivery to the brain. CPP is a measure of global blood flow and does not necessarily reflect blood flow on a regional level. Because ICP is infrequently measured in veterinary medicine, determination of CPP is not always possible. However, this equation stresses the importance of optimizing blood pressure in head trauma patients. Relatively small increases in ICP (e.g., 15 mm Hg) can result in inadequate CPP with a normal MAP of 80 mm Hg. Additionally, with normal ICP, if pressure autoregulation is no longer intact, minor decreases in MAP result in inadequate CPP.

ASSESSMENT

In the evaluation of animals with TBI, it is imperative that the examiner assess all body systems, rather than focus solely on the brain, because head trauma often occurs coincident with traumatic injuries to other body systems. It has been reported that 50% to 65% of dogs with TBI have sustained blunt vehicular trauma, a common cause of multisystemic injury. Common injuries seen after blunt trauma, such as pulmonary contusions, pneumothorax, and hemoabdomen, can impair systemic oxygenation and perfusion and perpetuate secondary injury if not rapidly addressed. Developing a systematic approach to the traumatized pet that focuses on evaluation of the major body systems, cardiovascular and respiratory stabilization, followed by a secondary assessment and definitive medical therapy, can help the clinician prioritize treatment goals and can improve the outcome (see Chapter 117). A full neurologic examination is not necessary and may not be in the animal's best interest during the initial assessment. Instead, an abbreviated neurologic assessment that focuses on three main categories—level of consciousness, brain stem reflexes, and motor activity/posture—should provide ample information for initial assessment and stabilization.

An altered level of consciousness indicates abnormalities in the cerebral cortex or brain stem (reticular activating system). Level of consciousness can be divided into four main categories: alert, depressed/obtunded, stuporous, or comatose. Depressed to obtunded animals are aware of but less responsive to their environment. An obtunded animal should still respond to noise or touch. Stupor indicates a severely impaired level of consciousness, with response only to noxious stimuli. A truly comatose dog or cat exhibits no response to any type of manipulation, including repeated noxious stimuli. The use of these standardized categories to describe level of consciousness allows for uniform comparison of neurologic function over time in individual animals. In the assessment of pets with altered levels of consciousness, it is important to remember that shock (decreased tissue oxygen delivery) can cause moderate alterations in consciousness, which should improve with treatment that improves tissue perfusion.

Brain stem reflex assessment should focus on pupils (size, symmetry, and position), pupillary light responses, and physiologic nystagmus. Miotic pupils indicate a lesion above the brain stem leaving the oculomotor nerve, a pupillary constrictor, intact and unopposed from higher centers. Mydriatic pupils are seen in animals with brain stem lesions affecting the oculomotor nerve on the side of the injury. Anisocoria may indicate a neurologic lesion affecting one side exclusively or simply one side more than the other. In the absence of other underlying ophthalmologic disorders, lack of a pupillary light response, unilaterally or bilaterally, indicates disruption or compression of the oculomotor nerve tracts ipsilateral to the injury. Ventrolateral strabismus may also be seen with oculomotor nerve damage. Physiologic nystagmus, a reflex that tests cranial nerves III and VIII, is intact when the normal tracking movements of the eye are seen in response to turning of the head from side to side. Absence of this reflex indicates injury to the central region of the brain stem, as may be seen with brain stem hemorrhage or compression caused by swelling or herniation.

Abnormalities in any of these brain stem reflexes can aid in the localization of neurologic lesions and in the grading of the severity of injury. Additionally, serial evaluation of these reflexes assists in the monitoring of progression or improvement of neurologic function. It is important to remember that pupils of normal size that are not responsive to light represent significant brain stem dysfunction and are only one step less severe than a fixed and dilated pupil. For example, if midrange or mydriatic pupils without a pupillary light reflex are present on initial examination and no progression is noted, brain stem hemorrhage may be suspected. These signs, in conjunction with a comatose state and loss of physiologic nystagmus, are associated with a grave prognosis. Alternatively, a gradual progression of pupils toward mydriasis or loss of pupillary light response may indicate the development of intracranial hypertension, as occurs with edema formation, which may potentially respond to therapy directed toward lowering ICP.

The animal's motor activity and posture may aid in the localization of neurologic lesions (e.g., focal subdural hematomas). Following TBI, ataxia, hemiparesis, or tetraparesis may be the result of a lesion in the cerebral cortex or brain stem. The presence of other cranial nerve abnormalities can help in the differentiation of intracranial from cervical neck lesions. Decerebrate rigidity (extension of all four limbs and opisthotonus) indicates a rostral brain stem lesion and is often associated with brain stem compression secondary to marked intracranial hypertension and/or herniation. Decerebellate rigidity (extension of the front legs with hindlimb flexion) indicates a cerebellar lesion, as may be seen with cerebellar herniation. Animals with decerebrate posturing have a markedly altered level of consciousness, whereas those with decerebellate posturing usually are alert and aware of their surroundings.

The Cushing (or CNS ischemic) response is a compensatory mechanism that can be seen with markedly elevated ICP. Intracranial hypertension results in decreased CBF, which is sensed in the vasomotor center of the brain. In response to local carbon dioxide (CO_2) accumulation from decreased blood flow, the vasomotor center emits a massive sympathetic discharge, resulting in peripheral vasoconstriction, which results in an elevation in MAP to maintain CPP. The increased blood pressure is sensed at baroreceptors, resulting in a reflex bradycardia. The combination of hypertension and bradycardia in an animal with a decreased level of consciousness should alert the clinician to the possibility of increased ICP and should prompt aggressive treatment.

THERAPEUTICS AND CARE

Extracranial Stabilization

It is essential that extracranial organ systems be assessed and stabilizing medical therapy be instituted before therapy

directed at lowering intracranial pressure is begun. The goals of extracranial stabilization should be to optimize systemic oxygenation, ventilation, and tissue perfusion. Abnormalities in these three areas are common, given the propensity for multisystemic injuries with blunt trauma and the possibility of direct damage to the respiratory center in the brain. Early stabilization of the extracranial system minimizes secondary neurologic injury.

Hypoxemia should be avoided at all costs. Episodes of desaturation have been shown to worsen the outcome in humans with head trauma. Oxygen supplementation should be provided to maintain a hemoglobin saturation above 97% or a partial pressure of arterial oxygen (PaO_2) greater than 90 mm Hg. When in doubt, especially when oxygenation cannot be measured, the clinician should provide supplemental oxygen to avoid any potential adverse consequences from hypoxemia. Oxygen can be supplemented by many routes, including oxygen cages, flow-by masks, and hoods. Intranasal and intratracheal routes should be avoided when possible, because they can cause sneezing or coughing, both of which transiently increase ICP. Insufficient oxygenation despite an inspired oxygen concentration up to 60% necessitates intubation and positive pressure ventilation.

Hypoventilation, resulting in an elevated partial pressure of arterial carbon dioxide ($PaCO_2$), can occur. Reasons for hypoventilation include direct damage to the respiratory center, sedatives, thoracic trauma that causes pain or pleural space disease, and head or neck trauma that causes mechanical airway obstruction. Acute hypercarbia results in a respiratory acidosis that is sensed at the central chemoreceptors. In response to this acidosis, vasodilatation of the cerebral vasculature occurs, thus increasing CBF and potentially exacerbating elevations in ICP. $PaCO_2$ should be maintained below 40 mm Hg in patients with TBI. If $PaCO_2$ concentrations cannot be maintained within a normal range, intubation alone or in combination with mechanical ventilation is required.

The primary goal of fluid therapy in the pet with TBI is rapid restoration of tissue perfusion and blood pressure such that CPP is maintained above 70 mm Hg. Restriction of fluids should be avoided, because only minimal decreases in ICP are achieved and the animal is placed at greater risk for hypovolemia, which detrimentally affects CPP and exacerbates cerebral ischemia. Fluid therapy should be directed toward restoration of euvolemia, provision of maintenance requirements, and replacement of ongoing losses while avoiding overhydration.

A variety of fluid types are available for intravascular volume replacement in veterinary head trauma animals, including isotonic crystalloids, hypertonic saline, artificial colloids, and blood products (see Chapter 114). No one fluid type is optimal for every situation. Hypotonic solutions (5% dextrose in water, 0.45% sodium chloride) should be avoided for resuscitation, because these types of fluids preferentially expand the intracellular space and may exacerbate cerebral edema. Hypertonic saline (7.5%) is considered by many to be a superior fluid for resuscitation because of its ability to rapidly restore euvolemia due to its hyperosmolarity, which allows small volumes (3 to 5 mL/kg given over 10 to 15 minutes) to be used for resuscitation. Additional attractive properties of hypertonic saline are its ability to lower ICP by means of an osmotic effect and its ability to minimize vasospasm, excitotoxicity, and the inflammatory response in the brain.

Intracranial Stabilization

Once the cardiovascular and respiratory systems have been addressed, steps may be taken to stabilize the brain. The goals of intracranial stabilization are to limit intracranial hypertension by decreasing cerebral edema and optimizing intracranial blood volume and to minimize elevation of the cerebral metabolic rate.

Cerebral edema is a common problem in TBI. It can cause a progressive increase of ICP. Mannitol has traditionally been the drug of choice to help decrease cerebral edema. In addition to its osmotic properties, mannitol may scavenge free radicals involved in oxidative stress and improve microvascular flow within the injured brain. The concern that mannitol may exacerbate intracranial hemorrhage is unfounded, and the global beneficial effects of its use far outweigh this potential risk. Mannitol should not be administered unless euvolemia has been restored, because the osmotic diuresis resulting from its use will further intravascular volume contraction and potentially worsen CPP. With hypovolemia, hypertonic saline (7.5%) may be a better choice, because this fluid will both restore intravascular volume and exert osmotic effects on the brain.

The use of corticosteroids to decrease cerebral edema has fallen out of favor, because multiple prospective clinical trials in human head trauma patients have shown no benefit. This, in combination with the many adverse effects of corticosteroids (hyperglycemia, immunosuppression, gastric ulceration, delayed wound healing, and exacerbation of a catabolic state), precludes its recommendation for use in animals with TBI.

Another mechanism by which ICP can be lowered is optimization of intracranial blood volume. Elevating the head and neck uniformly 15 to 30 degrees above the rest of the body facilitates venous drainage from the brain. Angles higher than 30 degrees and kinking of the neck such that the jugular veins become occluded should be avoided because arterial inflow and venous outflow can be compromised. Hyperventilation can be used as a short-term method of decreasing intracranial blood volume, because cerebral vasoconstriction occurs in response to alkalosis. Care should be taken to avoid excessive hyperventilation ($PaCO_2$ no lower than 30 mm Hg), because this can worsen cerebral ischemia.

Although less common in veterinary medicine than in humans, space-occupying masses, such as subdural hematomas, may require surgical evacuation in the face of static or worsening neurologic status. Computed tomography (CT), rather than magnetic resonance imaging (MRI), is the diagnostic tool of choice for dogs and cats with TBI, because it provides good detail for bone, cerebral edema, and acute hemorrhage; it is more readily available; and it allows for greater access to the animal during the scan.

Minimizing elevations in the cerebral metabolic rate is another important concern for animals with TBI. Seizures should be controlled with anticonvulsants. Hyperthermia, which can be a result of direct trauma to the thermoregulatory center or of excitement, paddling, iatrogenic causes (heating pads), or pain, should be avoided.

Ancillary Therapeutics and Monitoring

Analgesia and nutrition are two important treatment concerns. Adequate analgesia is essential, using drugs that minimize cardiovascular and respiratory depression (e.g., butorphanol or hydromorphone). Barbiturates, propofol, and etomidate are acceptable anesthetic agents because they do not adversely affect cerebral blood flow or the cerebral metabolic rate. Ketamine, acepromazine, and xylazine do affect these functions and should be avoided. Immediately after head injury, a hypermetabolic state develops that persists for many days. Early institution of nutritional support is crucial in order to minimize protein catabolism and supplement important antioxidants needed to limit oxidative injury.

Careful monitoring and diligent nursing care are vital to successful management. Physical examination parameters that characterize tissue perfusion (i.e., mucous membrane color, capillary refill time, heart rate, respiratory rate, and pulse quality) should be assessed frequently. Oxygenation and blood

pressure should be monitored continuously or as often as feasible in the early phase of treatment, with the goals of maintaining oxygen saturation above 97% (PaO_2 greater than 90 mm Hg) and mean arterial blood pressure above 80 mm Hg. Likewise, $PaCO_2$ should be monitored to assess for adequate ventilation. The blood glucose, hematocrit, and total protein concentrations should be checked at least twice daily to ensure adequate fuel, oxygen-carrying capacity, and oncotic pressure. Sampling from the jugular vein should be avoided, because even temporary occlusion of this vessel can result in a rapid elevation in ICP. Given the propensity for excessive free water loss through the kidney with mannitol therapy, at minimum, electrolytes (particularly sodium) should be measured daily and urine output should be quantified. An effort should be made to adjust fluid input to account for ongoing losses.

Nursing care should focus on provision of adequate bedding, frequent turning, and passive range of motion physical therapy on the limbs to prevent pressure sores and limb contraction. The eyes should be lubricated frequently if the palpebral reflex is absent. Also, if an indwelling urinary catheter is not in place, the bladder should be manually expressed in animals that do not urinate voluntarily. Colonic enemas may be required.

Initially the neurologic status should be evaluated and recorded hourly to assess the response to treatment. The Small Animal Coma Scale, a modification of the Glasgow Coma Scale used in human medicine, has been developed for veterinary medicine to allow quantitative scoring of the severity of neurologic injury. This scale recently was validated retrospectively in dogs with head trauma and was shown to correlate with the 48-hour outcome. Serial evaluation of scores can be used to objectively evaluate improvement or deterioration over time.

Successful management of the dog or cat with severe TBI can be a rewarding experience. When neurologic signs have improved or reached a static level and the pet is able to maintain hydration and nutritional requirements (voluntarily or with a feeding tube), it can be sent home. Neurologic recovery may be completed over a period of time, or residual deficits may persist. Owners need to be dedicated and educated to the fact that substantial caretaking may be required of them once their pet has been sent home.

CHAPTER 114

Crystalloid and Colloid Fluid Therapy

Rebecca Kirby
Elke Rudloff

The goal of fluid resuscitation and maintenance is to restore perfusion and hydration while preventing volume overload and its complications of pulmonary, peripheral, and brain edema. The choice of the type and amount of crystalloid or colloid fluid to use begins with determination of where the fluid deficit is located. Capillary dynamics and the composition of the fluids administered govern how those fluids are distributed. The challenge is to deliver the right fluid, in the right amount, at the right time.

FLUID COMPARTMENT AND CAPILLARY DYNAMICS

Fluids and solutes are dispersed among the intracellular, interstitial, and intravascular compartments. The rate and volume of distribution within these spaces depends on membrane permeability, capillary dynamics (Starling's forces), and osmotic forces (Figures 114-1 and 114-2). Intracellular compartments are surrounded by membranes permeable to water but not to most charged particles (e.g., sodium). The space between blood vessels and cells is the interstitial compartment. Filtering and exchange of interstitial fluid are critical for cellular metabolism and survival. The arteries, veins, and capillaries contain the fluid of the intravascular compartment. Starling's forces affect the volume of fluid exchanged between the intravascular and interstitial compartments.

FLUID CHARACTERISTICS

The number, charge, and size of the particles in water, together with capillary dynamics, determine the movement of that fluid throughout the different fluid compartments. The dynamics of the various fluid compartments change during critical illness and shock. Inflammatory mediator action at the postcapillary venule causes endothelial cells to contract, resulting in large interendothelial gaps. Intravascular albumin (69,000 daltons) and other similar-sized molecules pass across the capillary membrane into the interstitium. The characteristics of a particular fluid affect the distribution of that fluid between the fluid compartments.

By osmosis, water passes through the membrane toward the side with the greater concentration of solutes. *Osmolality,* the osmotic pressure generated by a solution (in milliosmoles per kilogram of H_2O), opposes movement of water across a membrane. Sodium is the most significant osmotic ion in the extracellular space. The ability of a solution to move water across the cellular membrane depends on the osmolality of the solution compared to the intracellular osmolality; this is called *tonicity.* The tonicity of the administered fluid determines the resultant fluid shifts between the body compartments (Figure 114-3).

Proteins are the only dissolved substances in the plasma and interstitial fluid that do not readily cross the capillary membrane. Proteins are responsible for the osmotic pressure at the capillary membrane, called the *colloid osmotic pressure (COP)* or *oncotic pressure.* A serum protein concentration of 5.2 to

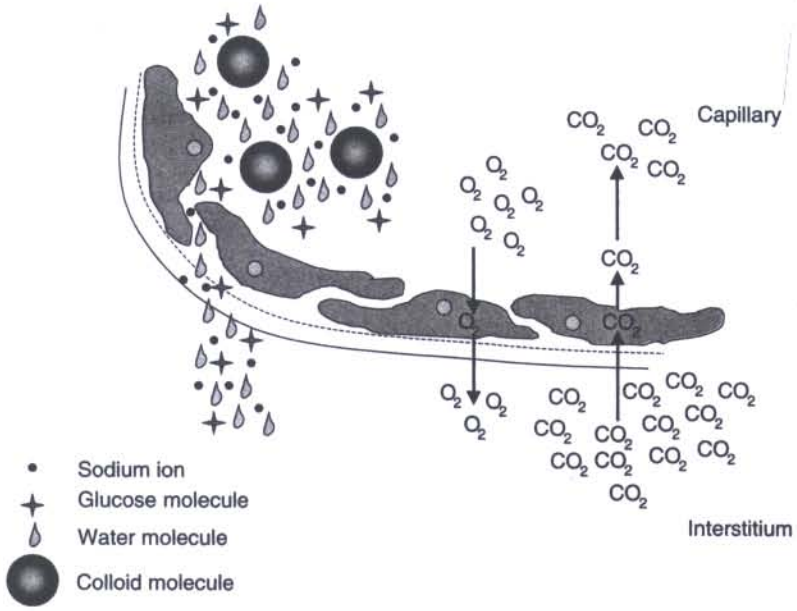

Figure 114-1 Cross section of a capillary. Lipid-soluble molecules, such as oxygen and carbon dioxide, diffuse through the interstitial and intravascular space. Non-lipid-soluble particles, to include water, must pass through intercellular clefts between endothelial cells. Colloid molecules that are too large to pass through the membrane cleft are retained in the capillary.

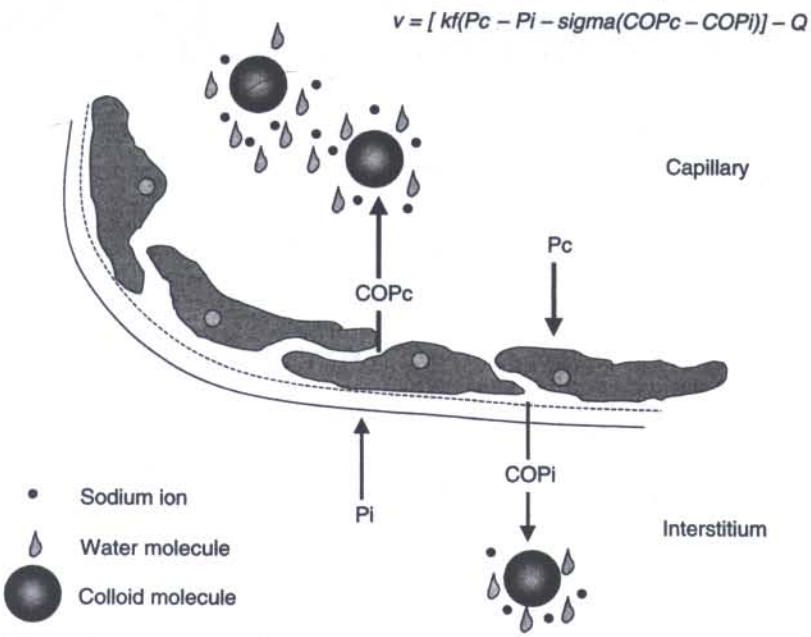

Figure 114-2 Illustration of Starling's forces between the intravascular and interstitial compartments. The intravascular and interstitial fluid compartments are separated by a semipermeable membrane. In solution in the intravascular compartment are large molecular weight molecules, called colloids, that cannot easily cross the membrane because of the minute size of the membrane pore. The force exerted on the membrane from the osmotic gradient created by these colloids is the colloid osmotic pressure (COP). The smallest and most numerous of the protein particles in plasma that create COP is albumin (~69,000 daltons). The overall negative charge of albumin increases its osmotic capability by 50% (called the Gibbs-Donnan effect). Whether fluid remains in the intravascular space or moves into the interstitium is the result of the cumulative effects of Starling's equation. The volume of fluid *(v)* that filters between the capillary *(c)* and interstitium *(i)* across the capillary wall depends on the interendothelial pore size *(sigma)*, the pore's reflection coefficient *(kf)*, and transcapillary forces of hydrostatic pressure *(P)* and COP, which oppose lymph removal *(Q)* of fluid. Intravascular fluid moves into the interstitial space when (1) Pc (capillary hydrostatic pressure) is increased over COPc (capillary colloid osmotic pressure); (2) capillary membrane pore size increases; or (3) COPc drops below COPi (capillary hydrostatic pressure).

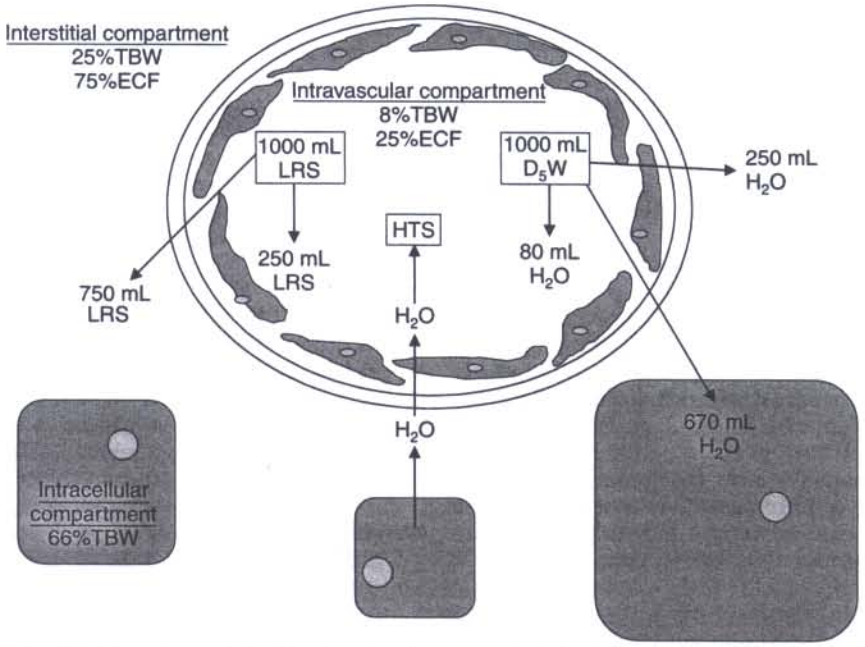

Figure 114-3 Tonicity and the distribution of various crystalloid fluids between body fluid compartments. Sixty percent of body weight is water. Of this water (total body water [TBW]), 66% is intracellular and 33% is extracellular fluid (ECF). Of the TBW that is extracellular, 25% is intravascular and 75% is interstitial. The membrane separating the intravascular and interstitial compartments is freely permeable to water and small ions, whereas the membrane surrounding the intracellular space is permeable only to water.

When solute-free water (e.g., D_5W), which has no osmotically active particles, is infused, it is distributed according to each body water compartment's percentage of TBW. Infusion of 1 L of solute-free water results in a net intravascular expansion of only 80 mL after 30 minutes of equilibration time.

When a hypertonic solution (HTS) is infused (e.g., 7% hypertonic saline or mannitol), the high concentration of osmotically active solutes draws water from the interstitial space into the intravascular space. The resulting increase in interstitial osmolality forces intracellular water to flow out into the interstitial space.

When a solution isotonic with plasma (e.g., LRS, Plasmalyte-A, Normosol-R) is infused, no alteration occurs in extracellular osmolality, and water remains in the extracellular space. Therefore, after infusion of 1 L of an isotonic solution, 250 mL remains in the intravascular space and 750 mL flows into the interstitial space after 45 minutes of equilibration time.

5.4 g/dL creates a COP of 17 mm Hg. When the serum protein falls below this range, the intravascular COP may be reduced. The type of fluid selected for therapy depends on the fluid's osmotic and colloidal properties and on the compartment requiring fluid.

FLUID SELECTION

The two major types of fluid administered are crystalloids and colloids. A *crystalloid* fluid is a water-based solution with small molecules that are permeable to the capillary membrane. A *colloid* fluid is a crystalloid solution that contains large molecules that are not readily permeable at the capillary membrane. The most commonly used crystalloids, colloids, and hemoglobin-based oxygen carriers (HBOCs) and their specific characteristics are listed in Table 114-1.

Crystalloids

Crystalloid fluids replace and maintain extracellular volume. Because 75% to 80% of the isotonic crystalloids administered intravenously move to the extravascular space within 1 hour in a normal animal, crystalloids are necessary for interstitial rehydration (see Figure 114-3). The needs of the patient are weighed against the specific electrolyte concentration, osmolality, and pH of the fluid selected.

The sodium and glucose concentrations of crystalloids determine the osmolality and tonicity of the fluid and therefore the distribution between the fluid compartments. In most critical situations, an isotonic, balanced electrolyte *replacement* crystalloid solution, such as lactated Ringer's solution (LRS), Plasmalyte-A, or Normosol-R, is used to replace electrolytes and buffers in concentrations typical of the extracellular fluid. Normal saline (0.9% sodium chloride solution) is also an isotonic replacement fluid but is not "balanced" with electrolytes or buffers.

Hypotonic solutions, such as 5% dextrose in water (D_5W), contain water in excess of solutes. Once the dextrose has been rapidly metabolized, the remaining water is distributed among all fluid compartments (see Figure 114-3). The use of hypotonic fluids should be restricted to slow infusion to replace calculated free water deficits; slow administration of constant-rate infusion drugs; or combination with replacement fluids to create half strength *maintenance* fluids.

Crystalloid solutions are made hypertonic by the addition of sodium or glucose. Hypertonic crystalloids comprise 3%, 7%, and 7.5% saline and 5% glucose in replacement solutions. The concentrated solutes produce an osmotic gradient, drawing water into the vascular space after intravenous administration (see Figure 114-3 for more information). If ongoing loss of plasma water is a factor or if the interstitium is dehydrated, these fluids should be avoided. Hypertonic saline is often combined with colloids to prolong intravascular volume retention.

The basal need for solute-free water by the cells directs the sodium concentration in *maintenance* fluids to be approximately 50% of the plasma concentration. Potassium requirements for maintenance are up to three times the replacement fluid concentrations. Maintenance crystalloid solutions are made isotonic by the addition of glucose to make a 2.5% concentration.

Colloids

Colloid solutions are primarily intravascular volume-replacing fluids (see Table 114-1). Whole blood, plasma products, and concentrated albumin contain natural colloids in the form of proteins, primarily albumin. Dextran 70 and hydroxyethyl starches (hetastarch and pentastarch) are synthetically derived colloids. It is the difference in their macromolecular structure and weight that dictates their colloid osmotic effect, method of excretion, and solution half-life. The greater the number of small molecules per unit volume, the greater the initial colloid osmotic effect and plasma volume expansion. Colloid solutions, in order of greatest plasma volume expansion, are 25% albumin, dextran 70, Oxyglobin, pentastarch, hetastarch, whole blood, and plasma. Often a combination of colloid solutions is the best therapeutic approach.

Natural Colloids

Natural colloid solutions are selected when the animal requires a colloid (albumin) as well as red blood cells, coagulation proteins, and/or antithrombin. A concentrated 25% albumin solution is available for rapid, low-volume resuscitation. In humans, 25% albumin is administered to the edematous patient who requires intravascular volume resuscitation. Although concentrated canine and feline albumin is not readily available, the human form has been used therapeutically in hypoalbuminemic dogs.

Dogs and cats receiving red blood cells in any solution should be blood typed and cross-matched. If time is a limiting factor, a dog erthrocyte antigen (DEA) 1.1-negative transfusion is preferred for the dog. Blood products should be warmed to normal body temperature prior to infusion and administered within 6 hours via an 18-μ micropore filter. The serum calcium should be monitored during multiple transfusions. Administration of large volumes of blood products can also cause a dilutional coagulopathy.

Synthetic Colloids

Synthetic colloid solutions were developed to provide timely and convenient fluid resuscitation while increasing the COP beyond that attainable with natural colloid solutions. They can be used in conjunction with whole blood or plasma but are not considered a substitute for blood products when albumin, red blood cells, antithrombin, or coagulation proteins are needed. Dextrans and hydroxyethyl starches (HES) are synthetic colloids, each with a pharmacology, specific qualities, and potential side effects that make it unique (see Table 114-1). The selection of a specific synthetic colloid is based on these individual characteristics.

Hemoglobin-Based Oxygen Carriers

Stroma-free hemoglobin solutions (e.g., Oxyglobin) are hemoglobin-based oxygen carriers (HBOCs) made of polymerized bovine hemoglobin suspended in LRS. These solutions have colloidal properties similar to those of hetastarch and exert a vasopressor effect. Administration of HBOCs improves oxygen saturation in the pulmonary capillary, with oxygen release at the tissue capillary at oxygen pressures of 40 mm Hg. Dosages up to 30 mL/kg/day have been approved for use in anemic dogs, with the rate of infusion equal to or less than 10 mL/kg/hour. When a HBOC is used in an animal with normal blood volume, slow administration and careful monitoring are necessary to prevent volume overload.

FLUID THERAPY PLAN

The fluid therapy plan must be adequate to replace fluid deficits in a timely manner, to replace continuing losses, and to meet the patient's ongoing requirements. Normal kidney and cardiovascular systems can correct most fluid therapy miscalculations, but these functions may be compromised in a critically ill animal. Often the clinician is challenged to promote organ perfusion while avoiding life-threatening interstitial edema. A fluid therapy plan should be formulated in a logical sequence, using end-point resuscitation techniques.

RESUSCITATION

During resuscitation, fluid therapy rapidly replaces a fluid deficit that is causing or has the potential to cause life-threatening organ compromise. A fluid deficit in the intravascular space manifests primarily as a *perfusion* problem. With a fluid deficit in the interstitial or intracellular space, the physical signs reflect a *hydration* problem.

Perfusion

Perfusion problems are manifested as changes in the heart rate, pulse intensity, mucous membrane color, capillary refill time, and rectal temperature. Resuscitation of perfusion deficits associated with hypovolemia requires rapid intravascular volume expansion by intravenous or intraosseous routes of administration. Fluid selection and doses are in part based on the animal's cardiovascular status and emergency data base (packed cell volume; total protein; serum glucose; sodium, calcium, potassium, and blood gas values; Table 114-2 and Box 114-1).

Crystalloids can be administered without colloids; however, perfusion end-points (Table 114-3) may be more difficult to reach without complications of edema. Large volumes of crystalloids rapidly administered intravenously cause an immediate increase in intravascular hydrostatic pressure and a reduction in COP, leading to extravasation into the interstitium. Extreme care must be taken when crystalloids alone are administered during resuscitation of animals with pathology of the brain, lungs, kidneys, or heart. The total amount of fluid required for resuscitation may be less or more than the estimated plasma volume (50 to 60 mL/kg in the dog; 40 to 50 mL/kg in the cat), requiring titration of volumes to effect.

Resuscitation using both colloids and crystalloids requires less volume and achieves faster resuscitation times. When colloid is added, crystalloid infusion rates can be reduced by 40% to 60% of that required if crystalloids were used alone. Synthetic colloids increase the COP effect, resulting in an increase in intravascular volume greater than the volume infused. Resuscitation of conditions with increased capillary permeability necessitates selection of a solution containing colloids larger than the pore size of the capillaries. This makes hetastarch, pentastarch, or stroma-free hemoglobin the preferred colloids. When the animal requires red blood cells, clotting factors, antithrombin, or albumin, natural colloids are the

Table • **114-1**

Characteristics of Crystalloids and Colloids

NAME	FLUID COMPARTMENT	OSMOLARITY (mOsm/L)	pH	Na^+ (mEq/L)	Cl^- (mEq/L)	K^+ (mEq/L)
CRYSTALLOID						
Replacement						
0.9% Saline	Extracellular	308 (isotonic)	5.0	154	154	0
Lactated Ringer's solution	Extracellular	275 (isotonic)	6.5	130	109	4
Plasmalyte-A (pH 7.4)	Extracellular	294 (isotonic)	7.4	140	98	5
Normosol-R	Extracellular	295 (isotonic)	5.5-7	140	98	5
7% Saline	Extracellular	2396 (hypertonic)		1197	1197	0
5% Dextrose in water	Intracellular	252 (hypotonic)	4.0	0	0	0
Maintenance						
2.5% Dextrose in ½ strength lactated Ringer's solution	Extracellular	264 (isotonic)	4.5-7.5	65.5	55	2
ProcalAmine	Extracellular	735 (hypertonic)	6-7	35	41	24
3% FreAmine III	Extracellular	405 (hypertonic)	6-7	35	41	24
COLLOID						
Natural						
Fresh whole blood Stored whole blood	Intravascular	300 (isotonic)	Variable	140	100	4
Fresh frozen plasma, frozen plasma	Intravascular	300 (isotonic)	Variable	140	110	4
25% Albumin	Intravascular	300 (isotonic)	Variable	130-160	0	1
Synthetic						
6% Hetastarch	Intravascular	310 (isotonic)	5.5	154	154	0
10% Pentastarch	Intravascular	326 (isotonic)	5.0	154	154	0
Dextran 70	Intravascular	310 (isotonic)	3-7	154	154	0
Hemoglobin-Based Oxygen Carriers						
Stroma-free hemoglobin (e.g., Oxyglobin)	Intravascular	300 (isotonic)	7.8	150	118	4

Na^+, Sodium; Cl^-, Chloride; K^+, potassium; Mg^{++}, magnesium; Ca^{++}, calcium.

Mg^{++} (mEq/L)	Ca^{++} (mEq/L)	DEXTROSE (g/L)	BUFFER	COP (mm Hg)	ADDITIONAL CHARACTERISTICS
0	0	0	None	0	Fluid of choice for treating hyperkalemia or hypochloremia associated with alkalosis.
0	3	0	Lactate	0	Should not be administered in the same lines with citrate-containing transfusions.
3	0	0	Acetate, gluconate	0	
3	0	0	Acetate, gluconate	0	
0	0	0	None	0	Should not be used in a dehydrated patient or during hyperosmolar disease states.
0	0	50	None	0	Primarily used as a carrier for constant rate infusion drugs.
0	1.5	25	Lactate	0	
5	0	30	Acetate, phosphate	0	Contains 3% amino acid solution + 3% dextrose; beneficial during partial anorectic states.
5	0	0	Acetate, phosphate	0	Contains 3% amino acid solution; beneficial during partial anorectic states.
0	0	0-4	None	20	Contains red blood cells, albumin, fibrinogen, globulins, alpha macroglobulins, coagulation proteins, and antithrombin. Factors V and VIII and platelets are absent in stored whole blood.
0	0	0-4	None	20	Contains albumin, fibrinogen, globulins, alpha macroglobulins, coagulation proteins, and antithrombin. Factors V and VIII are absent in frozen plasma.
0	0	0	None	100	Used during resuscitation of hypovolemic, edematous states. Slow infusion is used during hypoalbuminemic states.
0	0	0	None	30	Molecular weight range is 10,000-3,400,000 daltons. Half-life is 25 hours. May increase plasma amylase and coagulation times.
0	0	0	None	25	Molecular weight range is 10,000-1,000,000 daltons. Half-life is 2.5 hours. May increase plasma amylase and coagulation times.
0	0	0	None	60	Molecular weight range is 15,000-160,000 daltons. Half-life is 25 hours. May increase coagulation times.
0	4	0	Lactate	40	Molecular weight range is 65,000-500,000 daltons. Half-life is 30-40 hours. Higher doses may result in darkening of plasma color, which may affect serum and urinalysis results.

Table • 114-2

Emergency Data Base Information That Guides Formulation of a Fluid Therapy Plan

TEST	VALUE	COMMENTS
PCV (%)	≤20 or declining trend	Administer RBCs or HBOCs.
	>60	Causes hyperviscosity. Need rapid and aggressive hemodilution with crystalloids (+/– colloids).
Total protein (g/dL)	<5.0	Administer hetastarch during resuscitation and maintenance.
	>9.0	Need rapid and aggressive hemodilution with crystalloids (+/– colloids).
Glucose (mg/dL)	<60	May require 0.5 g/kg IV dextrose bolus.
	>400	Use slow rehydration to avoid rapid drop in plasma osmolality and cerebral edema. May require insulin therapy after resuscitation.
Sodium (mEq/L)	≥175 or ≤130 mEq/L	Give small volume resuscitation with 0.9% saline.
Potassium (mEq/L)	≥8.0	Use 0.9% saline if oliguric.
	≤2.0	Supplement resuscitation fluids if respiratory muscle fatigue is present.
	2.0-5.5	Supplement maintenance fluids.
Total calcium (mg/dL) (corrected value)	≥13.0	Use 0.9% saline for calciuresis.
pH and bicarbonate	Metabolic alkalosis	Use 0.9% saline if patient is hypochloremic.
	Metabolic acidosis	Aggressive fluid resuscitation usually corrects acidemia; recheck values after resuscitation.

RBC, Red blood cells; *HBOC*, hemoglobin based oxygen carrier; *PCV*, packed cell volume.

Box • 114-1

Steps for Formulating a Fluid Therapy Plan

1. Determine whether a fluid deficit exists based on the physical examination findings.
   a. Poor perfusion (intravascular loss): Consider colloid and isotonic replacement crystalloid combination.
   b. Dehydration (interstitial loss): Use isotonic replacement crystalloid.
2. Determine the resuscitation technique and end-points to be used.
   a. Small volume resuscitation is used in the cat (Figure 114-5).
   b. Most causes of hypovolemic shock in the dog warrant rapid intravascular resuscitation (Figure 114-4).
   c. Complications such as heart disease, hemorrhage, lung or brain pathology, hyperglycemia, or hypernatremia warrant small volume resuscitation (Figure 114-4).
3. Assess the emergency data base (Table 114-2).
4. Determine which crystalloid to administer.
   a. Each fluid therapy plan incorporates crystalloids.
   b. A balanced isotonic crystalloid (e.g., Plasmalyte-A, Normosol-R, LRS) is usually selected for initial resuscitation.
   c. 0.9% saline is used if hypernatremia, hyponatremia, hypercalcemia, hypochloremic metabolic alkalosis, or oliguric renal failure is a factor.
5. Determine which colloid to administer if poor perfusion is the result of hypovolemia.
   a. Hetastarch is the colloid of choice if systemic inflammatory response syndrome is anticipated or if the patient is hypoalbuminemic.
   b. Dextran 70 can be used for initial resuscitation if systemic inflammatory response syndrome is not suspected.
   c. Anemia (PCV ≤20% or rapidly declining) may require administration of whole blood, packed red cells with a colloid, or stroma-free hemoglobin.
6. Evaluate for vascular leakage, vasodilatation, and third spacing of body fluids, which may require larger volumes of fluid to reach end-points of resuscitation.
7. If unable to reach or maintain end-points of resuscitation:
   a. Evaluate for causes of nonresponsive shock (e.g., inadequate volume replacement, ongoing hemorrhage, ongoing fluid loss, heart failure, brain failure, hypoglycemia, hypoxia, hypokalemia, excessive vasodilatation/vasoconstriction).
   b. Consider administering Oxyglobin in 5 mL/kg increments (dogs) for vasopressor and COP effects if not used previously.
   c. Consider administering dopamine (5 to 15 µg/kg/min) as a constant-rate infusion.
8. After perfusion has been restored (Table 114-5), estimate the percentage of dehydration and calculate the fluid deficit.
   a. % Dehydration × Body weight (kg) = Fluid deficit (L)
      Example: 30 kg dog that is 10% dehydrated:
      0.10 × 30 = 3.0 L fluid deficit

Continued

Box • 114-1

Steps for Formulating a Fluid Therapy Plan—cont'd

9. Rehydration therapy may require a crystalloid different from that used to resuscitate the perfusion deficit.

Maintenance Fluid Plan

1. Estimate ongoing losses caused by vomiting, diarrhea, third spacing of body fluids, and polyuria.
   a. Use isotonic balanced replacement crystalloid fluids (e.g., Plasmalyte-A, Normosol-R, or LRS).
   b. Use 0.9% saline if hypernatremia, hyponatremia, hypercalcemia, hypochloremic metabolic alkalosis, or oliguric renal failure is a factor.
   c. Add crystalloid (2 mL/kg/h; see steps 2a and 2b below) to the volume of the estimated ongoing losses.
   d. Supplement potassium in fluids:

Serum Potassium (mEq/L)	Potassium Supplementation
4.0-5.5	5 mEq/250 ml fluids
3.0-3.9	7 mEq/250 ml fluids
2.5-2.9	8 mEq/250 ml fluids
≤2.5	10 mEq/250 ml fluids

2. Maintenance crystalloid fluids (see Table 114-1) are selected when no ongoing losses are present.
   a. Administer 2 mL/kg/h to replace free water and electrolytes consumed during metabolism and insensible losses.
   b. Dosage increases 1-2 mL/kg/h if fever or hyperpnea is present.
3. During anesthesia, replacement crystalloids (5-8 mL/kg/h) are used for maintenance.
   a. Adjust potassium supplementation according to the fluid rate; potassium-supplemented fluids are not used for rapid volume replacement.
   b. Keep warm bags of replacement crystalloids that do not contain potassium supplementation within easy reach, in the event rapid, large-volume boluses are required for resuscitation during the period of anesthesia.
4. For hypernatremia (Na^+ ≥170 mEq/L) with normal perfusion and hydration: Replace solute free water using maintenance crystalloids.
   a. [(Measured Na^+ – 140)/140] × Body weight (kg) × 0.3 = Free water deficit (L).
   b. Replace free water deficit over 24 to 48 hours: Lower 1 mOsm/kg/h.
   c. Add volume for metabolism and insensible losses (see steps 2a and 2b, above).

administered products. With natural colloids, the blood volume is increased by an amount equal to the amount infused. A combination of crystalloid, synthetic colloid, and natural colloids often is required to meet the patient's needs.

Rapid Intravascular Volume Resuscitation for Dogs

Dogs experiencing shock due to hypovolemia or maldistribution of blood flow from nontraumatic causes can benefit from rapid intravascular resuscitation techniques (Table 114-4). Whole blood products can be administered rapidly in catastrophic hemorrhagic situations, with input at least matching ongoing losses. Additional colloids can be administered using small volume intravascular resuscitation techniques if perfusion has not improved to the desired end-point after the initial bolus (see Figure 114-5). Rapid intravascular volume resuscitation techniques are not recommended in the cat in shock.

Small Volume Intravascular Resuscitation

Hypovolemic dogs with closed cavity hemorrhage, head trauma, pulmonary contusions, cardiogenic shock, oliguric renal failure, hypernatremia, or hyperglycemia can benefit from careful resuscitation using small volume intravascular resuscitation techniques (Figure 114-4). This also applies to all hypotensive cats (Figure 114-5). Hypothermia, especially in the cat, can significantly blunt cardiovascular responses to fluid resuscitation. Active external warming should occur once fluid resuscitation has been initiated. The goal is to reach a rectal temperature above 98° F within 30 minutes to maximize catecholamine receptor response. If no heart disease is present, small volume resuscitation efforts with crystalloids and synthetic colloid infusion is continued until the desired end-points are obtained.

When the dose of hetastarch and dextran 70 exceeds 40 mL/kg/day in the dog and 20 mL/kg/day in the cat, plasma transfusions may be necessary to maintain adequate coagulation times. Stroma-free hemoglobin can be used in the dog, the total not exceeding 30 mL/kg/day. If the arterial blood pressure remains below 70 mm Hg after the maximum recommended doses have been administered, an investigation into causes of nonresponsive shock (e.g., severe vasodilatation/vasoconstriction, cardiac dysfunction) should be started, and administration of dopamine (5 to 15 µg/kg/min in a constant-rate infusion [CRI]) or stroma-free hemoglobin (if not yet used) should be considered for vasopressor effects.

Rehydration

Fluid deficit in the extravascular space (interstitial and intracellular) causes *dehydration*. Severe dehydration can lead to impaired perfusion due to fluid movement from the intravascular space to the dehydrated interstitium. To replenish the interstitial space, crystalloid fluids isotonic to plasma that contain specific electrolytes based on the patient's needs should be administered (see Table 114-1). The amount of crystalloid is determined by using physical parameters to estimate the percent dehydration (see Box 114-1 and Table 114-5). Intravenous or intraosseous administration of the fluid is preferred, although subcutaneous routes can be used.

The rate of administration should be determined by the urgency of the situation. Acute loss warrants acute replacement

Table • 114-3

End-Point Parameters Monitored During Resuscitation

PARAMETER	NORMAL	COMPENSATORY STAGE	EARLY DECOMPENSATORY STAGE	LATE DECOMPENSATORY STAGE	RESUSCITATION END-POINT	TECHNICAL NOTES
Mentation	Alert	Excited and alert	Normal to decreased	Decreased to comatose	Alert	
Heart rate (beats/minute)	Dog: 60-120 Cat: 170-200	Dog: >140 Cat: Variable	Dog: >140 Cat: Variable	Dog: <140 Cat: <160	Dog: 80-140 Cat: 180-220	Ensure pain relief. Examine ECG with abnormal rate/rhythm and correct arrhythmia if contributing to perfusion deficit.
Mucous membrane color	Pink	Brick red	Pale	Grey/blue	Pink	Yellow color may also suggest icterus.
Capillary refill time (sec)	1-2	<1	>2	>2	1-2	Can be determined by examining gums, conjunctiva, vulvar/preputial membrane.
Mean arterial blood pressure (mm Hg)	80-100	>80	Variable	<80	80-100* 60-80**	Renal blood flow is affected at MAP <60 mm Hg; cerebral and coronary perfusion pressures are affected at MAP <70 mm Hg. Acute hypertension can occur with compensatory stages of shock.
Central venous pressure (cm H_2O)	0-2	Variable	<5	Variable	5-10* 2-8**	Tip of catheter should be in the superior vena cava at the level of the right atrium. Unexpected elevations can occur with right heart failure, loss of venous compliance, and increased intrathoracic pressure.
Urine output (mL/kg/h)	>1.67	Variable	<0.27	<0.08	>1	With decreased urine output, check for urine obstruction first (patent urine collection). MAP >60 mm Hg is required for adequate renal blood flow.

SpO_2	>97%	>97%	Falsely low levels can be caused by poor peripheral perfusion, dark pigmentation, bilirubinemia, and severe anemia. Falsely increased levels can be caused by carboxyhemoglobinemia or methemoglobinemia.
Packed cell volume	Dog: 40%-55% Cat: 30%-45%	25%-30%	Transfusion products containing red blood cells (whole blood, packed red cells) or a HBOC (in the dog) should be used; HBOCs do not change the PCV, therefore the hemoglobin level must be monitored. Ongoing hemorrhage must be controlled.
Hemoglobin (g/dL)	13.8-21.4	7-10	HBOC can be administered when the hemoglobin is <7 g/dL.
Albumin (g/dL)	2.6-3.9	>2.0	Plasma or albumin transfusion is required when the serum albumin is <2.0 g/dL.
Colloid osmotic pressure (mm Hg)	Dog: 21-25 Cat: 23-25	14-20	
Rectal temperature (° F)	100-102.5	98-102	

ECG, Electrocardiogram; *MAP*, mean arterial pressure; *SPO_2*, pulseoximeter hemoglobin saturation of oxygen; *HBOC*, hemoglobin based oxygen carrier; *PCV*, packed cell volume.
*Supranormal.
**Hypotensive.

Table • 114-4

Options for Fluid Types and Doses During Resuscitation

CARDIOVASCULAR STATUS	FLUID TYPE	COMMENTS
Compensatory shock	Isotonic crystalloid	If EP is not reached with several boluses, consider adding synthetic colloid.
	or	Treat for pain.
	Isotonic crystalloid + synthetic colloid	Not a condition typically seen in the hypovolemic cat.
Early decompensatory shock	Isotonic crystalloid	Rapidly correct hypothermia.
		Treat for pain.
		If EP is not reached with several boluses, consider adding synthetic colloid.
	or	
	Isotonic crystalloid + synthetic colloid	Rapidly correct hypothermia.
		Treat for pain.
		If EP is difficult to maintain, place patient on HES CRI, 0.8 mL/kg/h.
		Do not administer HTS to a dehydrated animal or one with pulmonary injury or cardiac disease.
Late decompensatory shock	Isotonic crystalloid + synthetic colloid	Rapidly correct hypothermia.
		Treat for pain.
	or	If EP is not reached with multiple boluses, consider administering vasopressors or oxyglobin boluses (5 mL/kg), up to 30 mL/kg/day (dog).
	Isotonic crystalloid + 7% HTS + synthetic colloid	If EP is difficult to maintain, place patient on HES CRI, 0.8 mL/kg/h.
	or	
Acute hemorrhage (PCV <25%; Hg <8 g/dL)	Whole blood	May require active hemostasis.
	or	Crossmatch and typing are preferred, time permitting.
	Packed red blood cells and/or	Can be reconstituted with isotonic saline, plasma, HES, or DEX.
	Oxyglobin	May require additional red cell transfusion.
Hypovolemia with pulmonary injury, head injury, or cardiac insufficiency	Isotonic crystalloid + HES	If EP is difficult to maintain, place patient on HES CRI, 0.8 mL/kg/h.
Low plasma albumin (<2.0 g/dL)	Plasma	Repeat as needed to increase albumin >2.0 g/dL and/or to normalize clotting times.
Coagulopathy (prolonged PT/PTT)		Use fresh frozen plasma if factor V or VIII deficiency is present.
Low antithrombin		Consider heparin if DIC is suspected.

HES, hydroxyethyl starch; *DEX*, dextran-70; *HTS*, hypertonic saline; *EP*, end-point; *CRI*, constant rate of infusion; *PCV*, packed cell volume; *Hg*, hemoglobin; *PT*, prothrombin time; *PTT*, partial thromboplastin time; *DTC*, disseminated intravascular coagulation.

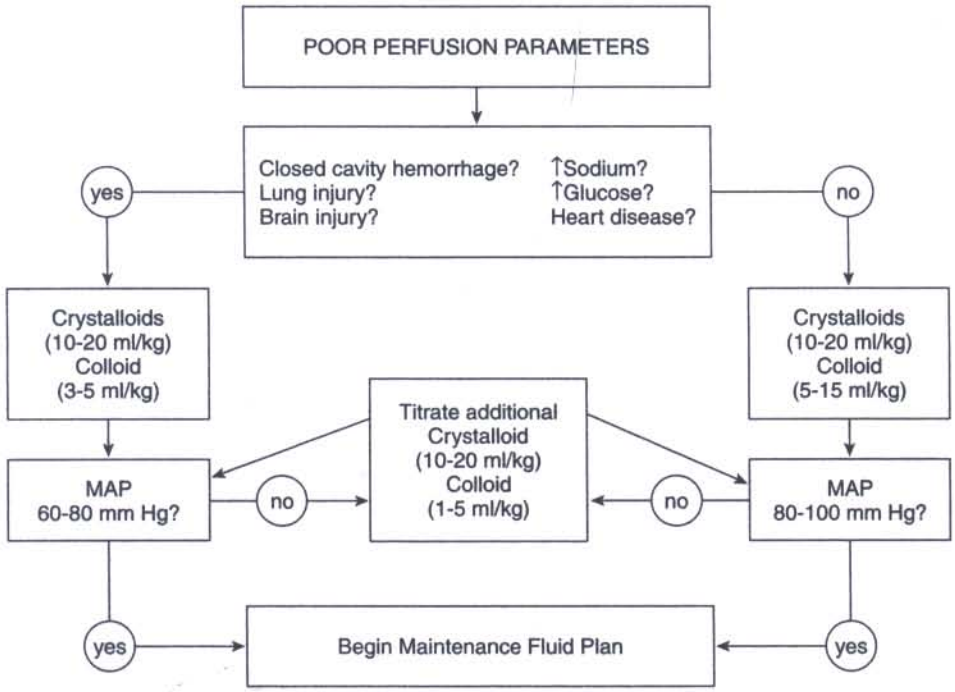

Figure 114-4 Resuscitation technique for the dog with poor perfusion. Low-volume resuscitation (left arm of algorithm) is used when the consequences of fluid overload are life-threatening (e.g., lung, brain, or heart disease; closed cavity hemorrhage; or hyperosmolar condition). Low-volume bolus doses of crystalloid and colloid fluids are administered until the mean arterial pressure (MAP) is in the low-normal range. When the risk of fluid overload is not as likely, resuscitation fluid volumes are maximized (right arm of algorithm) to establish a high-normal MAP using larger volume boluses of crystalloid and colloid fluids. When the dose of colloid has reached 40 mL/kg without response, an investigation for causes of nonresponsive shock is begun, and use of vasopressors may be required.

over 1 to 4 hours. Chronic losses or dysfunction of the lungs, heart, or brain usually require slower resuscitation rates, over 4 to 12 hours. The total amount given and the rate of administration should be determined by monitoring for specific end-point parameters (see Table 114-3).

End-Point Resuscitation

Successful resuscitation therapy depends on the administration of quantities of fluids sufficient to reach specified end-points. This process is termed *end-point resuscitation*. Prior to resuscitation, the clinician should determine the end-point values that will indicate successful resuscitation. Physical, hemodynamic, and blood chemistry parameters are the mainstays of end-point monitoring (see Table 114-3). The inciting cause of the fluid deficit, as well as vital organ function, dictate the end-points selected and the end-point resuscitation techniques used.

For hypovolemic shock and systemic inflammatory response syndrome (SIRS), if brain or lung compromise is not a factor, resuscitation of perfusion to supranormal values to

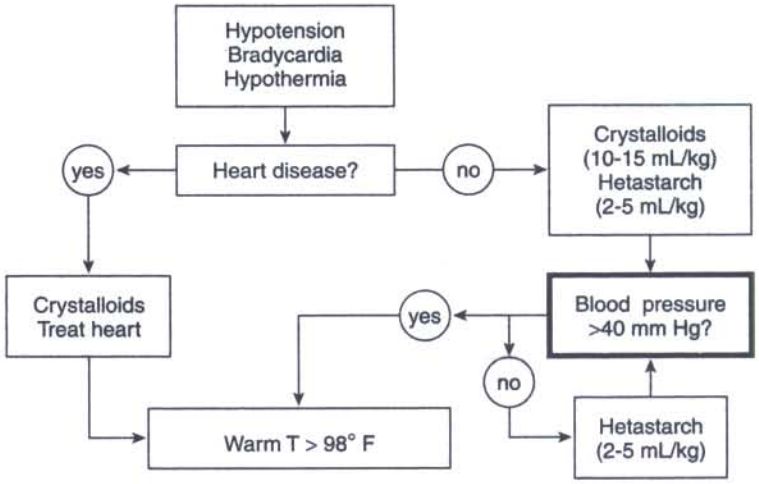

Figure 114-5 Resuscitation technique for the cat with poor perfusion. When heart disease is suspected (auscultation of a murmur, arrhythmia, moist lung sounds, pleural effusion), isotonic replacement crystalloid fluids are administered at a maintenance rate; treatment of heart disease is instituted; and active external warming is provided. When poor perfusion is not attributed to heart disease, low volumes of crystalloid and colloid fluids are administered in bolus doses until the blood pressure registers above 40 mm Hg, and the cat is actively warmed. When the dose of colloid has reached 20 mL/kg without response, an investigation for causes of nonresponsive shock is begun, and use of vasopressors may be required.

Table • 114-5

Parameters Used to Estimate Interstitial Fluid Deficit

ESTIMATED % DEHYDRATION	CLINICAL PARAMETERS
4-6	Sticky mucous membranes History of vomiting, diarrhea, lack of water intake
6-8	Loss of skin moisture Dry mucous membranes
8-10	Loss of skin moisture Dry mucous membranes Sunken eyes
>12	Loss of skin moisture Dry mucous membranes Dull mentation Dull corneas Perfusion deficit present

increase oxygen delivery is recommended. Restoration of physical perfusion parameters (lower heart rate, stronger pulses, normal capillary refill time, and pink mucous membranes) is used in conjunction with hemodynamic parameters (e.g., packed cell volume [PCV], COP, arterial blood pressure, urine output, and central venous pressure) as a measure of therapeutic success.

Traumatic shock with closed cavity hemorrhage and/or brain hemorrhage warrants hypotensive resuscitation. The animal is resuscitated to end-points of improved physical perfusion parameters, but the target blood pressure is in the low-normal range (see Figure 114-4). This method is used to avoid dislodging clots that may be providing life-saving hemostasis.

Maintenance

Crystalloids are the mainstay of fluid therapy, and the type of fluid chosen is based on the needs of the animal (see Table 114-2 and Box 114-1). Maintenance fluids can provide electrolytes, COP support, proteins, coagulation factors, glucose, or nutrients, depending on the fluid selected and the way it is supplemented (see Table 114-1). Increased capillary permeability and hypoproteinemic states can require ongoing maintenance of COP by a constant-rate infusion of hetastarch combined with maintenance crystalloid.

Normal maintenance fluid rates account for insensible, obligatory (urinary and fecal), and metabolic losses of water and electrolytes. The standard crystalloid fluid maintenance requirement is estimated to be 40 to 60 mL/kg/day. Ongoing losses through diuresis, fever, vomiting, diarrhea, or extravasation of fluid into third body spaces should be estimated and replaced with isotonic replacement crystalloids. This estimated volume is added to the total daily "maintenance" volume requirement, and oral intake volumes should be subtracted. The maintenance fluid therapy plan must be reassessed for the duration of therapy, with adjustments made accordingly.

CHAPTER • 115

Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar Syndrome

Michael Schaer

Dogs and cats afflicted with either diabetic ketoacidosis (DKA) or hyperglycemic hyperosmolar syndrome (HHS) can become acutely ill and benefit from prompt diagnosis and treatment. These disorders usually occur in middle-aged to old pets, often after a variable period of time characterized by polydipsia, polyuria, and weight loss. Alternatively, they can occur as acute metabolic complications of other conditions, such as acute pancreatitis or sepsis. The primary pathophysiology, clinical signs, and medical management of these interesting and challenging disorders are discussed in this chapter. Certain clinical findings shared by the two syndromes are discussed in the section on ketoacidosis.

PATHOPHYSIOLOGY OF KETOACIDOSIS

Hyperglycemia and accelerated ketogenesis occur when there is an absolute or relative deficiency of insulin and a relative excess of glucagon and other "counter regulatory hormones" such as cortisol, growth hormone, and epinephrine. Consequently, glucose and ketoacids are both overproduced and underutilized. Because the pathophysiologic details of DKA are discussed elsewhere in this text and throughout the medical literature, only those germane to the care of the critically ill patient are mentioned in this section.

The nitroprusside reaction is used to detect and semiquantitate plasma, serum, and urinary ketones. The test detects acetone and acetoacetate but does not react with beta hydroxybutyrate. This characteristic has clinical importance in situations in which shocklike states promote the production of beta hydroxybutyrate, thereby disabling clinical detection of ketoacidosis with the nitroprusside test.

After institution of insulin treatment, the beta hydroxybutyrate to acetoacetate (B:A) ratio decreases as a result of the metabolism of beta hydroxybutyrate to acetoacetate. Although acetoacetate concentrations eventually decrease, the shifting B:A ratio explains the clinical paradox occasionally encountered in which test results initially are negative for ketones but,

with the same test given on the second and third days of treatment, are positive despite clinical improvement. A lingering ketonuria can also occur as a dog or cat improves because of the delayed clearance of acetone. Therefore it is not uncommon for ketones to persist well into the third or fourth hospital day while the pet shows signs of improvement.

DIAGNOSIS

History and Physical Examination

The history for either DKA or HHS often indicates that anorexia, depression, weakness, and vomiting have been observed for only 1 to 3 days. A complete physical examination is essential to detect any concurrent disorders that can significantly affect the outcome. It has been suggested that both conditions are invariably associated with concurrent disorders. The term *diabetic coma* is frequently used to describe the mental effects of the ketoacidotic and hyperosmolar conditions, but only a small percentage of dogs or cats actually have profound decreases in consciousness.

DIAGNOSTIC EVALUATION

Medical evaluation of a sick diabetic dog or cat should be thorough and should include thoracic radiographs, abdominal ultrasound scans, hematology, serum chemistry, and urinalysis. The acquired information creates an important data base for subsequent medical and sometimes surgical management.

Because hepatic production of glucose is increased in diabetic dogs or cats, the degree of hyperglycemia is determined by the severity of plasma volume depletion. Therefore extreme levels of hyperglycemia tend to occur only when extracellular fluid volume and blood pressure have decreased so much that urine flow is impaired. This is most obvious in dogs or cats that have extreme increases in blood glucose concentrations with minimal glucosuria. Marked hyperglycemia may also signify oliguria.

Metabolic acidosis is mainly attributed to ketoacid buildup, but acidosis can be enhanced by coexisting disease, such as renal failure and lactic acid production. The metabolic acidosis often is accompanied by a large anion gap (AG) (greater than 30 mEq/L) that can be calculated using the following formula:

$$AG = (Na^+ + K) - (HCO_3^- + Cl^-)$$

Hyponatremia in both syndromes can be factitious (attributable to hypertriglyceridemia) or real (due to urinary or gastrointestinal loss of sodium ions). Spurious hyponatremia can also occur when increases in the plasma glucose concentration draw water into the extracellular space, thereby diluting plasma constituents.

The serum potassium concentration in DKA and HHS can range from low to normal to increased. Hyperkalemia can result from a shift of potassium from the intracellular to the extracellular space as a consequence of acidemia, insulin deficiency, and plasma hyperosmolarity. It may also be associated with oliguric or anuric acute renal failure.

Hypokalemia is the most common and most serious electrolyte disturbance. This is usually a reflection of a substantial reduction in total body potassium stores. Even patients with normokalemia may have a considerable deficit of total body potassium; because 98% of total body potassium is intracellular, these concentrations are not easily assessed. Potassium losses occur with vomiting and osmotic diuresis and can be further complicated by therapy. Serum dilution from rehydration, continued urinary losses, correction of acidosis, and increased cellular uptake can "unmask" hypokalemia.

Phosphorus is an integral component of lean body mass. The enhanced catabolism of muscle and fat that invariably occurs in diabetes mellitus results in increased urinary phosphorus excretion and phosphorus wasting.

Increased serum liver transaminase (ALT) and alkaline phosphatase (SAP) activity is commonly attributable to the hepatic lipidosis that occurs in patients with DKA. Hypovolemia-induced central lobular necrosis can also increase liver enzyme values. These hepatic changes are completely reversible, and serum liver enzyme activity moves toward normal after successful treatment. Because diabetic dogs and cats almost always have abnormal liver enzyme values, it is not common for these test results to completely "normalize."

Azotemia can be either prerenal or renal in origin. Extensive primary renal dysfunction is characterized by isosthenuria (fixed urine specific gravity of 1.008 to 1.012) in a dehydrated patient and an accompanying azotemia that does not readily resolve with rehydration. It should be remembered, however, that both glycosuria and hyperosmolarity can raise a urine specific gravity that remains "isosthenuric" (a specific gravity of 1.020 when the serum osmolality is 400 does not indicate good renal function). Urine sediment should be screened for any signs of infection such as pyuria and bacteriuria. Urine output should be monitored to detect oliguria or anuria.

A leukocytosis with a mature neutrophilia in the 20×10^3 range can be due to the stress associated with both disorders. Detection of bands and toxic cell changes should prompt a search for an inflammatory focus, which may or may not be accompanied by an infection.

TREATMENT

Fluid and Electrolytes

Disturbances in hydration and electrolyte balance are of great importance in DKA and HHS and require expedient correction (Figure 115-1). The calculated fluid requirements include the patient's dehydration deficits, the 24-hour maintenance needs, and extra losses that result from vomiting or diarrhea. The dehydration status is approximated on a scale ranging from mild (5%) to extreme (12%). The needed isotonic crystalloid fluid replacement volume can be calculated using either of the following equations:

- Dehydration volume deficit (mL) = Dehydration (%) × Body weight (kg) × 1000
- Dehydration (%) × Body weight (lb) × 500

The 24-hour maintenance volume is roughly estimated (assuming adequate urine output) at 66 mL/kg (30 mL/lb). Therefore the first 24-hour total fluid volume is the sum of the dehydration and the maintenance volumes plus any ongoing losses from vomiting or diarrhea.

If the animal is 8% to 12% dehydrated, half of the estimated dehydration deficit should be administered intravenously over the first 2 to 4 hours of hospitalization; the remaining replacement and maintenance volumes, given over the following 20 to 22 hours, should be accompanied by any adjustments necessitated by changes in urine volume.

Hydration alone can substantially decrease the blood glucose level and hyperosmolarity. Hypovolemia in DKA and HHS is corrected with isotonic solutions, such as lactated Ringer's solution or 0.9% saline. Recommended maintenance solutions include 0.45% saline or half-strength lactated Ringer's solution. Dextrose solutions (2.5% to 5%) are used when the patient's blood glucose declines to 250 mg/dL or less in the setting of continued insulin administration.

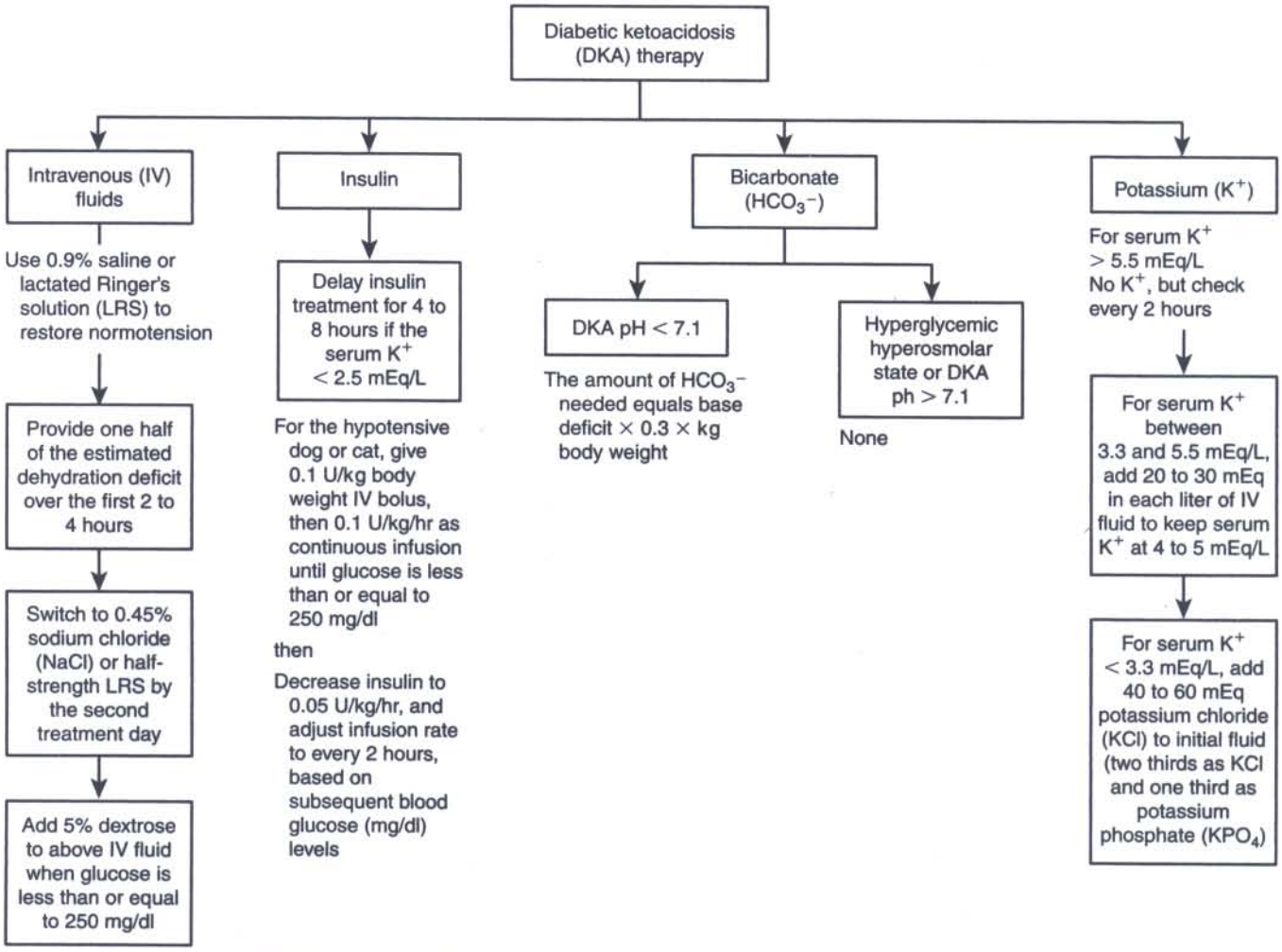

Figure 115-1 Algorithm for the management of the critically ill dog and cat with diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome. (Modified from Umpierrez GE et al: Hyperglycemic crises in urban blacks. Arch Intern Med 157:669, 1997.)

Hyponatremia for both disorders is corrected with intravenous 0.9% saline solution to avoid any plasma hypo-osmolality that might occur when the hyperglycemia is reduced with insulin treatment. Plasma hypo-osmolality can cause a reversal of osmotic gradients and overexpansion of the intracellular compartment with resultant cerebral edema.

Potassium supplementation is best provided by adding potassium chloride solution to the parenteral fluids. If concurrent hypophosphatemia is present, one third of the potassium supplement can be in the form of potassium phosphate. Potassium supplementation is best begun after the first 2-hour period of fluid replacement, when hydration, blood pressure, and urine output are improved. If the patient is initially hypokalemic, potassium chloride (KCl) can be added to the hydrating solution; however, the infusion should be slowed so that half the dehydration replacement volume is delivered over an additional 1 to 3 hours. Although most texts list the maximum rate of potassium ion administration as 0.5 mEq per kilogram of body weight (BW) per hour, the author's experience has shown that this rate can be safely doubled when the patient is severely hypokalemic (serum potassium level less than 2.5 mEq/L) as long as electrocardiographic and urine output monitoring is done. The recommended amount of potassium that can be added to the parenteral fluids *over a 24-hour period* is shown, using two different but equally effective methods.

- *Mild hypokalemia* (serum K^+ of 3.0 to 3.5 mEq/L): administer 2 to 3 mEq/kg *or* add 20 to 30 mEq KCl per liter of replacement fluid
- *Moderate hypokalemia* (serum K^+ of 2.5 to 3.0 mEq/L): administer 3 to 5 mEq KCl/kg *or* add 40 to 60 mEq KCl per liter of replacement fluid
- *Severe hypokalemia* (serum K^+ below 2.5 mEq/L): administer 5 to 10 mEq KCl/kg *or* add 60 to 80 mEq KCl per liter of replacement fluid.

Daily serum electrolyte determinations and the necessary treatment adjustments are made until normal values are obtained. Intravenous fluids are discontinued when serum biochemistry values are normal, hydration is normal, and the patient is able to eat and drink without vomiting.

Any needed phosphate replacement can be given as potassium phosphate solution at the recommended dose of 0.01 to 0.03 mmol/kg BW/hour, with repeat serum phosphorus determinations every 6 hours. Attention should be given to avoiding iatrogenic hyperphosphatemia and hypocalcemia.

Hypomagnesemia has been shown to cause specific problems, especially cardiac arrhythmias, in diabetic humans; however, its association with any particular dysfunction in diabetic

dogs and cats has not yet been demonstrated. The ionic and total bound forms of magnesium can be measured.

Sodium bicarbonate treatment for DKA is controversial. Advocates of this treatment cite concern that severe acidosis (blood pH less than 7.0) can adversely affect cardiovascular function; opponents base their concern on the treatment's causal relationship with paradoxical cerebrospinal fluid acidosis, hypokalemia, and worsened intracellular acidosis with overshoot alkalosis.

The use of sodium bicarbonate should be restricted to dogs or cats with a blood pH below 7.1 or those with a serum total carbon dioxide (CO_2) concentration less than 10 to 12 mEq/L. During most treatment courses, metabolic acidosis reverses without bicarbonate treatment because of the cessation of ketogenesis, the metabolic conversion of ketones to bicarbonate after initiation of insulin treatment, improved renal function, and conversion of the lactate in lactated Ringer's solution to bicarbonate. In severe cases of metabolic acidosis (i.e., an anion gap greater than 30 mEq/L and an arterial pH less than 7.1), sodium bicarbonate ($NaHCO_3$) can be given according to the following equation:

$$NaHCO_3\ (mEq) = \text{Base deficit (mEq)} \times 0.3 \times \text{Body weight (kg)}$$

Subsequent alkali treatment depends on the results of repeat plasma pH measurements; it should be discontinued when the blood pH has been restored to 7.2 or higher or until the serum total CO_2 concentration is greater than 10 to 12 mEq/L.

Insulin

The cornerstone of management of a sick DKA or HHS dog or cat is insulin administration. Regular crystalline insulin is used when the pet has signs of depression, dehydration, anorexia, and vomiting. Regular insulin has several advantages, including its various routes of administration (intravenous, intramuscular, and subcutaneous), rapid onset of action, and short duration of action. These properties allow adequate insulin titration throughout the day according to the animal's needs. The clinician must remember that the blood glucose concentration declines much earlier than ketones, allowing for the persistence of ketonuria for the first 48 to 96 hours.

Regular insulin given intravenously by slow constant-rate infusion (CRI) is the preferred method of treatment for the critically ill hypotensive pet. The pet's hypovolemia should be partially corrected over the first 2 hours, before the insulin is administered.

A separate intravenous cannula is usually necessary for the insulin infusion. The CRI insulin solution is prepared by adding 5 U of regular insulin to a 500 mL bottle of 0.9% saline or lactated Ringer's solution to make up a solution that provides 0.01 U of insulin per milliliter. The infusion is delivered by an automatic injection syringe, an intravenous infusion pump, or a pediatric intravenous infusion set to deliver a therapeutic insulin dose of 0.1 U/kg BW/hour. To prevent binding of insulin to the intravenous lines, some clinicians prefer to run some of the diluted insulin infusion through the line before attaching it to the patient. Before this slow infusion is begun, the patient can receive an initial intravenous insulin bolus at a dosage of 0.1 U/kg. To avoid any complicating osmotic disequilibrium effects on the brain, the rate of decline in the blood glucose level should not exceed 75 to 100 mg/dL/hour. When the blood glucose level has declined to 250 mg/dL, after several hours of the CRI insulin infusion, the rate should be decreased to half the initial amount (i.e., 0.05 U/kg/hour), and dextrose should be added to the intravenous fluid to achieve a 2.5% to 5% dextrose concentration. The blood glucose level subsequently should be determined every 2 hours, using glucose oxidase reagent strips or a reflectance meter. Thereafter the rate of insulin infusion should be adjusted to maintain a blood glucose range of 150 to 250 mg/dL to avert hypoglycemia.

The disadvantages of the CRI insulin administration technique are the frequent need for a separate intravenous cannula, intensive care monitoring, and frequent monitoring of the blood glucose and serum potassium concentrations. If the patient initially is hypokalemic, the clinician can begin treatment with isotonic fluids containing added potassium chloride and delay insulin treatment for the first 4 to 8 hours.

Low doses of regular insulin also can be given intramuscularly. Initially, 2 U are injected into the thigh muscles of cats and dogs weighing less than 10 kg. For dogs weighing more than 10 kg, the initial dose is 0.25 U/kg BW. Subsequent hourly injections of 1 U for cats and small dogs and 0.1 U/kg BW for larger dogs are given until the blood glucose level is less than 250 mg/dL, at which time the subcutaneous route can be used to administer the insulin every 6 hours or as needed. The low doses used in this technique can be accurately measured with a special low-dose calibrated syringe.

Subcutaneous administration of regular insulin is a suitable alternative to the intravenous and intramuscular methods when intensive care monitoring is unavailable and when the patient is alert and normotensive. The initial dose is 0.5 U/kg BW, with subsequent doses given every 6 to 10 hours, depending on the need.

The patient is regarded as stable when normal hydration has been restored, blood glucose levels are below 250 mg/dL, serum and urine ketones are minimal to absent, and eating resumes. Subsequent insulin treatment can be changed to the intermediate-acting or the ultra-long-acting type.

COMPLICATIONS

The main complications of insulin treatment include hypoglycemia, hypokalemia, cerebral edema, metabolic alkalosis, and paradoxical cerebrospinal fluid acidosis. Most of these problems are avoidable with meticulous medical management geared toward avoiding overtreatment of the patient.

HYPERGLYCEMIC HYPEROSMOLAR SYNDROME

The hyperglycemic hyperosmolar syndrome (HHS) is characterized by extreme dehydration, renal dysfunction, abnormal brain function, marked hyperglycemia, and the lack of significant ketoacidosis. The incidence of this disorder in the dog and cat has not been reported; however, isolated case reports can be found in the veterinary literature spanning the past 25 to 30 years. Underlying renal disease and a precipitating condition, such as an infection or pancreatitis, can often be found.

PATHOPHYSIOLOGY

Only the main pathophysiologic mechanisms are covered in this section. The development of HHS is attributed to three main factors: (1) decreased insulin utilization and glucose transport, (2) increased hepatic gluconeogenesis and glycogenolysis, and (3) impaired renal excretion of glucose.

Two concepts have been advanced to reasonably explain the pathophysiology of HHS. The first suggests that an insulinized liver (reflecting residual beta cell secretory activity) coexists with a diabetic periphery, resulting in inactivation of intrahepatic oxidation of incoming free fatty acids, which are directed largely along nonketogenic metabolic pathways, such as triglyceride synthesis. This could account for the absence of hyperketonemia. The second proposal suggests

that enhanced gluconeogenesis occurs in the liver due to the prevailing elevated portal vein ratio of glucagon to insulin. This effect, accompanied by severe dehydration (greater than 8%), is mainly responsible for the development of marked hyperglycemia.

The decrease in consciousness and the onset of the associated neurologic abnormalities that characterize HHS result from the direct effects of hyperosmolarity-induced dehydration on the brain parenchyma.

DIAGNOSTIC EVALUATION

Several clinicopathologic abnormalities characterize the HHS. The blood glucose levels are often elevated above 800 mg/dL. Serum osmolality is elevated (normal serum osmolality is 290 to 310 mOsm/kg body water) and can be determined by the freezing point depression method with an osmometer, or it can be calculated using the following formula:

$$sOsm = 2(Na^+ + K^+) + \frac{Glu}{18} + \frac{BUN}{2.8}$$

where Na^+ is serum sodium, K^+ is serum potassium, Glu is serum glucose, and BUN is blood urea nitrogen.

Most patients are azotemic, a condition that may be renal or prerenal in origin. The disturbances in serum electrolyte concentrations were described in the DKA section, above. It should be noted that an elevated serum sodium level during severe hyperglycemia can be explained only by significant plasma volume contraction caused by large water losses associated with hypotonic urine excretion.

TREATMENT

The main treatment objectives with HHS include reestablishment of normal hydration and adequate urine output; judicious use of insulin to avoid a precipitous decline in blood glucose levels; and ample potassium supplementation to make up the total body potassium deficit. Treatment techniques were described in the previous section. The regular insulin dosage requirements for the hyperglycemic hyperosmolar diabetic are oftentimes less than those needed to treat diabetic ketoacidosis, but the technique for delivery is the same.

The diabetic ketoacidotic and hyperglycemic hyperosmolar syndromes pose noteworthy challenges to the practicing clinician. A sound understanding of the underlying pathophysiology, along with logical and timely therapeutic intervention, can usually lead to a remarkably optimistic outcome.

CHAPTER 116

Gastrointestinal Emergencies

Elke Rudloff
Rebecca Kirby

Shock, dehydration, collapse, acute pain, electrolyte imbalances, respiratory distress, and cardiac arrhythmias are potential life-threatening consequences of gastrointestinal (GI) emergencies. The history, physical examination findings, and clinical signs attributed to the GI tract (e.g., vomiting, diarrhea, abdominal pain or distention) direct the investigation for either primary GI disease or pathology in other organs that manifests with GI signs.

Primary pathology involving the GI tract (i.e., the esophagus, stomach, small intestines, large intestines, cecum, rectum, and/or anus) can be a result of distention, inflammation, obstruction, hypoxia, and/or ischemia of affected GI tissues (Table 116-1).

Inflammatory mediators are released locally, causing local arteriolar and venous dilatation and increased capillary permeability. Severe inflammation results in loss of blood, fluids, electrolytes, and proteins from the capillaries into the GI tract (third body fluid spacing). Distension or inflammation of the GI tract can cause peripheral receptor stimulation of the vomiting center in the brain stem (Figure 116-1). Alterations in GI motility, secretory function, or permeability can result in diarrhea. Further increased vagal tone, aspiration pneumonia, bacterial translocation, and malnutrition are life-threatening consequences of vomiting and diarrhea.

Gastrointestinal signs can occur secondary to disease of other organs or to systemic diseases (see Table 116-1). Stimulation of receptors associated with the vomiting center and chemoreceptor trigger zone, as well as stimulation of peripheral GI receptors, can be caused by other organ inflammation or distention, circulating and ingested drugs or toxins, and central nervous system pathology (see Figure 116-1). Alterations in nerve conduction and smooth muscle action as a result of toxins and electrolyte or acid-base imbalances may also affect GI function.

The systemic consequences of vomiting and diarrhea are similar whether the cause is a primary or a secondary GI emergency. The animal must be rapidly assessed for life-threatening complications (primary survey) and rapidly resuscitated. Once the patient has been stabilized, diagnostic tests are performed to determine the underlying cause. One of the key immediate diagnostic goals is to determine whether the underlying pathology requires emergency surgical intervention. Careful monitoring is required during treatment and recovery.

PRIMARY SURVEY

The primary survey is a rapid evaluation of the patient's history and physical parameters to detect life-threatening complications that require immediate attention. The history may reveal evidence of vomiting, diarrhea, abdominal pain or distension,

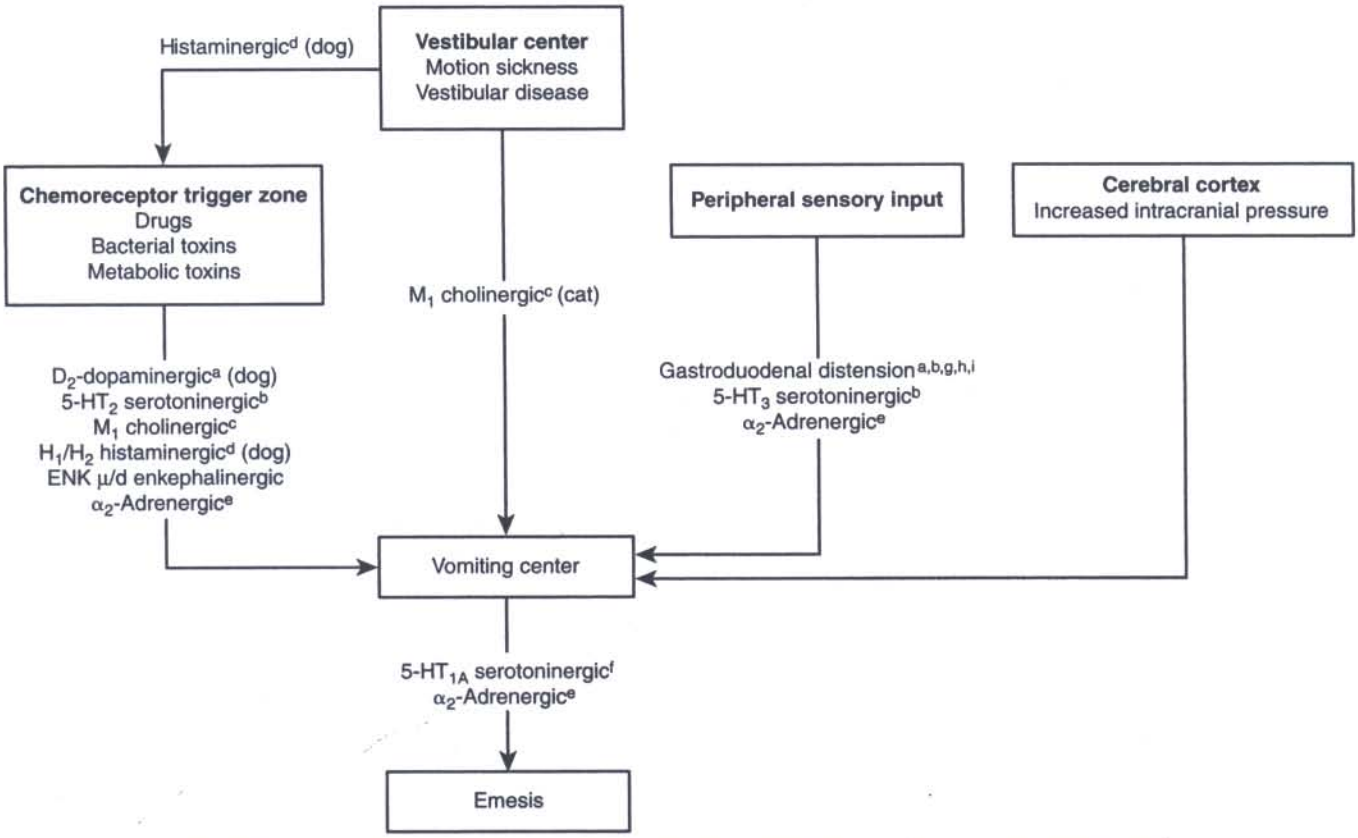

Figure 116-1 Vomiting reflex and antiemetics. Receptors in the vomiting center and chemoreceptor-trigger zone (CRTZ) in the brain stem can be triggered by sensory and chemical input from multiple sources. Targeting the different neurotransmitters is the basis of antiemetic therapy. Specific antiemetic therapy should be selected based on the most likely mechanism initiating the stimulus to vomit. (For a complete list of antiemetic drugs, please see this figure in the e-dition.)

Table • 116-1

Causes of Gastrointestinal Emergencies

PRIMARY	SECONDARY
Gastrointestinal Obstruction	Organ dysfunction
Foreign body*	Pancreatic disease
Neoplasia*	Urinary tract disease
Pyloric hypertrophy	Hepatobiliary disease
Intestinal stricture*	Pyometra/metritis
Functional ileus	Adrenocortical insufficiency
Gastrointestinal inflammation	Diabetic ketoacidosis
Infection (bacterial, fungal, viral, protozoal)	Central nervous system disorder
Trauma	Increased intracranial pressure
Diffuse neoplasia	Meningoencephalitis
Adverse reaction to food	Vestibular disease
Inflammatory bowel disease	
Hemorrhagic gastroenteritis	**Systemic Disorders**
Drugs/toxins	Electrolyte disorders
Ulcerative disease*	Acid-base disorders
Lymphangiectasia	Peritonitis
	Toxemia/sepsis
Gastrointestinal Hypoxia/Ischemia	
Gastric dilatation-volvulus*	**Toxin/Drug Reaction**
Mesenteric torsion*	
Intestinal volvulus*	
Intussusception*	
Mesenteric thromboembolic disease*	

*May require requires emergency surgical intervention for correction.

collapse, or respiratory distress. Airway, breathing, and circulation are rapidly assessed. Upper airway obstruction from aspiration of gastric contents can manifest with labored, loud breathing, heard without the aid of a stethoscope, and cyanosis. When aspiration pneumonia causes lung parenchymal pathology, physical evidence of a labored, synchronous breathing pattern with moist or harsh lung sounds may be heard on lung auscultation.

Poor perfusion can result from rapid fluid loss, organ hypoxia, and endotoxemia; it is evidenced by pale mucous membranes, a prolonged capillary refill time, poor pulse quality, and tachycardia (in the dog). Dehydration is detected by dry mucous membranes, increased skin tenting and, when severe, dry corneas. An altered level of consciousness or the presence of an arrhythmia can suggest electrolyte and/or acid-base imbalances, hypoglycemia, circulating toxins, or hypoxia. Bradycardia may be a result of excessive vagal stimulation or late-stage decompensatory shock. Abdominal pain or distension or a fluid wave alerts the clinician to shock, dehydration, and serious primary GI pathology.

RESUSCITATION

Life-threatening problems are immediately resuscitated prior to further diagnostics. Any breathing abnormalities warrant flow-by oxygen administration. An intravenous catheter is placed, and analgesia is provided if pain is present. If upper airway obstruction is evident, the oropharynx is suctioned, an airway is established and oxygenation and ventilation are provided. Poor perfusion and dehydration are treated with fluid therapy, specifically crystalloid (balanced isotonic type, 10 to 20 mL/kg given intravenously) and colloid (hetastarch, 5 mL/kg given intravenously) in increments to effect. If a gastric dilatation-volvulus is suspected, careful percutaneous decompression of the stomach is recommended during fluid resuscitation to relieve pain and reduce pressure on the diaphragm and vena cava. Depressed consciousness due to hypoglycemia is treated with dextrose (0.5 g/kg given intravenously). Life-threatening bradycardia is treated with atropine (0.02 mg/kg given intravenously) and warrants rapid assessment of the serum potassium level.

SECONDARY SURVEY

Once the patient's condition has been stabilized, information is obtained from a more thorough history and physical examination to determine the origin of the GI signs. Historical information should be obtained regarding the vaccination and internal parasite history, recent or chronic administration of medications (e.g., nonsteroidal or steroidal anti-inflammatory agents); changes in appetite; sudden changes or excessive fat content in the diet; access to garbage, bones, or moldy food; and the availability of string, foreign bodies, toys and balls, corncobs, socks, and other small items or toxins. Vomiting is differentiated from regurgitation. Nonproductive vomiting or retching may indicate the presence of a gastric dilatation-volvulus. Vomiting and/or diarrhea should be characterized with respect to color, consistency, and frequency (Table 116-2).

The rectal temperature can reveal fever associated with inflammation or hypothermia from poor perfusion. Digital examination demonstrates the consistency of the stool. Careful abdominal palpation can detect abdominal pathology associated with organ distension, thickening, masses, foreign body (FB), free fluid, or fluid in the bowel. Physical signs that increase the possibility of emergency surgical intervention include: gas distention of the stomach or bowel; nonresponsive shock with evidence of intra-abdominal pathology; progressive abdominal distension; palpation of intestinal plication or a painful mass or FB; and persistent, severe vomiting unresponsive to therapeutic intervention.

TESTS

Blood, urine, and fecal samples are collected and evaluated. An immediate data base (packed cell volume, total protein, blood glucose, electrolyte panel, acid-base panel, blood urea nitrogen, platelet estimate, and activated clotting time) may be useful in detecting the presence of hemorrhage, a coagulopathy, protein depletion, hypoglycemia (supporting sepsis), hypoxemia, or a gastric outflow obstruction (hypochloremia with a metabolic alkalosis). In addition, a complete blood count, serum biochemistry profile (including amylase and lipase), microscopic fecal examination, parvoviral fecal antigen test (when indicated), fecal cultures, urinalysis, and coagulation profile may aid in the determination of the underlying cause and whether secondary complications or additional organ dysfunction exists. Hyperphosphatemia is not unexpected with intestinal ischemia or severe inflammation. Specific diagnostic tests to identify secondary GI disease are performed as indicated (e.g., adrenocorticotropic hormone [ACTH] stimulation, preprandial and postprandial bile acids).

Two-view abdominal radiography (Table 116-3), as well as abdominal ultrasonography, may help identify the cause of the GI signs. A lateral thoracic radiograph may show a gas-dilated esophagus indicative of megaesophagus. When the pathology is likely intra-abdominal and the definitive cause cannot be determined by radiographs or ultrasound, abdominal paracentesis and/or diagnostic peritoneal lavage are indicated (see Chapter 72). Emergency surgical intervention becomes part of the diagnostic and therapeutic plan when primary GI pathology is suspected to be associated with ischemia, severe ongoing hemorrhage, or sepsis or when a diagnosis is lacking in a dog or cat whose condition is deteriorating.

MEDICAL INTERVENTION

Fluid therapy is adjusted to meet ongoing fluid, electrolyte, and acid-base abnormalities. Definitive treatment of the underlying pathology is initiated as soon as possible. When GI integrity is compromised, injectable antibiotics are administered against gram-positive, gram-negative, and anaerobic bacteria that translocate from the bowel into the bloodstream. Cefazolin (20 mg/kg given intravenously [IV] every 8 hours), in addition to metronidazole (10 mg/kg given via slow IV every 8 hours), can provide broad-spectrum coverage. Signs of pain are treated with opioid drugs (for mild pain: butorphanol, 0.4 mg/kg given intravenously, followed by a constant-rate infusion of 0.1 mg/kg/hour; for moderate pain: hydromorphone, 0.1 to 0.2 mg/kg given intravenously every 4 to 6 hours). Analgesia can be augmented with concurrent administration of antianxiolytic and sedative medication (e.g., diazepam, 0.5 mg/kg given intravenously).

The selection of antiemetic agents is based on the likely mechanisms of vomiting (see Figure 116-1). Motility inhibitors (e.g., centrine) are not used as antiemetics/antidiarrheals because they reduce GI motility, which allows toxins to accumulate, and they affect nutrient delivery and absorption. A nasogastric tube allows for continued gastric decompression, cold water lavage for severe intragastric hemorrhage, and trickle flow feeding of the gastric mucosa. Promotility agents are administered only after GI obstruction has been ruled out.

When esophageal or gastric ulceration is suspected, H_2-blockers (cimetidine, 4 mg/kg given intravenously every

Table • **116-2**

Character and Origin of Vomiting and Diarrhea

CHARACTER OF VOMIT OR VOMITING EPISODE	LESION	DIFFERENTIAL CAUSES
Occurs shortly after eating	Gastric inflammation	Gastric ulceration
	Gastric obstruction	Foreign body (FB)
		Toxin ingestion
		Infection
Large amounts of undigested food up to 6 hours postprandial	True vomiting: Pyloric outflow obstruction	Pyloric hypertrophy
		Pyloric mass
	Gastric atony	Foreign body
		Electrolyte imbalance
		Megaesophagus
	Regurgitation: Esophageal outflow obstruction	Esophagitis
		Esophageal FB/mass/stricture
		Persistent right aortic arch
		Hiatal hernia
Projectile vomiting	Pyloric or upper duodenal outflow obstruction	Pyloric hypertrophy
	Upper duodenal ileus	Mass
		Foreign body
		Pancreatitis
		Infiltrative bowel disease
Blood in vomit in the absence of nasal or oral disease	Esophageal hemorrhage	Ulceration
	Gastric hemorrhage	Coagulopathy
Streaks of blood	Duodenal hemorrhage	Severe inflammation
	Gastric mucosal damage	Persistent vomiting
White or mucoid fluid	Gastric fluid	Gastritis
	Swallowed saliva from true regurgitation	Megaesophagus
		Esophagitis
		Gastric dilatation-volvulus
		Gastric outflow obstruction
Yellow	Gastric fluid	Gastritis
		Foreign body
Green	Upper duodenum	Duodenal ileus/obstruction
Fetid brown fluid	Lower duodenum	Pancreatitis
	Jejunum	Intestinal obstruction
CHARACTER OF DIARRHEA	**LESIONS**	**DIFFERENTIAL CAUSES**
Watery	Small bowel inflammation	Infectious disease
		Partial small intestinal obstruction
		Pancreatitis
		Toxin/drug reaction
Mucoid	Large bowel inflammation	Infectious disease
		Partial large intestinal obstruction
		Toxin/drug reaction
Presence of digested blood (black stool) in the absence of nasal or oral disease	Esophageal hemorrhage	Ulceration
	Gastric hemorrhage	Coagulopathy
	Small bowel hemorrhage	Severe inflammation
		Ischemia
Presence of frank (bright red) blood	Large bowel hemorrhage	Ulceration
		Coagulopathy
		Severe inflammation
		Ischemia

Table • 116-3

Radiographic Changes Noted During Gastrointestinal Emergencies

RADIOGRAPHIC CHANGE	INDICATION	CAUSE
Generalized loss of radiographic detail	Intra-abdominal fluid	Ascites Peritonitis Hemorrhage
Diffuse gas dilatation of the small and large intestines	Ileus	Enteritis Mesenteric volvulus
Severe segmental gas dilatation of the small intestine	Obstruction	Foreign body Mass Mesenteric volvulus
Intestinal bunching, plication, "string of pearls"		Intussusception Linear foreign body
Severe segmental gas dilatation of the large intestine +/– colonic displacement	Colonic obstruction	Colonic torsion
Severe gas dilatation of the stomach without pyloric displacement	Gastric outflow obstruction	Foreign body Pyloric mass Pyloric hypertrophy Motility disorder
with pyloric displacement		Gastric dilatation-volvulus
Free intra-abdominal gas	Gastrointestinal (GI) rupture Infection	Rupture of GI tract Growth of gas-forming bacteria Abdominal wall perforation
Radio-opacities involving the GI tract	Foreign body Mass lesion	Foreign body Neoplasia
Duodenal loop sign or loss of contrast in right upper abdominal quadrant	Duodenal ileus Focal inflammation	Pancreatitis

6 to 8 hours, or ranitidine, 2 to 2.5 mg/kg given every 12 hours IV) or H-pump inhibitors (omeprazole, 0.7 mg/kg up to 20 mg given orally every 24 hours) are administered to reduce acid secretion and reflux and promote mucosal healing. Liquid sucralfate (0.5 to 1 g given orally every 4 to 8 hours) is administered to protect the area of ulceration once vomiting has been controlled.

SURGICAL INTERVENTION

When emergency surgery is indicated, rapid stabilization of perfusion and hydration is optimal prior to anesthetic induction. However, stabilization may be difficult to achieve with significant ongoing large-volume fluid loss, organ ischemia (gastric or intestinal volvulus/torsion, intussusception, necrosis), or uncontrollable hemorrhage. Rapid induction of anesthesia using injectable anesthetics is recommended, because ventilation capabilities may be impaired with significant abdominal distension, aspiration pneumonia, or analgesic medication. Oropharyngeal and esophageal suctioning may be required if gastric fluid has refluxed.

Surgical intervention for acute GI emergencies may require the use of specific equipment and access to a GI stapling device to reduce the surgical time. Clinicians are referred to surgical texts for detailed surgical techniques for specific GI problems.

Gastric dilatation-volvulus requires decompression, derotation, and gastropexy. Gastric necrosis requires resection of compromised tissue. If a gastric FB is palpated or gastric ulcers are present, a gastrotomy is performed. Ulcerative mucosal lesions are resected and submitted for histopathologic evaluation. When a GI foreign body is present, an attempt can be made to gently pull it from the intestines and out through the gastrotomy site. If resistance is felt, the FB is transected at the level of the pylorus and an attempt is made to massage the remaining FB through the intestines to the distal colon, where it can be removed by means of a digital rectal examination. When a linear FB is present, the gastric portion is cut and the remaining portion is sutured to a red rubber feeding tube, which can be massaged out through the colon. If the FB cannot be milked through the intestines into the distal colon, one or more enterotomies may be required to remove the object.

Ischemic or perforated bowel requires debridement or resection prior to closure. The most difficult regions requiring resection are the descending duodenal flexure (where the duodenum is fixed to the parietal peritoneum) and the ileocecal region (where various vascular supplies feed the region). When multiple ischemic sites in proximity are discovered, en bloc resection may prove more efficient and pose less risk of complications. Either simple interrupted or continuous closure can be performed, provided there is good apposition and minimal restriction of blood flow. GI stapling can also be used for rapid anastomosis.

Placement of a nasogastric, nasoesophageal, esophagostomy, gastric, or jejunal feeding tube is considered if injury to the GI tract is significant or if a prolonged time to voluntary oral nutrition (longer than 2 days) is expected. A gastrostomy tube can help maintain gastric decompression when motility disorders are present. When gastric or proximal intestinal tract dysfunction or procedures are a factor (e.g., pancreatitis, peritonitis, Billroth procedures), placement of a jejunostomy tube

allows immediate initiation of enteral feeding. The intra-abdominal tubes are placed prior to closure.

When bowel or peritoneal perforation has occurred, a decision must be made regarding open abdominal drainage or the placement of drains. If the peritoneal wall and serosal surfaces appear only mildly hyperemic and the repair is considered curative, copious saline lavage and suctioning may be all that is required. If inflammation of the peritoneal wall or serosal surfaces is localized to the surgical site, placement of an abdominal suction drain in the affected area may be of benefit. Open abdominal drainage is indicated with generalized abdominal contamination or inflammation or when re-examination of the surgical sites is desired.

If there is no nonresectable pathology of any organ, multiple biopsies are obtained. Tissue samples should be obtained from the liver, stomach, duodenum, jejunum, and mesenteric lymph nodes. Fluid from the duodenum is evaluated for *Giardia* organisms. Samples of the spleen, pancreas, and kidney, as well as fluid from the gallbladder and urinary bladder, are taken for histopathologic evaluation and are cultured at the discretion of the surgeon. Intensive care and monitoring are required during medical and postoperative treatment of GI emergencies.

RECOVERY

An organized, systemic approach is required during the recovery phase of the GI emergency. The *Rule of 20* provides a check list of critical parameters that must be monitored and treated for an optimal outcome (Box 116-1).

Box • 116-1

Rule of 20

Monitoring and treatment of the following critical parameters help ensure the best outcome for the recovery phase of a gastrointestinal emergency.

- Fluid balance
- Colloid osmotic pressure
- Serum albumin
- Blood pressure
- Heart rate and rhythm
- Electrolytes and acid/base balance
- Oxygenation and ventilation
- White blood cell count, immunity and antibiotic therapy
- Red blood cell and hemoglobin concentration
- Mentation
- Drug dosages and interactions
- Liver function and drug metabolism
- GI motility and integrity
- Nutrition
- Renal function
- Coagulation
- Wound care
- Nursing care
- Body temperature
- Pain control

CHAPTER 117

Global Approach to the Trauma Patient

Kenneth J. Drobatz

Trauma is defined as a "wound or injury" caused by numerous "accidents." The severity may range from mild to fatal. Trauma may affect only one organ system or multiple organ systems, either directly or indirectly. Therefore a global and thorough approach is required to improve survival and decrease morbidity in traumatized dogs and cats. The initial approach to the critically ill trauma patient often makes the difference in the eventual outcome. The veterinary staff should be well versed in the evaluation and therapy of a traumatized pet. The initial trauma assessment involves a primary survey that includes assessment of tissue oxygen delivery (respiratory and cardiovascular systems), the central nervous system, and the urinary system. The primary survey is followed by a secondary survey that involves a complete examination of all other systems.

PRIMARY SURVEY

The first goal with a critically injured trauma patient is to optimize oxygen delivery to the tissues. All assessments and therapeutics are oriented toward this goal in the initial approach and resuscitation. Emphasis on early detection and aggressive reversal of impaired tissue perfusion or oxygen delivery improves survival and minimizes multiorgan dysfunction. Oxygen delivery depends on the blood oxygen content and tissue perfusion (Figure 117-1).

BLOOD OXYGEN CONTENT

Maintaining oxygen saturation of hemoglobin through assessment and treatment of respiratory abnormalities is one of the first goals of the critical care team in maintaining oxygen delivery. Pale, cyanotic, or gray mucous membranes; signs of respiratory distress, such as increased respiratory rate and effort, extended head and neck, and open mouth breathing; and loud upper airway sounds and abnormal or diminished breath sounds on auscultation are all potential indicators of inadequate oxygen saturation of hemoglobin. More objective assessments of the oxygenation of blood include pulse oximetry and arterial

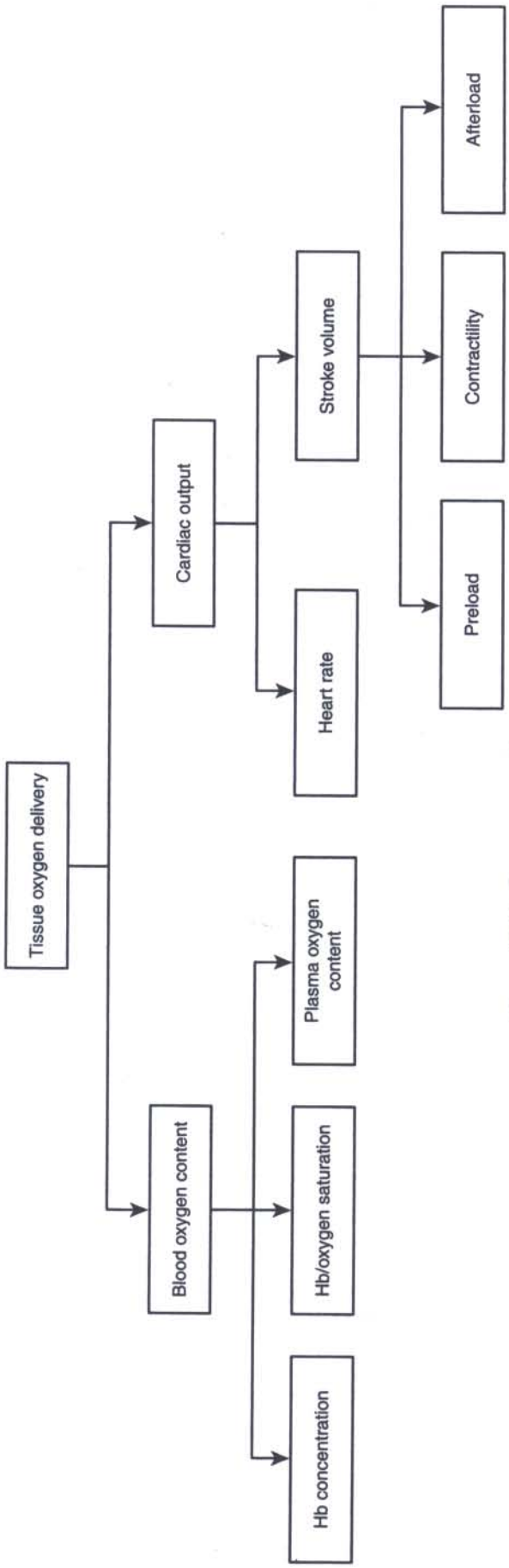

Figure 117-1 Determinants of tissue oxygen delivery.

blood gas analysis. Initially, supplemental oxygen should be provided to any critically ill traumatized animal until it is proved that oxygen supplementation is not necessary.

A variety of conditions associated with trauma can result in respiratory distress and decreased oxygenation of hemoglobin (Figure 117-2; also see Thoracic Trauma; Chapter 126), but the most common are pneumothorax and pulmonary contusions. In animals suspected of having pleural space disease (decreased lung sounds with signs of respiratory distress), thoracocentesis should be performed even before thoracic radiographs are taken. If done correctly, the benefits far outweigh the risks (see Thoracic and Pericardial Taps and Drains). Tension pneumothorax is rare but is an acute, life-threatening pleural space abnormality. It is characterized by extreme respiratory distress, poor tissue perfusion and, rarely, a "barrel chest" appearance. Rapid thoracocentesis is immediately indicated. A small incision in the intercostal space may release the air more quickly in animals in whom death or collapse is imminent.

Increased bronchovesicular sounds in a traumatized animal are commonly a result of pulmonary contusions. Pulmonary contusions often worsen before they improve. Intravenous fluid therapy for other conditions should be given with caution in these dogs and cats. There is no specific therapy for pulmonary contusions. Supportive care, with oxygen supplementation and pain relief, is the mainstay of treatment. Most dogs and cats with pulmonary contusions begin to improve 24 to 36 hours after the initial insult (see Thoracic Trauma; Chapter 126).

Other respiratory conditions include open chest wounds, flail chest, and rib fractures. The open chest wound should be covered and sealed as soon as possible. Once that has been done, the closed pneumothorax should be resolved by thoracocentesis. Treatment of an animal with a flail chest or rib fractures primarily involves oxygen supplementation and pain management. Surgical repair is rarely necessary.

Neurogenic pulmonary edema occurs rarely but is most often associated with severe head trauma. The pulmonary edema can range from mild to severe enough to require mechanical ventilation. Most of these cases are managed successfully with supportive care, such as oxygen supplementation and judicious diuretic therapy. Generally, respiratory problems in animals with neurogenic pulmonary edema caused by head trauma improve substantially within 48 hours, or the animal dies of severe respiratory compromise.

An adequate amount of hemoglobin in the vascular space is essential to maintenance of tissue oxygen delivery. A decreased hemoglobin content severely limits the oxygen-carrying capacity of the blood and can contribute to decreased tissue oxygen delivery. The packed cell volume (PCV) provides the most rapid estimate of the hemoglobin concentration in a traumatized dog or cat, but it should be interpreted in conjunction with assessment of the vascular volume status (see Tissue Perfusion, below) to get a complete assessment of the total hemoglobin content of the vascular space. Acute blood loss often is not reflected by the initial PCV measurement because of splenic contraction in the dog and the length of time it takes for interstitial fluid to shift into the vascular space to dilute the PCV. Initial total solids (TS) and serial measurements of the PCV and TS as intravenous fluid is administered are more sensitive indicators of acute blood loss. There is no specific PCV at or below which transfusion is required. Transfusion therapy should be based on whether the animal is affected by the decreased hemoglobin content, which is indicated by clinical signs such as pale mucous membranes, tachycardia, tachypnea, bounding or weak pulses, depressed mentation, or cardiac arrhythmias. As with any animal in critical condition, it is best to anticipate and treat problems before they cause physiologic compromise. For example, if the PCV is dropping rapidly, it is best to start a blood transfusion or administer hemoglobin solutions before the hemoglobin content drops to a life-threatening level.

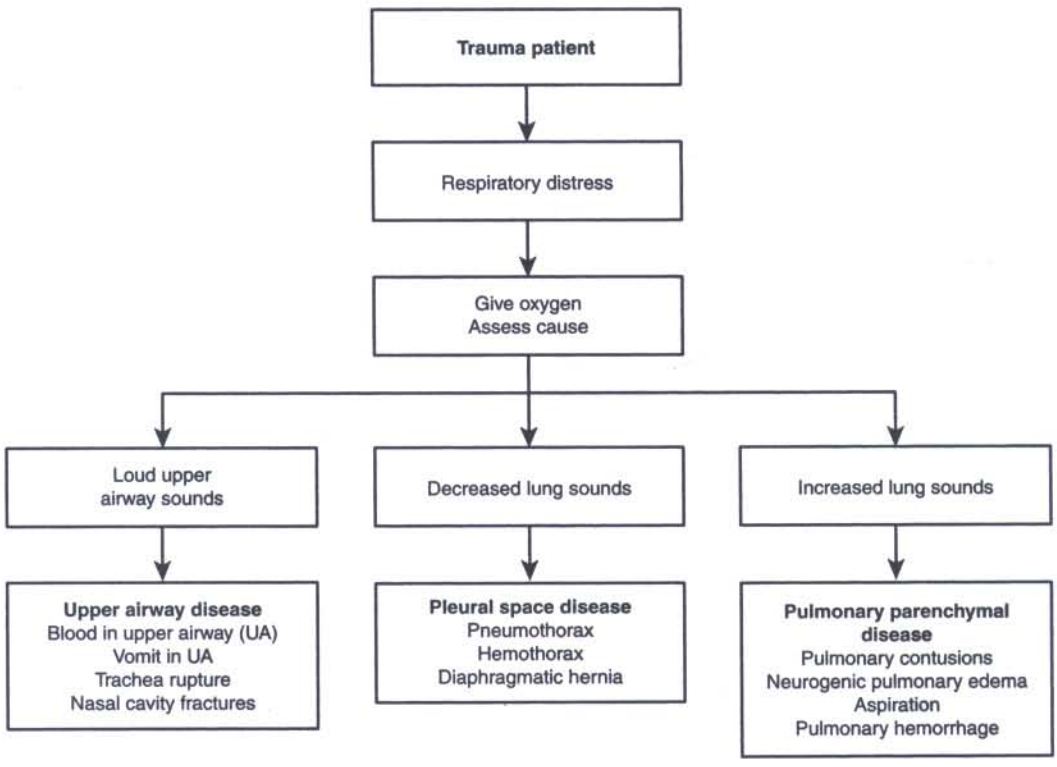

Figure 117-2 Causes of respiratory distress in a trauma patient.

TISSUE PERFUSION

Physical assessments of tissue perfusion on the first examination include mucous membrane color, capillary refill time, and pulse rate and quality (Figure 117-3). The arterial blood pressure should be measured directly or indirectly by Doppler or oscillometric techniques when possible. The most common clinical signs indicative of poor tissue perfusion are pale or gray mucous membranes, a prolonged capillary refill time, a rapid heart rate, and weak pulses. The most common cause of poor tissue perfusion after a traumatic event is hypovolemia secondary to hemorrhage.

Administration of a balanced electrolyte solution at a rate of 90 mL/kg body weight/hour in the dog (40 to 60 mL/kg body weight/hour in the cat) is indicated with physical evidence of poor tissue perfusion. Two separate, large-bore, intravenous catheters may be required in large dogs (i.e., body weight exceeding 20 to 30 kg). Mucous membrane color, capillary refill time, pulse quality, heart rate, and blood pressure (if available) should be assessed continuously and the intravenous fluid rate adjusted as perfusion parameters improve or worsen. In most uncomplicated situations, improvement in tissue perfusion often is seen by the time one half of a vascular volume of fluid (45 mL/kg in the dog, 20 to 30 mL/kg in the cat) has been administered.

If clinical perfusion parameters or the blood pressure has not significantly improved after this volume of fluid has been administered, an investigation into causes of nonresponsive cardiovascular shock should be pursued. Such causes include ongoing intravascular volume loss (most commonly due to ongoing hemorrhage) or, less commonly, cardiogenic causes, such as arrhythmias, pericardial effusion, myocardial depression or failure, electrolyte abnormalities, decreased venous return (e.g., tension pneumothorax), or ischemic organs. The most common location of substantial hemorrhage that can lead to hypovolemia is the peritoneal space. Less common locations are the pleural space and retroperitoneal space, external hemorrhage, and hemorrhage into the muscles surrounding the femur.

Abdominal binding may help control ongoing intra-abdominal hemorrhage (see Abdominal Trauma). However, this is no substitute for adequate intravascular volume supplementation. In human beings, some physicians advocate delayed resuscitation (see Abdominal Trauma). In animals with severe hemorrhage, the fluid of choice is whole blood, packed red blood cells and plasma, hemoglobin substitutes (e.g., Oxyglobin), and/or colloid supplementation, such as hydroxyethyl starch or dextran 70 (see Crystalloid and Colloid Therapy; Chapter 114). Hypertonic solutions can be considered after head trauma if the dog or cat is hypovolemic (see Traumatic Brain Injury; Chapter 113) or if the animal is in severe hypovolemic shock and may die before an adequate amount of balanced electrolyte solution can be administered (see Chapter 124).

Traumatized animals are physiologically dynamic and should be continuously monitored until physiologic parameters are stable. Close monitoring of cardiovascular and respiratory trends allows early detection of problems, before they become life-threatening.

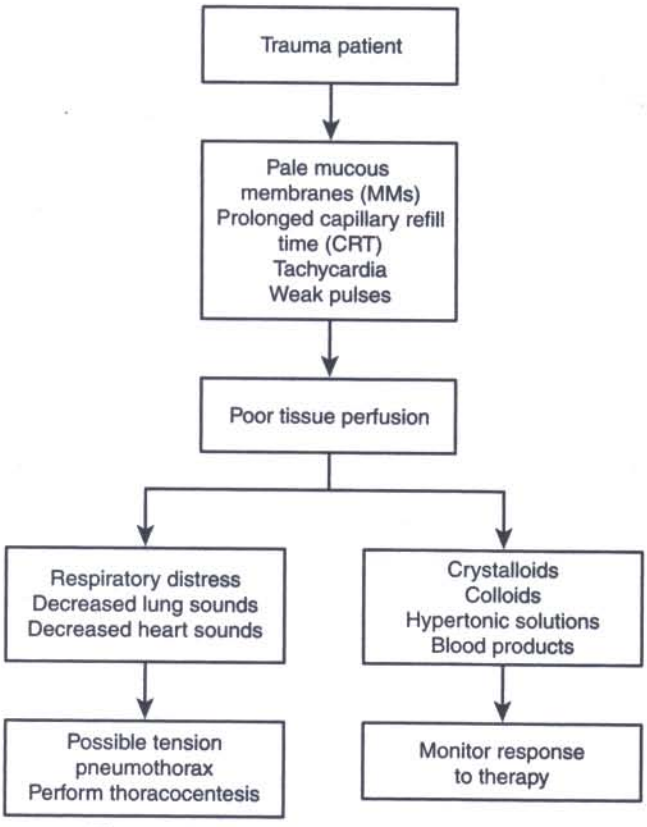

Figure 117-3 Assessment of tissue perfusion.

CENTRAL NERVOUS SYSTEM AND URINARY TRACT

The central nervous system (CNS) (brain and spinal cord) and the renal system are two other organ systems that should be assessed and supported as priorities. Compromise of either of these systems can result in irreversible damage. After the initial assessment and treatment of the cardiovascular and respiratory systems, it is important that the clinician do a thorough neurologic examination, including assessment of mentation and of cranial nerve and spinal cord function, to establish a baseline for further monitoring and potential therapy. Brain dysfunction may be a result of poor oxygen delivery to the brain, direct brain tissue damage, intracranial hemorrhage, cerebral edema, ischemia, and/or increased intracranial pressure. Therapeutic considerations with head trauma and brain dysfunction include optimization of tissue perfusion, administration of mannitol (0.5 g/kg given intravenously), mild elevation of the head (avoiding flexion of the neck and occlusion of the jugular veins), hyperventilation, and maintenance of oxygenation (see Traumatic Brain Injury; Chapter 113).

Spinal cord assessment should include thorough palpation of the spine and assessment of spinal function, including voluntary motor movement, conscious proprioception, ambulation, spinal reflexes, and pain sensation.

Assessment of neurologic function should always be evaluated in light of how well the central nervous system is perfused. In most animals, head trauma is obvious. However, those with severely compromised perfusion may have severely depressed mentation, as well as diminished pain sensation. The mentation and sensation abnormalities may normalize with correction of the poor tissue perfusion.

Manifestations of urinary tract injury or dysfunction may not be immediately evident and may not be detected until after several hours of continuous monitoring. Potential renal system abnormalities include direct kidney damage (e.g., contusions, hematomas, avulsion), ureteral rupture, bladder rupture, and urethral trauma. Any animal that has been traumatized may have experienced renal system trauma. Therefore serial assessment of the blood urea nitrogen, creatinine, and serum potassium levels, as well as of urine output, should be considered. It should be remembered that animals with a ruptured urinary bladder might still urinate. Ureteral rupture may result in urine accumulation in the retroperitoneal

space, a situation in which abdominocentesis fails to obtain fluid. Abdominal radiographs, abdominal ultrasound scans, and intravenous contrast studies may be necessary to diagnose ureteral rupture. If free abdominal fluid is present, it should be analyzed for the creatinine and potassium concentrations, which should be compared to the concentrations in peripheral blood. If the fluid is urine, the creatinine and potassium concentrations are higher.

SECONDARY SURVEY

After assessment of tissue oxygen delivery, CNS function, and renal function, a full physical examination should be performed. Limb function should be evaluated and should include palpation of the entire appendicular and axial skeletal system. The eyes and oropharyngeal area should be examined for evidence of trauma. The mouth should be manually opened and closed to assess for malocclusion, pain, or crepitus. A rectal examination should be performed, and attention should be paid to palpation of the pelvic canal for fractures or instability and evidence of blood in the rectum. The skin should be thoroughly examined for lacerations, abrasions, and bruising.

MONITORING

After the initial assessment, all the above systems should be monitored for at least 24 to 48 hours, despite how well the animal looks when first examined. In general, if problems are going to occur, they usually occur within this time frame. The intensity and duration of the monitoring should be proportional to the degree of compromise. The owner should also be warned that rarely, complications may arise several days later. For example, clinical signs of a ruptured gallbladder are not often manifested until several days after the traumatic injury.

In summary, assessment of tissue oxygen delivery should be performed at presentation and treated appropriately. Assessment should also include the CNS and renal systems, as well as the musculoskeletal, cutaneous, and peripheral nervous systems. A global approach, with emphasis on the most life-threatening conditions first, optimizes the outcome.

CHAPTER 118

Heatstroke

Roger Gfeller

Heatstroke is a syndrome of cellular damage caused by a marked increase in body temperature with loss of thermoregulatory control. This potentially fatal syndrome occurs when heat production (high ambient temperature, metabolism) overwhelms normal heat dissipation mechanisms (conduction, convection, evaporation, and radiation). Heatstroke can result in damage to nearly every body system. The degree of injury is determined by the magnitude and duration of core temperature elevation. Direct thermal injury occurs at approximately 109° F (42.8° C), resulting in enzymatic alterations and denaturation of proteins. Systemic damage has been reported in patients with *sustained* temperatures as low as 105° F (40.6° C). On the other hand, literature reports at least one case of full recovery in a patient that had a core temperature of 115.7° F (46.5° C).

Most cases of heatstroke are reported during the time of year when ambient temperatures are high and pets are not acclimated. Predisposition to heatstroke may arise from environmental factors (high temperature, high humidity, lack of water, poor ventilation), medical factors (obesity, laryngeal paralysis, upper airway obstruction, concurrent heart disease, concurrent central nervous system disease, hyperthyroidism, seizures, lack of conditioning), and variable other factors (previous episodes of heatstroke, toxins, drugs, exertion). The most common cause of heatstroke in dogs is confinement in a closed automobile, in which ambient temperatures can reach dangerously high levels in minutes. Cats are commonly affected when they get trapped in clothes dryers.

Heatstroke affects almost all systems of the body. Acute renal failure is common; it can manifest as oliguric or polyuric renal failure and can be fatal. Oliguric renal failure causes acidemia, hypokalemia, inactivation of heparin, and possibly cerebral edema. These patients are prone to volume overload and electrolyte imbalances. Polyuric renal failure causes fluid and electrolyte loss. Protein loss accompanies polyuric renal failure if the glomerulus is damaged.

Disseminated intravascular coagulation (DIC) is very common in heatstroke and may appear early or late. Activation of coagulation and fibrinolysis occurs early and is profound and sustained in heatstroke. Liver dysfunction related to heatstroke results in loss of production of active coagulation proteins.

The cardiovascular system may be in a compensatory or hyperdynamic state (high cardiac output, low systemic vascular resistance) early in the course of heatstroke. With continued hyperthermia this state progresses to the hypodynamic state, in which signs of hypotension, hypoxemia, hypoperfusion, and hypovolemic shock are manifest. Cardiac myocyte necrosis rarely causes overt heart failure, but rather initiates arrhythmias up to 36 hours after the initial insult.

Central nervous system (CNS) injury can occur as a result of: direct thermal injury, respiratory alkalosis, thrombosis, or hypoperfusion from shock. DIC and hyperthermia lead to intraparenchymal hemorrhage that can result in seizures, thus sustaining hyperthermia. Complications of CNS injury include seizures, hypoventilation, coma, respiratory arrest, and cardiac arrest. CNS dysfunction and future episodes of heat stroke may be sequelae.

The gastrointestinal tract (GIT) is exquisitely sensitive to heatstroke. Direct thermal injury damages the gastrointestinal barrier. Hypoperfusion and hypoxemia result in necrosis, death,

and sloughing of the mucosa, leading to bacterial translocation. Bacterial translocation can cause sepsis and systemic inflammatory response syndrome (SIRS). Mucosal ulceration and loss of the gastrointestinal barrier leads to hemorrhage into the GIT, fluid and protein losses, and electrolyte imbalances.

Direct thermal injury and hypoxemia from hypoperfusion also damage the liver. Liver dysfunction results in loss of protein synthesis, including albumin and several coagulation factors. Complications associated with liver failure can include hypoalbuminemia, hyperammonemia, coagulopathies, icterus, and hypoglycemia. Persistent hypoglycemia or hypoalbuminemia is associated with increased mortality. Damage to the monocyte-macrophage system of the liver may result in endotoxemia and sepsis, leading to SIRS.

Heatstroke damages the muscles of the body, especially if it is the result of excessive exertion (seizures, excessive exercise without adequate training). Widespread necrosis of muscle cells results in hyperkalemia, hypocalcemia, lactic acidosis, and rhabdomyolysis. Rhabdomyolysis results in systemic release of myoglobin, which is toxic to kidney cells. Fibrinolysis is initiated by release of thromboplastin from injured myocytes. Conditions associated with muscle damage include acute renal failure, cardiac arrhythmias, DIC, pain, and hypocalcemic tetany.

Acid-base and electrolyte balances are affected by heatstroke. Initially animals pant, which does not increase alveolar ventilation and does not affect the acid-base balance. As the core temperature increases, panting gives way to hyperventilation, resulting in respiratory alkalemia. Respiratory alkalemia is associated with hypokalemia and hypophosphatemia. Later, respiratory alkalemia gives way to metabolic acidemia as shock induces lactic acidosis. Metabolic acidemia is associated with hyperkalemia, heparin inactivation, cardiac arrhythmias, loss of peripheral vascular tone and ongoing hypotension, and decreased myocardial contractility.

Clinical signs of heatstroke are related to the systems affected and the degree of injury to those systems. Early signs include panting, hypersalivation, tachycardia, hyperemic mucous membranes with shortened capillary refill time (CRT), bounding pulses, and increased blood pressure. The patient is often excited and hyperactive. The rectal temperature is often elevated.

Signs of shock become more pronounced as the syndrome progresses. The rectal temperature may be high, normal, or low. Tachycardia is common. The mucous membranes are pale and have a prolonged CRT. Blood pressure is often low. Tachypnea and hyperventilation are noted. Dehydration (often severe) is common. Hematemesis, hematochezia, and melena accompany injury to the GIT. The pupils are commonly dilated but may be miotic if the syndrome has caused CNS damage. Altered mentation and cortical blindness have been reported. Respiratory distress with or without cyanosis may be noted later in the syndrome. Generalized petechiation, evidence of thromboembolism, and/or hemorrhage can be seen as DIC progresses. Muscle tremors, seizures, collapse, and coma often precede cardiopulmonary arrest.

Laboratory findings are also variable and, again, depend on the systems affected and the severity of injury. The packed cell volume (PCV) is often high due to dehydration, but it may be low if significant blood loss through the GIT has occurred. Total solids are often high as a result of the acute dehydration but also may be low due to renal and/or gastrointestinal protein losses or fluid shifts due to increased vascular permeability. Leukocytosis is common, but severely affected patients can be leukopenic. Thrombocytopenia is common. Nucleated red cells are often seen in blood smears as a result of thermal damage to bone marrow.

Azotemia (elevated blood urea nitrogen and creatinine levels) is a common finding and may be prerenal or renal in origin. These values can increase over 24 to 48 hours as renal failure progresses. Hypoglycemia is common early in the syndrome. Persistent hypoglycemia is associated with a poor prognosis. Liver enzymes are elevated due to direct thermal damage and hypoperfusion of the liver. Cholestasis is common. Hyperbilirubinemia is associated with a poor prognosis. Rhabdomyolysis results in increased levels of serum creatine kinase and myoglobinemia.

Blood gas and electrolyte values are variable. Respiratory alkalosis as a result of hyperventilation and metabolic acidosis as a result of shock and lactic acid production are commonly found in a mixed acid-base disorder. Sodium and potassium levels are normal, high, or low, depending on the degree of dehydration, the severity of muscle damage, and whether vomiting and/or diarrhea is present. The onset of renal failure also affects electrolyte levels.

Urinalysis may reveal tubular cell casts, proteinuria, glucosuria in the absence of hyperglycemia, and increased urine gamma glutyl transferase (GGT), all of which indicate renal damage. Myoglobinuria indicates muscle damage and rhabdomyolysis and can exacerbate tubular necrosis.

Coagulation tests often reveal prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT). Thrombocytopenia is common. Hypofibrinogenemia and elevated levels of fibrin degradation products (FDPs) are common. Test values for D-dimer are often increased, whereas antithrombin 3 levels are decreased.

Early, aggressive treatment of heat-related signs and proactive treatment protocols directed at the complications of heatstroke reduce patient morbidity and mortality (see Figure 118-1). The most important aspect of treatment is to lower the core temperature. The pet owner should be instructed to initiate cooling measures before and during transportation. Effective cooling measures include wetting the patient with cool or tepid water and enhancing evaporation by providing air movement around the patient. It is important to note that ice water or cold water results in cutaneous vasoconstriction and loss of heat dissipation. It is also uncomfortable for the patient and can initiate the shivering reflex, resulting in heat production. More aggressive cooling techniques, such as cold water (or saline) enemas or gastric (or peritoneal) lavage with cool fluids, have not been shown to be any more effective than cool water baths and provision of air movement. Application of isopropyl alcohol has been recommended, but cutaneous vasodilatation may lead to absorption and intoxication. This measure is no longer recommended.

Cooling measures should continue upon arrival at the hospital if the core temperature is greater than 104° F (40° C). If the core temperature is 104° F (40° C) or lower, cooling measures must be discontinued and the patient protected from hypothermia, which increases morbidity and mortality. The patient should be given supplemental oxygen by mask, flow-by, oxygen hood, or nasal catheter.

Intravenous fluids are often required in the treatment of heatstroke, but their use must be determined on a case by case basis. Early in heatstroke or in cases of hyperthermia related to seizures, tremors, or ineffective panting, fluid imbalances are minimal, and aggressive fluid therapy can lead to volume overload. In more advanced cases of heatstroke, the patient has relative and absolute fluid losses that result in hypovolemia and perfusion deficits. These patients need aggressive fluid therapy.

Depending on the aggressiveness of fluid therapy needed, one or two catheters are implanted. In the least severe cases, crystalloid fluids (lactated Ringer's solution, Normosol-R, Plasmalyte, normal saline) are administered rapidly until perfusion parameters improve. The fluids should be room temperature. The clinician must administer "enough" fluid but not "too much." "Enough" improves mucous membrane color, capillary refill time, blood pressure, heart rate, pulse quality, and urine

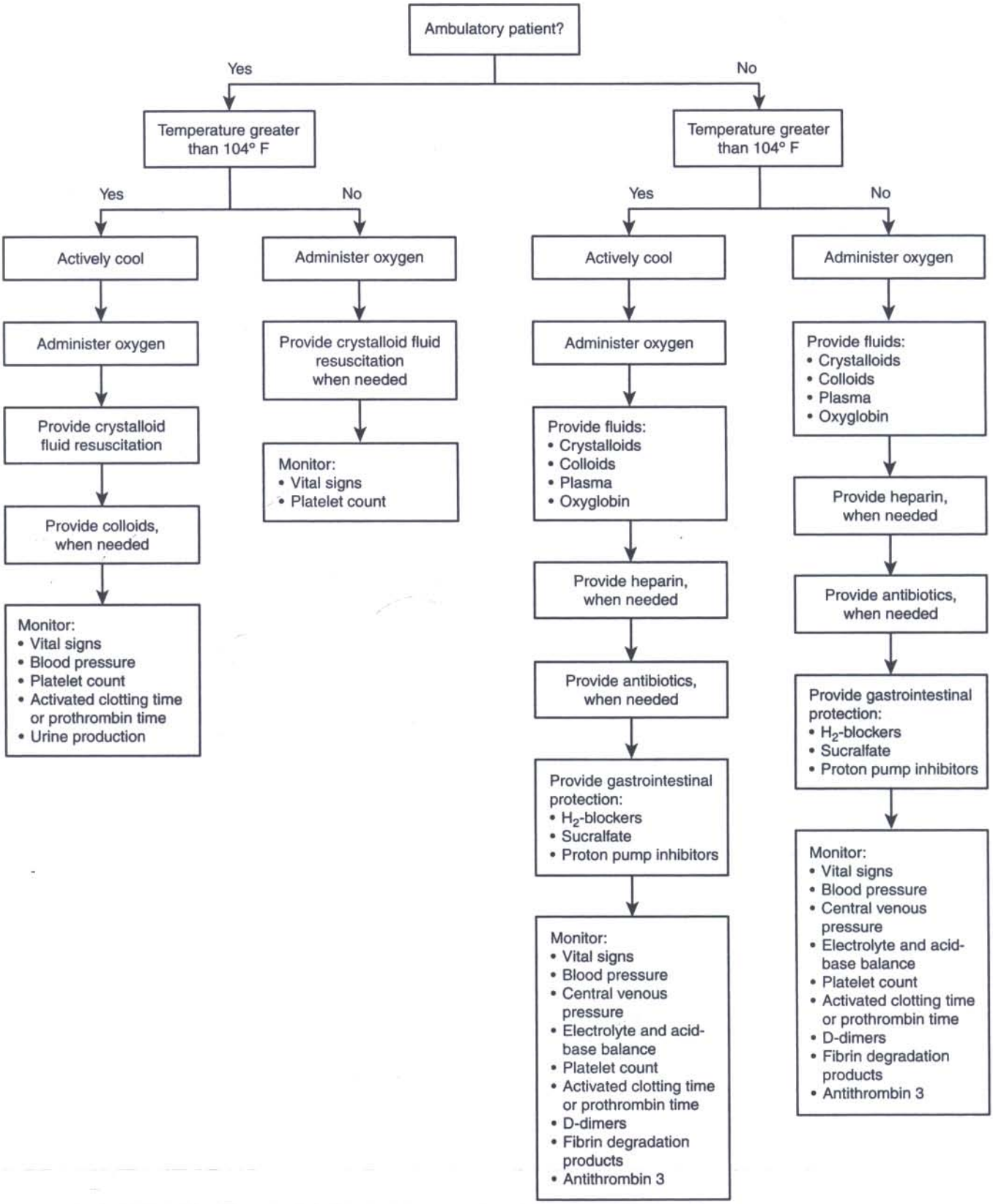

Figure 118-1 Treatment of heatstroke.

production. "Too much" causes dilutional anemia, hypoproteinemia, and edema formation, particularly pulmonary edema.

In more severe cases of heatstroke, a combination of crystalloid and colloid fluids (dextrans, hetastarch, pentastarch) is recommended. Again, fluids are administered rapidly to achieve targeted end-points. When colloids are used, the volume of crystalloid can be reduced by as much as 40% to 60%. Colloids expand the intravascular volume more effectively than crystalloids and minimize fluid loss from the increased vascular permeability that often accompanies heatstroke.

Although not approved by the U.S. Food and Drug Administration for use in heatstroke, Oxyglobin (BioPure Corp., Cambridge, Massachusetts) has been reported to be of benefit. Oxyglobin is a potent colloid that carries oxygen and is effective in improving oxygen delivery. Because many heatstroke patients suffer decreased oxygen delivery, Oxyglobin would seem to be an effective treatment modality. The manufacturer's recommended dosage is 10 to 30 mL/kg; however, it is likely more appropriate to administer it "as needed" to achieve specific hemodynamic end-points. Anecdotal reports indicate that the dosage is often not as high as the manufacturer's recommendations.

Vasculitis, increased capillary permeability, and DIC are common in heatstroke. These conditions require the use of fresh, fresh frozen, or frozen plasma. Because early diagnosis of these conditions is difficult, experts often recommend administration of plasma and advocate a proactive treatment protocol rather than a reactive one. The author's rule of thumb is: if the patient had to be carried into the hospital, plasma should be given. The dose of plasma is variable; 10 to 20 mL/kg can be used as a guideline.

Although controversial, heparin should be considered (50 to 250 U/kg given subcutaneously every 6 to 8 hours) when plasma is administered.

Use of corticosteroids (CCS) in heatstroke is controversial. When swelling and inflammation play a role (e.g., brachycephalic syndrome), use of these drugs likely is appropriate. Although CCS are said to stabilize membranes, suppress inflammation and cytokine production, and decrease the severity of endotoxemia, as well as have antipyretic properties, they are also known to worsen gastrointestinal ulceration and ischemic damage to the kidneys. Studies of the use of CCS have shown mixed results. The use of CCS is not routinely recommended, nor is it contraindicated if other appropriate therapy has been initiated. Nonsteroidal anti-inflammatory drugs are contraindicated.

Broad-spectrum antibiotic therapy is recommended. Combinations of ampicillin, amoxicillin, cefazolin, and enrofloxacin are acceptable in most cases. Aminoglycosides may be used only after renal function has been evaluated.

Sedatives (e.g., diazepam) are given to control seizures but must be used with caution. The use of sedatives often results in hypothermia. Intravenous dextrose is necessary in hypoglycemic patients. Gastrointestinal protectant drugs, such as sucralfate, famotidine or other H_2-blockers, and/or omeprazole, are recommended if signs of GIT inflammation or ulceration are present. Intense nursing care and vigilant monitoring are essential for successful treatment of heatstroke.

CHAPTER • 119

Hepatic and Splenic Emergencies

David E. Holt

HEPATIC AND SPLENIC EMERGENCIES ASSOCIATED WITH HEMOPERITONEUM

Traumatic injury to the liver or spleen or rupture of splenic or hepatic masses can cause life-threatening intraperitoneal hemorrhage. Trauma to the liver and spleen is often associated with motor vehicle accidents, falls, and accidental or malicious blunt abdominal injuries, such as kicks. The most common nontraumatic cause of hemoperitoneum in dogs is rupture of splenic hemangiosarcomas. Hemorrhage from other vascular, intra-abdominal masses, including splenic hematomas and hepatic tumors, can also occur in dogs but is less common. Hemorrhage from hepatic and splenic neoplasms accounts for approximately half of feline nontraumatic hemoperitoneum cases.

Traumatized animals have often sustained severe injuries to several organs. A rapid initial examination that focuses on life-threatening injuries to the central nervous, respiratory, and cardiovascular systems should be performed. Common clinical findings in animals with traumatic hemoperitoneum include depressed mentation, pale mucous membranes, delayed capillary refill time, a rapid heart rate, and poor peripheral pulse quality. The abdomen may or may not be visibly distended. Animals with nontraumatic, bleeding splenic or hepatic masses show either acute collapse or more chronic problems, including lethargy, anorexia, weight loss, or vomiting that has acutely worsened. The physical examination findings associated with poor tissue perfusion are similar to those in animals with traumatic hemoperitoneum; however, a mass is often detected on abdominal palpation.

Intravenous (IV) access is mandatory in animals with either traumatic or nontraumatic hemoperitoneum. The veterinarian may consider placing two large-bore IV catheters. Blood samples are obtained for a minimum data base, and resuscitation can commence. The rate and type of IV fluid resuscitation is based on the assessment of the animal's perfusion deficits and the presence of concurrent injuries. Full shock doses of crystalloids (60 to 90 mL/kg/hour in the dog; 45 to 60 mL/kg/hour in the cat) or hypertonic saline and dextran (5 to 7 mL/kg given over 5 minutes) followed by crystalloids may be necessary. Fluid resuscitation should be limited in animals suspected of having pulmonary contusions (10 to 20 mL/kg given intravenously for the first hour). Temporary application of a tight abdominal bandage (abdominal counterpressure)

can slow or arrest bleeding by raising intra-abdominal pressure. However, increasing intra-abdominal pressure for prolonged periods can adversely affect renal and hepatic blood flow.

The response to therapy and ongoing requirements for crystalloid or colloid fluids should be continually assessed from repeated clinical, laboratory, and monitoring (urine output, EKG, blood pressure, pulse oximeter) evaluations. Blood component therapy is often required to maintain the animal's packed cell volume (PCV) above 25%. Autotransfusion can be a lifesaving source of red blood cells in dogs or cats when fresh whole or stored blood is not available. Intra-abdominal sepsis or neoplasia is a contraindication to autotransfusion; hence, animals with no history of trauma should not be autotransfused. Peritoneal fluid is evaluated cytologically before autotransfusion.

Hemoperitoneum may be suspected from the history and physical examination findings. A focal or generalized loss of serosal detail on abdominal radiographs indicates free peritoneal fluid. The diagnosis of hemoperitoneum should be confirmed by peritoneal fluid evaluation. A sample is obtained by abdominocentesis with or without ultrasound guidance. In animals with hemoperitoneum, the peritoneal fluid sample should not clot unless the spleen has been inadvertently aspirated. The PCV of abdominal fluid usually is greater than or equal to that of the peripheral blood. Unfortunately, peritoneal fluid cytology is rarely helpful in diagnosing neoplastic causes of hemoperitoneum. In animals with either a palpable abdominal mass or no history of trauma, splenic neoplasia is a distinct possibility. Obvious pulmonary metastatic disease should be ruled out by evaluation of opposite lateral and dorsoventral thoracic radiographs. Abdominal ultrasonography may be useful for defining an intra-abdominal mass and for evaluation of other abdominal organs for evidence of metastatic disease.

Definitive treatment varies, depending on the underlying cause of the hemoperitoneum and the response to medical stabilization. Some dogs and cats with traumatic splenic or hepatic hemorrhage stabilize with fluid resuscitation, blood transfusion, and abdominal counterpressure. Surgery is indicated in animals with traumatic hemoperitoneum that continue to hemorrhage despite appropriate medical treatment. In humans, such circumstances would initially be investigated with interventional radiologic techniques, and obvious bleeding arteries would be embolized. These techniques are currently investigational at several veterinary schools. In animals with hemoperitoneum secondary to a bleeding splenic or hepatic mass, the aims of surgery are to stop ongoing hemorrhage, remove the mass, obtain a histopathologic diagnosis, and perform a complete exploratory to rule out gross metastatic disease. The prognosis for these animals depends on the tumor type. The two most common splenic masses in dogs are hemangiosarcoma and hematoma. Dogs have an excellent prognosis after hematoma removal; dogs with splenic hemangiosarcoma have a very guarded long-term prognosis even with chemotherapy.

Splenic and Liver Lobe Torsion

Although uncommon, splenic torsion should be considered in any dog with either chronic gastrointestinal (GI) signs or signs of acute abdominal disease. The pathogenesis of splenic torsion and the predisposing factors for this condition are not completely understood, but Great Danes and German shepherds are at increased risk. In many dogs, the history includes chronic signs of abdominal discomfort and GI disease, such as depression, anorexia, vomiting, and weight loss. However, some dogs with splenic torsion are initially examined as true emergency cases with signs of acute, worsening abdominal disease. The physical examination findings depend on the degree of cardiovascular instability and may include pale mucous membrane color, poor capillary refill time, and poor peripheral pulse quality. Splenomegaly may be detected on abdominal palpation in most cases and should increase the clinician's suspicion for splenic disease.

The differential diagnosis for such animals should include gastric dilatation-volvulus syndrome, GI foreign body obstruction, mesenteric torsion, peritonitis, and other causes of splenomegaly, including neoplasia. A complete blood count, serum biochemical screening, and abdominal imaging are indicated to further define the underlying disease. Radiographs show splenomegaly in all affected dogs; some can also have a loss of abdominal detail associated with peritoneal effusion or hemorrhage. Abdominal ultrasound findings of a hypoechoic pattern in the splenic parenchyma and decreased flow through the splenic veins strongly support a diagnosis of splenic torsion.

Animals should be stabilized with IV fluid resuscitation prior to induction of anesthesia. Some animals with moderate to severe anemia may require preoperative or intraoperative transfusions. Because many dogs with splenic torsion have evidence of abnormal coagulation, a coagulation screen and blood type and crossmatch are indicated prior to surgery. A protocol of balanced anesthesia with minimal cardiovascular depression should be used. Ventricular arrhythmias commonly develop intraoperatively or postoperatively, therefore electrocardiographic and blood pressure monitoring is vital. At surgery, the spleen should be removed without untwisting the splenic pedicle. Many surgeons also recommend concurrent gastropexy to prevent subsequent gastric volvulus. The prognosis is good for dogs with splenic torsion when appropriate emergency resuscitation and critical care management are combined with prompt diagnosis and surgical treatment.

Liver lobe torsion occurs rarely in dogs and cats. Clinical signs and laboratory data are nonspecific. A distended abdomen or a palpable abdominal mass can sometimes be detected on physical examination. The diagnosis is confirmed at exploratory laparotomy. The affected liver lobe should be resected either manually or with stapling equipment and submitted for histopathology.

Hepatic and Splenic Abscesses

Hepatic and splenic abscesses are both uncommon clinical entities in dogs but may present as true emergencies. The clinical signs and physical examination findings in dogs with these conditions are not specific. Dogs most commonly have a history of anorexia and lethargy that may be accompanied by vomiting and diarrhea. They are often febrile and have pain and hepatomegaly or splenomegaly on abdominal palpation. Occasionally, dogs with hepatic abscessation have evidence of epistaxis, ecchymosis, or hematochezia, indicating abnormal blood clotting function.

A complete blood count, serum biochemical profile, coagulation screen, and abdominal imaging studies are logical diagnostic steps in animals with these physical examination findings. Historically, all dogs with hepatic abscessation have had increased serum alkaline phosphatase (ALP) and alanine aminotransferase (ALT) activity, and the majority have a leukocytosis, thrombocytopenia, and hypoalbuminemia. The results of abdominal radiography may not be diagnostic; in one study of dogs with hepatic abscesses, most had hepatomegaly, one third had splenomegaly, and one third had a loss of abdominal detail. Abdominal ultrasound is useful in these cases and shows either hypoechoic or anechoic changes in one or more liver lobes. Samples can be obtained from affected lobes for cytology and aerobic and anaerobic culture and sensitivity testing using ultrasound guidance. If ultrasonography is not available, peritoneal lavage or exploratory laparotomy may be required to make a definitive diagnosis.

The etiology of hepatic and splenic abscesses is the subject of debate and probably is multifactorial. However, given that hematogenous bacterial spread is a potential cause, once a

diagnosis has been established, possible reservoirs of bacterial infection, such as the urinary tract and heart valves, should be investigated. The animal can also then be evaluated for concurrent conditions associated with hepatic and splenic abscessation, such as biliary tract disease, diabetes mellitus, pancreatitis, neoplasia, and endogenous or exogenous glucocorticoid excess. Thoracic radiographs are indicated to rule out pneumonia; in one study, radiographic evidence of alveolar infiltrates consistent with pneumonia were found in nearly half the cases examined.

Initial stabilization in affected animals involves cardiovascular support with IV fluids and administration of broad-spectrum bactericidal antibiotics with gram-positive, gram-negative, and anaerobic coverage pending the results of culture and sensitivity tests. Bacteria cultured from canine hepatic abscesses have included *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, enterococci, and clostridia. Treatment involves surgical resection of the abscessed liver lobe or lobes. In cases with diffuse hepatic involvement, percutaneous, ultrasound-guided drainage of abscesses may be appropriate. All affected animals should be treated with long-term antibiotic therapy (6 to 8 weeks). Follow-up ultrasound evaluations are recommended to monitor the response to treatment.

Rupture of the Biliary System

Rupture of the biliary system has been more commonly seen in dogs than cats and is usually caused by abdominal trauma or is associated with severe cholecystitis and rupture of the gallbladder. In animals with trauma-associated biliary leakage, there is usually a lag time of days to weeks between the initiating trauma and the development of clinical signs associated with bile peritonitis. Animals with underlying cholecystitis may have chronic or intermittent clinical signs associated with the hepatic and GI systems. Once the biliary tract begins to leak substantially, clinical signs of peritonitis develop, prompting owners to seek veterinary attention.

Clinical signs vary in severity, depending on the extent of the peritonitis (local or general) and whether secondary bacterial infection of the bile and peritoneal fluid is a factor. Clinical signs may include lethargy, anorexia, vomiting, and diarrhea. On physical examination, the mucous membranes may be icteric; parameters indicating perfusion, such as the capillary refill time, heart rate, and pulse quality, are variably altered, depending on the severity of the peritonitis. The abdomen is often distended and painful. Plain abdominal radiographs show a local or generalized loss of abdominal detail. In cases of necrotic cholecystitis, choleliths and/or free gas may be visible in the cranial abdominal quadrant. Blood work often shows a leukocytosis and an increase in the serum bilirubin concentration and ALP and ALT activity. A diagnosis of bile leakage potentially can be made from analysis of peritoneal fluid samples. The finding of free bile crystals on cytology or a peritoneal fluid bilirubin level higher than that of serum should prompt exploratory surgery.

Prior to surgery, the animal is rapidly and aggressively stabilized with IV crystalloids and possibly colloids. Broad-spectrum bactericidal antibiotics are administered, because bile peritonitis often involves gram-negative bacterial contamination. A preoperative coagulation screen is mandatory in these cases, because the absence of bile salts in the duodenum and jejunum precludes absorption of fat and fat-soluble vitamins such as vitamin K. Fresh frozen plasma is required to prevent excessive surgical hemorrhage secondary to lack of coagulation factors. Vitamin K supplementation should be given immediately (1 to 2 mg/kg subcutaneously). In cases of traumatic biliary leakage, the biliary system is directly repaired or bile is diverted by means of a cholecystoenterostomy. In cases of gallbladder rupture secondary to cholecystitis, a cholecystectomy is performed. Samples are taken from the liver and peritoneal cavity for bacterial culture and sensitivity testing. The liver is biopsied. The peritoneal cavity is copiously lavaged with sterile isotonic fluid and either closed or left open. (Chapter 43 presents a more detailed description of the management of peritonitis.)

Acute Hepatic Failure

Peracute hepatic failure has many potential causes in small animals, including chemical agents; biotoxins; anesthetics and other drugs; viral, bacterial, and other infectious agents; neoplasia; copper storage disease; and hepatic lipidosis in cats. Hepatic failure is diagnosed in humans that have hepatic encephalopathy (HE) and a concurrent coagulopathy. Hepatic encephalopathy is a complex syndrome of neurologic alterations seen in association with moderate to severe liver disease. The cause of the neurologic signs seen in HE is multifactorial; elevations in serum and central nervous system (CNS) ammonia levels alter the glutamate, gamma amino butyric acid, and serotonin neurotransmitter systems. Changes in the central and peripheral benzodiazepine receptor systems also occur. Small animals often have clinical signs of weakness, depression, collapse, anorexia, vomiting, and diarrhea. Physical examination findings are rarely specific; signs of spontaneous hemorrhage, including ecchymosis, icterus, and cranial organomegaly, increase suspicion for liver disease but do not differentiate between an acute hemolytic crisis and extrahepatic biliary obstruction. Owners should be questioned carefully about possible drug or toxin exposures.

A diagnosis may be suspected from the history and physical examination findings and the results of serum biochemical and liver function tests, including a coagulation profile. Abdominal ultrasonography may be helpful for visualizing the liver and obtaining either aspirates or biopsy specimens for cytology, culture, and histopathology. Treatment is largely supportive and involves cardiovascular support with crystalloid and colloid fluids, correction of electrolyte and acid-base imbalances, reduction of serum ammonia levels, and treatment of any seizurelike activity. The clinician should pay particular attention to hypokalemia and alkalosis, because both of these conditions increase ammonia uptake to the CNS. Serum ammonia is lowered by administering lactulose, a nondigestible disaccharide that acidifies the colon, decreasing ammonia production and converting ammonia into nonabsorbable ammonium ions. In comatose animals, lactulose is administered as an enema (10 to 80 mL). In some instances administration of flumazenil, a benzodiazepine receptor antagonist (0.02 mg/kg given intravenously), is helpful. In animals with HE and seizurelike activity, propofol is administered as a bolus (0.5 1 mg/kg given intravenously) and then as an infusion (0.05 to 0.1 mg/kg/minute given intravenously).

CHAPTER 120

Pulmonary Emergencies

Fred A. Mann

Exacerbation of any pulmonary disease can result in life-threatening hypoxia requiring emergency treatment. Pulmonary emergencies that occur as a direct result of acute injury or disease in previously normal lungs include pulmonary edema, pulmonary contusion, aspiration pneumonia/pneumonitis, smoke inhalation, near-drowning, pulmonary thromboembolism, and acute lung injury/acute respiratory distress syndrome.

PULMONARY EDEMA

Pulmonary edema is the accumulation of fluid in the pulmonary interstitium and alveoli due to imbalance among the six interstitial fluid control factors: (1) capillary hydrostatic pressure, (2) capillary oncotic pressure, (3) interstitial hydrostatic pressure, (4) interstitial oncotic pressure, (5) capillary wall integrity, and (6) pulmonary lymphatic function (Figure 120-1).

Cardiogenic pulmonary edema is due to increased capillary hydrostatic pressure induced by congestive heart failure. Noncardiogenic pulmonary edema may result from alterations in any one or more of the interstitial fluid control factors, including capillary hydrostatic pressure. Examples of conditions that can cause noncardiogenic pulmonary edema include head injury, seizures, and electrical shock, all of which have unknown mechanisms but seem to involve both increased capillary hydrostatic pressure and increased capillary permeability; smoke inhalation, near-drowning, aspiration pneumonia/pneumonitis, acute lung injury/acute respiratory distress syndrome, uremia, pancreatitis, and toxins, all of which are thought to involve altered capillary permeability; liver disease, protein-losing enteropathy, protein-losing nephropathy, and burns, all of which are characterized by hypoproteinemia and decreased capillary oncotic pressure but may involve other interstitial fluid control factors; infiltrative pulmonary neoplasia, which may result in pulmonary edema due to lymphatic obstruction; postobstruction pulmonary edema; and re-expansion pulmonary edema. Postobstruction pulmonary edema occurs when correction of airway obstruction results in loss of intrinsic positive end-expiratory pressure (PEEP). Exhalation against an obstruction creates a PEEP that is suddenly gone when the obstruction is relieved, resulting in interstitial and alveolar flooding. Re-expansion pulmonary edema occurs when atelectatic lungs are rapidly re-inflated through (manual or mechanical) positive pressure ventilation. The rapidity of reinflation, not the chronicity of the atelectasis, is the cause. Re-expansion pulmonary edema is thought to be a form of increased-permeability pulmonary edema arising from hypoxic injury to capillary and alveolar membranes followed by a rapid increase in capillary hydrostatic pressure during re-expansion.

Pulmonary edema is life-threatening because it impairs pulmonary compliance, vital capacity, and pulmonary gas exchange. Treatment is directed at the underlying cause but also includes oxygen administration and the use of bronchodilators and diuretics. Failure of oxygen and medical therapy to resolve hypoxemia necessitates ventilation therapy and PEEP. Monitoring of pulmonary edema involves thoracic radiography; however, clinical signs may precede, and pulmonary recovery may lag behind, the radiographic appearance.

PULMONARY CONTUSION

Pulmonary contusion, the accumulation of hemorrhage in lung parenchyma as a result of traumatic injury, can cause fatal pulmonary impairment. Fortunately, most pulmonary contusions are self-limiting and respond to supportive treatment with oxygen administration, rest, and judicious fluid therapy. Fluid overload is a concern because many pulmonary contusion patients are in shock and require intravascular volume expansion. Overzealous fluid administration for resuscitation may be avoided by using hypertonic saline (4 to 5 mL/kg given intravenously) followed by isotonic crystalloids to achieve targeted perfusion parameters. Diuretic therapy may be required to treat fluid overload. Antibiotics are not indicated for treatment of pulmonary contusions. If the patient remains hypoxic on supportive treatment, ventilation therapy with PEEP is required.

Because pulmonary contusions can worsen over 48 to 72 hours, they require close monitoring, and in some cases, therapeutic interventions for concurrent injuries must be postponed. Thoracic radiographs are used to monitor the progression and resolution of pulmonary contusions, but the radiographic appearance may not correlate with the clinical signs and the ability of the injured lungs to accommodate another insult, such as anesthesia. Radiographic resolution may precede full recovery of pulmonary function.

ASPIRATION PNEUMONIA AND PNEUMONITIS

Pneumonia and *pneumonitis* are characterized by the accumulation of inflammatory fluid in the pulmonary interstitium and alveoli (Figure 120-2). Emergent onset of pneumonia or pneumonitis occurs as a result of aspiration. If an infectious substance, such as oropharyngeal bacteria, is aspirated, the inflammatory condition is referred to as *aspiration pneumonia*. If acidic stomach contents are aspirated, a noninfectious, chemical-induced inflammation, referred to as *aspiration pneumonitis*, may occur. It is important to distinguish between pneumonia and pneumonitis because of important differences in therapy. Antibiotic therapy is not indicated, at least initially, with aspiration pneumonitis because the antibiotic may select for resistant organisms. Conversely, antibiotics should be promptly administered in cases of aspiration pneumonia after a transtracheal wash sample has been obtained for culture and susceptibility testing. Lungs with aspiration pneumonitis experience oxygen toxicity at typically safe levels of oxygen administration and therefore can be harmed by excessive oxygen, whereas lungs with aspiration pneumonia may benefit from standard oxygen therapy. If pneumonitis is suspected,

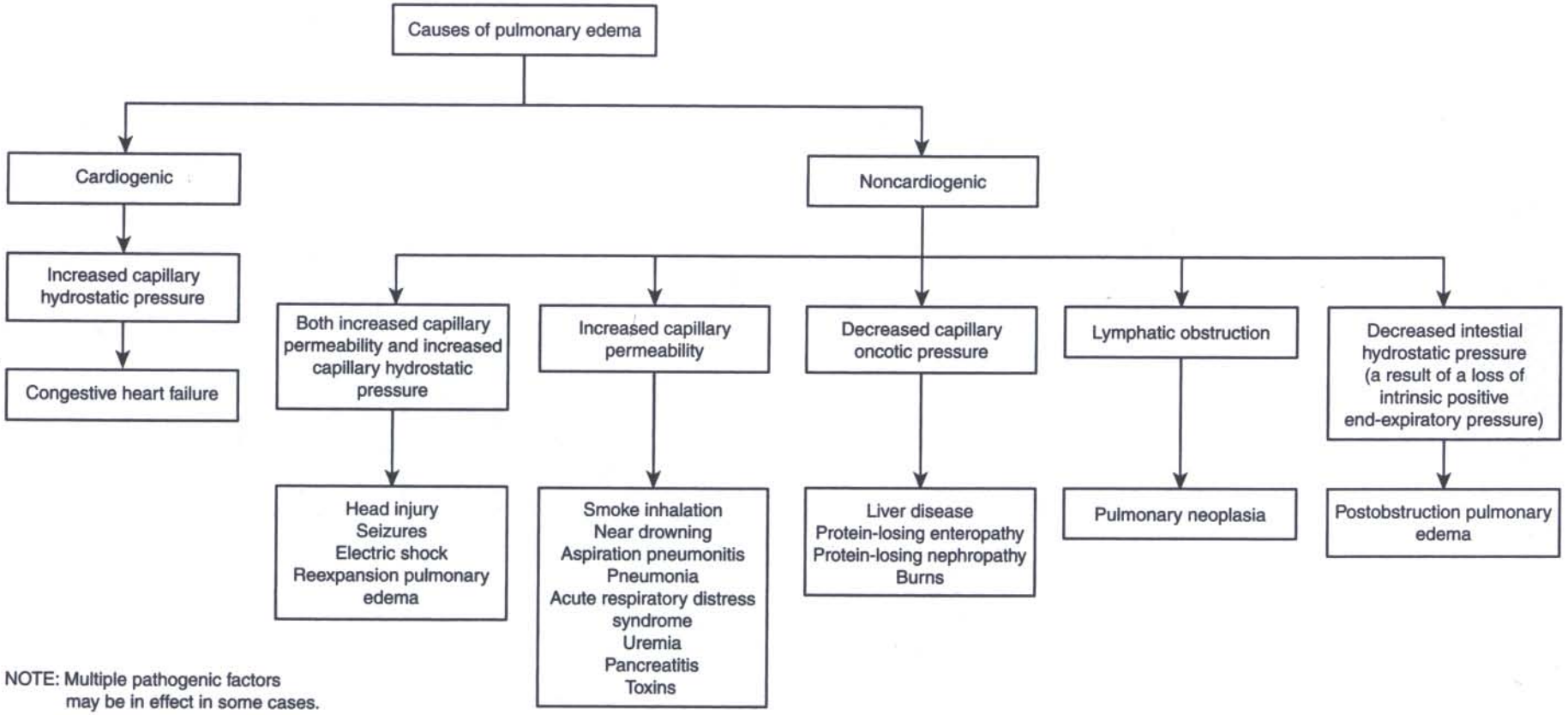

Figure 120-1 Causes of pulmonary edema.

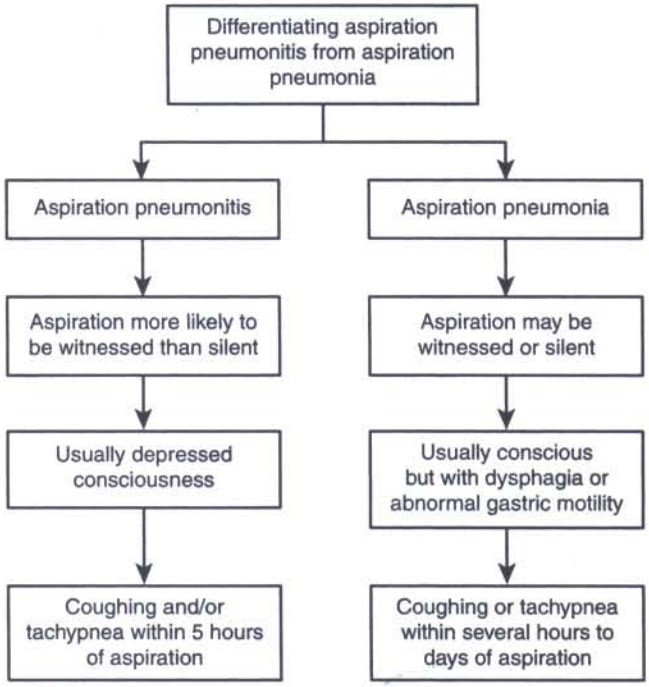

Figure 120-2 Differentiation of aspiration pneumonia and pneumonitis. *Note:* Because of the difficulty in clinical differentation, treatment strategy is based on whether the aspiration event is witnessed.

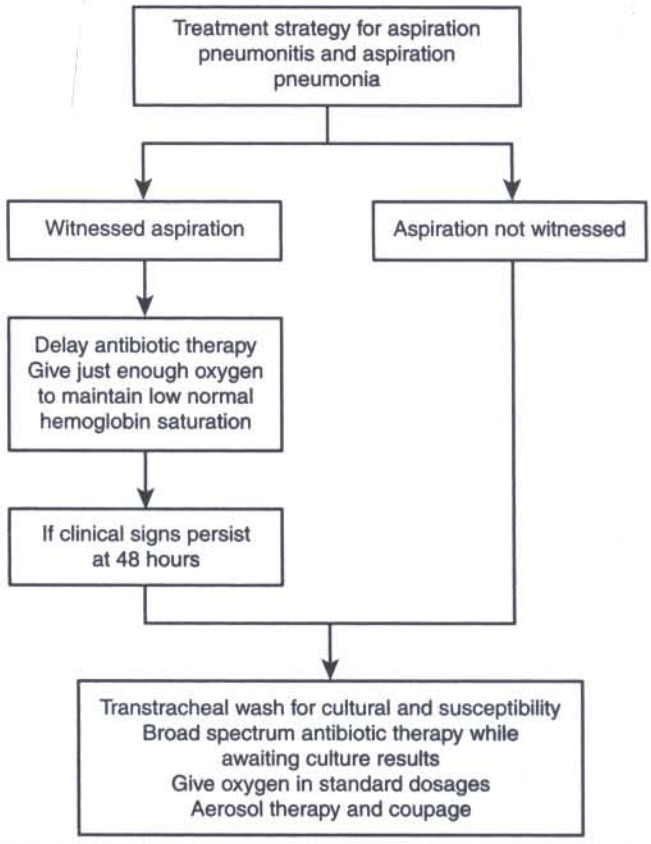

Figure 120-3 Treatment strategy for aspiration pneumonitis and pneumonia.

the lowest inspired oxygen concentration that maintains normal hemoglobin saturation is used.

Unfortunately, the differentiation between pneumonitis and pneumonia is not straightforward. Both types of aspiration may be witnessed or silent, but aspiration pneumonitis is more likely if the aspiration event is witnessed. Pneumonitis is more common in patients with depressed consciousness, whereas pneumonia is more common in patients with dysphagia and/or gastric motility disorders. Clinical signs may be absent in both, but when they occur, the onset may differ. Coughing and/or tachypnea typically occur within 5 hours of aspiration in pneumonitis, but they occur later (several hours to days) in pneumonia, depending on how long it takes the aspirated bacteria to reach pathogenic numbers.

Because of the difficulty in differentiation, the following therapeutic approach is recommended (Figure 120-3):

- *If the aspiration event is witnessed:* Antibiotic therapy is delayed, and just enough oxygen is administered to maintain normal oxygen saturation of hemoglobin. Antioxidant therapy, such as administration of vitamin E, may also be beneficial. If clinical signs fail to resolve within 48 hours, broad-spectrum antibiotic therapy is begun, preferably after transtracheal wash samples have been obtained.
- *If the aspiration event is not witnessed:* A transtracheal wash is performed, and broad-spectrum antibiotic therapy is pursued until culture and susceptibility results become available. Standard doses of oxygen are administered to maintain normal oxygen saturation of hemoglobin. With pneumonia, aerosol therapy and coupage may be used to facilitate both delivery of antibiotics to the respiratory tree and elimination of excessive respiratory secretions.

SMOKE INHALATION

Thermal injury from inhaled smoke is typically limited to the airways, but carbon monoxide and other toxic substances in smoke may cause pulmonary injury and dysfunction. Carbon monoxide binds with great affinity to hemoglobin, and the resultant carboxyhemoglobin is unable to carry oxygen. Administration of 100% oxygen shortens the half-life of carboxyhemoglobin from 4 hours to 30 minutes. As such, the most important treatment for smoke inhalation is early, preferably at the scene, oxygen therapy. Toxic substances may injure the lungs to the point of pulmonary edema, necessitating diuretics, careful fluid therapy, continued oxygen, and supportive care. Fluid therapy cannot be avoided, particularly if concurrent burns are a factor, but fluid rates must be monitored closely, preferably incorporating central venous pressure monitoring, to avoid fluid overload. The prognosis for smoke inhalation injury is good if no signs of pulmonary impairment are present on the day of admission. The prognosis is also good for patients with signs of respiratory dysfunction upon admission if the signs do not worsen the day after admission.

NEAR-DROWNING

The ultimate concern in near-drowning is hypoxic brain injury. In the lungs, abnormalities of gas exchange may occur as a result of (1) fluid aspiration and destruction of surfactant, (2) disruption of alveoli and capillaries, and/or (3) pulmonary hypertension, all of which contribute to the development of pulmonary edema. The most successful near-drowning cases are those in which immediate reversal of hypoxia is achieved,

before permanent neurologic impairment ensues. Immediate resuscitation provides the best possible outcome; however, first-responder cardiopulmonary-cerebral resuscitation at the scene is not widely available in veterinary medicine. Once the resuscitated near-drowning victim reaches the hospital, priorities are given to maintaining normoxemia, treating pulmonary edema, assessing neurologic function, and providing neurologic support therapies.

PULMONARY THROMBOEMBOLISM

Pulmonary thromboembolism (PTE) is rarely diagnosed ante mortem and is probably responsible for many acute unexpected deaths. Clinical diagnosis of PTE is based on unexplainable dyspnea concurrent with normal thoracic radiographs or thoracic radiographs with hypovascular lung regions or alveolar infiltrates that do not correlate with the degree of respiratory distress. The diagnosis is supported by known risk factors, such as dirofilariasis, nephrotic syndrome, immune-mediated hemolytic anemia, hyperadrenocorticism, pancreatitis, sepsis, neoplasia, and any condition that sets the stage for Virchow's triad: (1) hypercoagulable state, (2) vascular stasis, and (3) disruption of vascular endothelium.

Treatment for pulmonary thromboembolism includes symptomatic respiratory support and anticoagulant therapy. Rarely is thrombolytic therapy used. Most commonly, the patient is heparinized. A baseline activated partial thromboplastin time (aPTT), prothrombin time (PT), and activated clotting time (ACT) are obtained, and an initial intravenous dose of heparin (200 U/kg) is given, followed by 100 to 200 U/kg given subcutaneously or intravenously every 6 hours. The actual repeat doses are often even lower and are based on maintenance of the aPTT at one and one half to two times normal. The ACT can be used to adjust doses such that it is prolonged to 15 to 20 seconds over baseline; however, the aPTT should be monitored at least once daily. Heparin therapy may be slowly discontinued if the inciting cause is reversed. If prolonged anticoagulant therapy is needed, Warfarin may be given per os at a dosage of 0.2 mg/kg once, followed by 0.05 to 0.1 mg/kg to achieve a PT of one and one half to two times normal. Warfarin must be started before heparin is discontinued because Warfarin may be thrombogenic initially.

ACUTE LUNG INJURY AND ACUTE RESPIRATORY DISTRESS SYNDROME

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are severe conditions that result from direct lung insult, such as pulmonary contusion, pneumonia, smoke inhalation, near-drowning, and oxygen toxicity, or from indirect lung injury associated with sepsis, systemic inflammatory response syndrome, shock, pancreatitis, parvoviral enteritis, organ torsion, and some toxicities. Differentiation of ALI from ARDS is based on the severity of hypoxemia; the ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO_2:FIO_2) in ALI is 200 to 300, whereas the ratio for ARDS is less than 200. All ARDS cases result from progression of ALI, but not all ALI cases lead to ARDS. The hallmark of ALI/ARDS is hypoxemia refractory to increasing amounts of oxygen.

In ALI/ARDS, direct or indirect injury to pulmonary vascular endothelium and/or alveolar epithelium results in local inflammation that for unknown reasons spreads to the entire pulmonary system. Edema worsens. Flooded alveoli are perfused but cannot be ventilated; therefore, refractory hypoxemia results. Edema leads to decreased functional residual capacity, airway closure, atelectasis, decreased compliance, and increased work of breathing. Clinical signs, which are usually seen within 24 hours of the inciting cause, include dyspnea (which may be the only sign in early stages), tachypnea, increased abdominal effort, crackles, and harsh lung sounds. Hypotension and fever may also be present. The most common radiographic finding is diffuse alveolar infiltrates with normal cardiac silhouette and pulmonary vasculature. The diagnosis is supported by the presence of hypoxemia and alveolar infiltrates in the absence of congestive heart failure.

Treatment of ALI/ARDS consists of identification and treatment of the underlying cause and maintenance of adequate oxygen delivery to tissues. Tissue oxygenation is promoted by treatment or avoidance of edema, hypotension, volume overload, infection, and oxygen toxicity. Supplemental oxygen is given to maintain the arterial hemoglobin saturation above 90% and the PaO_2 above 60 mm Hg, to decrease the work of breathing, and to decrease the myocardial workload. Oxygen supplementation at an FIO_2 of less than 0.5 is administered to avoid oxygen toxicity. If a higher FIO_2 is necessary after 8 hours of supplementation, ventilation therapy with PEEP is warranted. Strict fluid balance, usually with a combination of crystalloids and colloids, is necessary to ensure tissue perfusion while avoiding fluid overload, because most deaths are the result of secondary organ failure rather than the pulmonary disease. Likewise, supportive management should include monitoring of blood pressure, coagulation, hemoglobin content, renal function, and nutrition, and appropriate therapeutic intervention when needed.

CHAPTER 121

Renal Emergencies

Cathy E. Langston

Immediate care is required for a dog or cat that is not excreting an adequate amount of urine (i.e., 1 to 2 mL/kg/hour). The patency of the urinary tract should be evaluated for obstruction or rupture. To restore adequate urine flow, the structural problem must be alleviated or bypassed (Figure 121-1).

Insufficient blood flow to the kidney from prerenal causes can substantially decrease the glomerular filtration rate (GFR). Long-standing ischemia may also lead to intrinsic renal failure. A wide variety of factors can cause acute intrinsic renal failure (ARF), which may exist as oligoanuria (less than 0.25 mL/kg/hour), nonoliguria (0.25 to 2 mL/kg/hour), or polyuria (greater than 2 mL/kg/hour). Dogs and cats with chronic renal failure may have a decompensated uremic crisis, which initially should be managed as nonoliguric acute renal failure.

The pet may have a known history of potential renal insult (e.g., ingestion of a nephrotoxic drug or antifreeze, a recent ischemic event), or it may have signs suggestive of ARF (recent onset of polyuria and polydipsia, vomiting, and anorexia). The physical examination may reveal renomegaly, pain, uremic ulcers, or halitosis.

In the initial stages of ethylene glycol intoxication (30 minutes to 12 hours after ingestion), clinical signs may include central nervous system (CNS) depression, incoordination, ataxia, somnolence, seizures, and coma. Hypothermia and vomiting are also common. Marked polydipsia occurs in dogs, and both dogs and cats initially become polyuric. These signs may resolve, to be followed by signs of ARF after 24 to 72 hours in dogs and as early as 12 hours in cats.

With leptospirosis, clinical signs commonly encountered include fever, musculoskeletal pain, severe and persistent vomiting and diarrhea, oculonasal discharge, hemorrhagic diathesis, peripheral lymphadenopathy, and dyspnea. The presence of icterus in an animal with ARF is suggestive of leptospirosis, although not all serovars are associated with hepatic involvement. Leptospirosis is a zoonotic disease, and appropriate precautions should be taken when handling any dog suspected of having the disease.

Test results consistent with ARF include an increased anion gap, metabolic acidosis, hypocalcemia, or hyperkalemia. Ethylene glycol toxicity may cause hyperglycemia. In addition to isosthenuria, urinalysis may reveal proteinuria, glucosuria, hematuria, pyuria, or cylindruria. Oxalate crystals may be present with ethylene glycol toxicity.

Abdominal radiographs typically show either normal or enlarged kidneys; the contours should be smooth with ARF. With ethylene glycol toxicity, the kidneys may appear more radiopaque than surrounding soft tissue structures. Abdominal ultrasonography usually shows normal to enlarged kidneys with normal architecture. Ethylene glycol toxicity frequently results in hyperechoic cortices compared with the liver. Thoracic radiographs may show an interstitial pattern with leptospirosis or an interstitial to alveolar pattern if volume overload has led to pulmonary edema.

A serum chemistry panel documents azotemia and hyperphosphatemia. Liver enzyme activity may be increased in leptospirosis, with peak liver involvement occurring about 6 to 8 days after the onset of renal involvement. Changes in the complete blood count are usually nonspecific. Dogs with leptospirosis may have a mild, nonregenerative anemia, leukocytosis, or thrombocytopenia. Urine culture may demonstrate bacterial growth in animals with bacterial pyelonephritis.

Specific tests available for ARF include an ethylene glycol test to confirm exposure. However, because of the limits of detection of the test, cats can have nephrotoxic ethylene glycol concentrations and yet produce a negative test result. The test result may be negative in both dogs and cats 12 hours after ingestion as a result of metabolism of ethylene glycol. Leptospirosis serology is not available on an emergency basis.

Fluid therapy is one of the first considerations for treatment of renal emergencies. Rehydration should take place over 4 to 24 hours, depending on the animal's cardiovascular status. Most ARF patients should be rehydrated over a short time (4 to 6 hours). If the animal is hydrated, a fluid volume equal to 3% to 5% of body weight should be administered to account for clinically undetectable dehydration. Urine output should be assessed after rehydration, and fluid therapy should be tailored to fluid output (ins-and-outs). Administered fluid should be at a base rate equaling insensible loss (22 mL/kg/day) plus the volume of sensible loss (urine production) over the previous time period. If vomiting is profuse, an estimate of this volume is added to measurements of urine output. This method is appropriate both for oliguric/anuric animals, to avoid overhydration, and for polyuric dogs and cats, in which the volume of urine frequently exceeds the clinician's estimate. Plasma or colloids (e.g., hetastarch, dextran) may be indicated.

If urine output remains low (less than 0.25 mL/kg/hour) in a hydrated animal with a blood pressure adequate to perfuse the kidneys (mean arterial pressure [MAP] greater than 80 mm Hg), diuretics are indicated. Mannitol (0.5 g/kg given intravenously over 20 minutes) is an osmotic diuretic but is contraindicated in dehydrated or overhydrated animals. Furosemide, a loop diuretic, may induce urine flow within 20 to 30 minutes after an initial intravenous bolus of 2.2 mg/kg. If this does not occur, the dose can be doubled, up to 10 mg/kg. Higher doses may lead to ototoxicity. Furosemide and mannitol can be given together. Use of dopamine as a diuretic is controversial, although it is useful at higher doses as a pressor agent for hypotensive patients.

Treatment of metabolic acidosis is recommended when the serum pH is below 7.2 or the serum bicarbonate concentration is less then 16 mEq/L. Sodium bicarbonate should be dosed according to the following formula:

$$\text{Body weight (kg)} \times 0.3 \times (20 - \text{Patient's bicarbonate concentration})$$

One quarter to one third of the dose is administered over 10 to 20 minutes, and an additional ¼ to ⅓ of the dose is administered over the next 4 to 8 hours. Rapid administration, excessive dosing, or administration to an animal with impaired respiratory function can lead to paradoxical CNS acidosis.

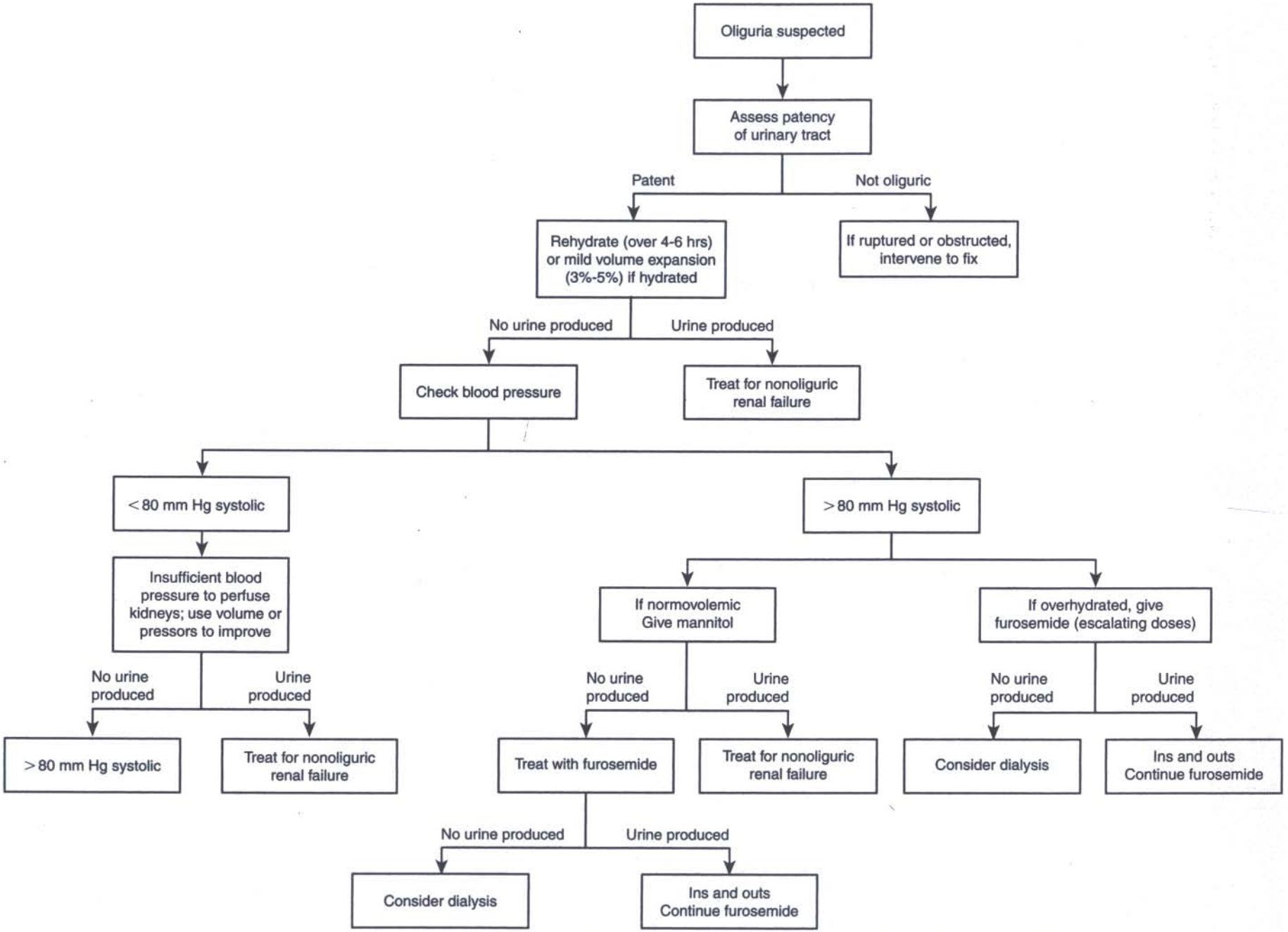

Figure 121-1 Algorithm for the management of a dog or cat suspected of having oliguric or anuric acute renal failure.

Hyperkalemia may cause cardiac or ECG abnormalities, characterized by bradycardia; wide, flattened, or absent P waves; peaked T waves; wide QRS complexes; atrial standstill; idioventricular rhythm; ventricular fibrillation; or asystole. Regular insulin (0.1 to 0.25 U/kg given intravenously) with dextrose to prevent hypoglycemia (1 to 2 g/unit of insulin as an intravenous bolus, followed by 1 to 2 g/unit over the next 4 to 8 hours) or bicarbonate (0.5 to 2 mEq/kg given intravenously) temporarily shifts potassium intracellularly, with an effect occurring within about 20 to 30 minutes. If a more immediate effect is needed, 10% calcium gluconate (0.5 to 1.0 mL/kg) can be administered as a slow intravenous bolus for its cardioprotective effect, although it does not decrease plasma potassium concentrations. These emergency treatments must be followed by procedures that remove potassium from the body (i.e., induction of urine flow or dialysis).

Uremia may induce gastritis or gastric ulceration. Histamine (H_2 receptor) blockers are commonly used to treat gastritis. They include famotidine (0.5 to 1 mg/kg given intravenously every 24 hours), ranitidine (2.2 mg/kg given intravenously every 24 hours), or cimetidine (2.5 to 5 mg/kg given intravenously every 12 hours). Because renal excretion of ranitidine and cimetidine is significant, this is a reduced dose. Sucralfate (0.25 to 1 g given orally every 6 to 8 hours) aids healing of uremic ulcers. It should be given at least 30 to 60 minutes before oral antacids. Uremic toxins can induce nausea by stimulating the chemoreceptor trigger zone. Metoclopramide (0.2 to 0.5 mg/kg given intravenously or intramuscularly every 6 to 8 hours, or 0.25 to 0.5 mg/kg/day given intravenously as a constant-rate infusion) is a centrally acting antiemetic. It is also a dopamine receptor antagonist and should not be administered concurrently with dopamine. Other antiemetics, such as chlorpromazine, can cause hypotension if the animal is not adequately hydrated. Little information is available on the use of 5-HT_3 serotonin receptor antagonists (e.g., ondansetron or dolasetron) in the treatment of vomiting associated with renal failure in animals.

Hyperphosphatemia is common in both acute and chronic renal failure as a result of decreased renal excretion. An acute increase in the phosphate concentration causes a compensatory decrease in the calcium concentration. Because the ionized calcium concentration is usually maintained within normal limits, signs of hypocalcemia tetany are infrequently observed. Oral phosphate binders (e.g., aluminum hydroxide) should be used once vomiting has been controlled and the animal is being fed enterally.

Respiratory compromise from pleural effusion caused by volume overload may require thoracocentesis. No effective method of addressing pulmonary edema exists in anuric animals other than ultrafiltration by means of dialysis. Careful attention to fluid therapy and urine output is crucial to avoid this complication.

Hypertension may accompany either acute or chronic renal failure, and excessive volume expansion (particularly in the face of oliguria or anuria) can exacerbate the condition. Therapy may not be necessary if the hypertension is mild and renal failure is resolving rapidly. However, in more severe cases emergency therapy may be necessary to prevent catastrophic effects.

Anorexia is common with acute renal failure. Because of the highly catabolic state associated with ARF, nutritional support should be started early in the course of the illness. If vomiting can be adequately controlled pharmacologically, enteral feeding with a feeding tube should be started. If enteral feeding is not possible, partial or total parenteral nutrition should be instituted. Calories should be predominantly carbohydrates, with restricted protein content. Ideally, protein should be supplied as essential amino acids.

Uremia induces a thrombocytopathy, and the risk of bleeding should be considered when invasive procedures are planned (e.g., renal biopsy, feeding tube placement). Because coagulation parameters and platelet numbers may be normal, a buccal mucosal bleeding time is the preferred method of assessment.

For ethylene glycol toxicity, specific antidotes are indicated. Four-methylpyrazole (4-MP (fomipezole); Antizol-Vet, Orphan Medical, Minnetonka, Minnesota) is effective in dogs if given within 8 hours of ingestion. Standard doses are not effective in cats. Dosing for dogs is 20 mg/kg initially, given intravenously, then 15 mg/kg at 12 and 24 hours, and 5 mg/kg at 36 hours. If 4-MP is not available, 20% ethanol can be used to competitively inhibit alcohol dehydrogenase. A dose of 5.5 mL/kg every 4 hours for five treatments, then every 6 hours for four treatments, can be given as an intermittent intravenous bolus but is better administered as a constant-rate infusion. In cats, 20% ethanol can be dosed at 5 mL/kg every 6 hours for five treatments, then every 8 hours for four treatments. Drinking alcohol (50% ethanol [100 proof]) can be diluted with saline. Respiratory depression can be profound with alcohol. Neither 4-MP nor alcohol is effective if started more than 8 hours after toxic ingestion.

Antibiotics should be administered if leptospirosis or pyelonephritis is suspected or documented. High doses of penicillin are effective at clearing leptospiremia. Doxycycline (2.5 mg/kg PO or IV every 12 hours) is effective at clearing leptospiremia and possibly leptospiuria. The most common cause of bacterial pyelonephritis is *Escherichia coli* infection. Empirically used antibiotics should have a good gram-negative spectrum and should not be nephrotoxic.

Adequate monitoring of animals with acute renal failure is essential. They are acutely and severely ill. Their status can change rapidly and dramatically. Urine output should be monitored in all animals with renal failure. This is most accurately accomplished with an indwelling urinary catheter with a closed collection system. Changes in body weight over the course of hospitalization primarily reflect changes in body water content and hydration. Other parameters (e.g., blood pressure, central venous pressure, packed cell volume) should be monitored as needed.

If conventional medical management fails to induce diuresis in an oliguric or anuric dog or cat, if life-threatening complications are present (i.e., hyperkalemia, volume overload), or if azotemia fails to improve after 24 hours of therapy, dialytic therapy (either hemodialysis or peritoneal dialysis) should be considered. (see Figure 121-1.)

The outcome of acute renal failure is poor. Approximately 60% of dogs and cats die or must be euthanized. Renal trauma may require emergency surgery to control massive hemorrhage.

CHAPTER • 122

Gynecologic Emergencies

Saralyn Smith-Carr

Most gynecologic emergencies occur during the periparturient, diestrus, or postestrus periods. It is the responsibility of the veterinarian to act quickly to ensure preservation of the life of the bitch, the neonate and future reproductive potential of the bitch (in that order). The reasons owners seek veterinary assistance for reproductive emergencies are listed in Table 122-1. A complete breeding history should always be obtained along with a thorough physical examination. Details of each reproductive disorder have been reviewed elsewhere.

DYSTOCIA

Dystocia is the inability of the female to expel the fetus through the birth canal at parturition. The bitch's body temperature drops below normal (<100° F), 8 to 24 hours before the onset of labor, due to serum progesterone, decreasing to less than 2 ng/dl. There are three stages of labor. During the first stage, the bitch may become anxious, restless, or seek seclusion. There are no obvious uterine contractions but cervical dilation occurs and clear vaginal fluid discharge may be seen, which indicate chorioallantois membrane rupture. During stage II labor there are noticeable abdominal contractions, fetal membranes are visualized at the vulva, and the puppy or kitten is immediately expelled. Delivery of the first newborn usually occurs within 20 to 30 minutes of the onset of stage II labor. Stage III labor is a resting period, during which the placental membranes are passed and the bitch cares for the neonate. Causes of dystocia may be maternal or fetal in origin. Specific details on maternal and fetal causes of dystocia have been reviewed elsewhere.

Regardless of the origin of dystocia, maternal or fetal, either primary or secondary uterine inertia occurs and the owner seeks veterinary assistance. After taking a history, a general physical examination should be performed to determine the degree of maternal compromise. Next, detailed examination of the reproductive tract should be performed beginning with visual inspection of the vulva for presence of discharge, fetal membranes, or fetal parts. Mucoid or greenish black (lochia) vaginal discharge are normal findings but may indicate obstruction if present for more than 2 hours without delivery. Sanguineous or bloody vaginal discharge may indicate vaginal trauma or uterine torsion. Reddish brown fetid discharge indicates fetal death and subsequent metritis.

Presence of fetal membranes or fetal parts should prompt digital examination of the vagina and/or rectum to palpate for any obstruction. Abdominal palpation should be performed to ascertain fetal presence and discern fetal movement. Auscultation of the abdomen for fetal heartbeats should be performed although absence may not indicate fetal death. Fetal heart rates below 200 bpm may indicate fetal compromise and dictates need for immediate treatment. If obstruction of the birth canal is suspected, surgery rather than medical therapy should be chosen. Therefore, abdominal radiographs are recommended to evaluate fetal size and position related to the birth canal of the dam. Abdominal ultrasound should be performed to determine fetal viability and presence of uterine or abdominal fluid that may indicate infection or peritonitis, respectively.

In a periparturient bitch that demonstrates signs of compromise, a CBC and serum chemistry should be performed to aid in evaluating for sepsis, hypoglycemia, hypocalcemia, and her general health. Parenteral oxytocin administration, with

Table • 122-1

Reasons for Seeking Veterinary Assistance for Reproductive Disorders

PRESENTING COMPLAINT	DISORDER(S)
No signs of labor at >24 hours after temperature decrease to <100° F	Normal or dystocia
More than 1 week overdue	
Fetal membranes in vulva >15 minutes	
Strong contractions >30 minutes without delivery	
No fetus produced after 4-6 hours of onset of stage II labor	Dystocia
More than 3 hours between fetal delivery	Dystocia in canine
Vaginal discharge	Dystocia, metritis, pyometra
Temperature >103.5° F in the bitch	Dystocia, metritis, pyometra, uterine torsion, mastitis
Profuse vomiting, diarrhea and toxemia in bitch	
Incessant crying of offspring	
Anorexia, lethargy, depression >24 hours postpartum	Metritis, mastitis
Hot, painful, swollen mammary glands	Mastitis
Extreme restlessness, panting, tremors, and stiff gait	Eclampsia

or without calcium and glucose, may be all that is needed. Often, however, dogs and cats with dystocia usually require C-section. It is important to consider the effects of anesthesia on the bitch and fetus. Anesthetic protocols should be chosen to minimize respiratory depression of either fetus or the bitch. Surgical preparation of the bitch needs to be performed prior to anesthesia induction, which decreases exposure of bitch and fetus to cardiac and respiratory depression caused by general anesthetics. The physiologic changes of the pregnant bitch should also be taken into consideration and appropriate measures taken to treat respiratory and cardiovascular compromise due to increases in intra-abdominal pressure. Supplemental oxygen during anesthesia induction, along with intravenous fluid administration and tilting the surgery table toward the surgeon during surgery, are recommended.

Fluid therapy may be needed to correct dehydration due to vomiting or hypovolemia due to shock. Pregnant bitches may be prone to vomiting. Therefore antiemetics may be needed. Care should be taken to resuscitate neonates. Therefore trained staff should be available to remove fetal membranes, stimulate respiration, remove fluid from their nares using gentle suction, and to ensure proper clamping and cutting of umbilical cords. Proper care of neonates has been reviewed elsewhere.

ECLAMPSIA

Hypocalcemia usually occurs in the second or third weeks of lactation. Less commonly, hypocalcemia occurs in the first or fourth weeks of lactation. Rarely, it is diagnosed in the final 1 or 2 weeks of gestation. Hypocalcemia is due to a loss of calcium into the milk more rapidly than it can be absorbed from bone and because some of these dogs fail to eat properly. Predisposing factors are high-calcium diet during pregnancy, calcium supplementation during pregnancy, and heavy lactation demands postpartum. Clinical signs include nervousness, panting, salivation, stiff gait, ataxia, and clonic-tonic muscle contractions that may progress to seizures. If not treated, death may result. Diagnosis is usually based on history and clinical signs. Laboratory finding of hypocalcemia is not usually necessary. If assessed, total serum calcium concentrations are usually below 7 mg/dL in bitches and less than 8 mg/dL in queens. Serum ionized calcium concentrations provide more direct information on biologically available calcium. However, treatment should be instituted before serum calcium results are available, if blood is taken.

Calcium should be administered intravenously slowly at 5 to 10 mL increments. The heart should be monitored for bradycardia and arrhythmias during calcium administration via auscultation and ECG. A 10% to 20% calcium gluconate solution is usually given; however, other calcium preparations have been used. Once acute signs have resolved, subcutaneous calcium may be given at 8-hour intervals. Caution is advised in the choice of calcium supplements since calcium concentration differs and some are irritating when given IM or SQ. Dogs and cats should then be placed on oral calcium supplementation for the remainder of their lactation period with close monitoring for return of clinical signs. If signs return, puppies or kittens should be weaned or bottle-fed.

METRITIS

Metritis may occur during the postpartum period due to obstetric manipulations, retained fetal remains, or retained placenta. Clinical signs may include reddish brown fetid vaginal discharge, fever, anorexia, lethargy, or lack of interest in the neonate. Physical examination may reveal an enlarged uterus and clinical signs of sepsis. Abdominal radiographs and ultrasound should confirm the presence of an enlarged, fluid-filled uterus. The CBC typically reveals a leukocytosis, neutrophilia, and a left shift. Serum chemistry profiles reflect degree of dehydration and may demonstrate hypoglycemia in some septic animals. Increases in liver enzyme activities may occur due to endotoxemia. Abdominal ultrasound may be used to determine the thickness of the uterine wall. If there is evidence of a thin uterine wall or medical therapy is unsuccessful, ovariohysterectomy is recommended. Medical therapy consists of oxytocin or prostaglandin therapy for emptying the uterus. Broad-spectrum antibiotics should be administered also chosen with consideration of the nursing neonate.

MASTITIS

Mastitis is bacterial infection of the mammary gland. Clinical signs can occur during the postpartum period alone or accompanying metritis or in pseudopregnancy. Clinical signs may include fever, anorexia, lethargy, and lack of interest in the neonate. Physical examination may reveal fever, hardened, painful mammary glands, and in some cases gangrenous mammary glands. Infection of the mammary gland is considered ascending but could be due to hematogenous spread. Diagnosis is based on history, clinical signs, and physical examination findings. Cytology and culture of mastitic milk often reveals degenerating neutrophils and, typically, pure colonies of staphylococci, streptococci, or *Escherichia coli*. Treatment consists of broad-spectrum antibiotics while culture results are obtained. The dog or cat should be switched to an appropriate antibiotic after culture results are obtained. Choice of antibiotic should consider the nursing neonate. Puppies or kittens should be allowed to nurse (actually encouraged) except if the glands are abscessed or gangrenous. Abscessed and/or gangrenous glands should be surgically treated.

UTERINE TORSION

Uterine torsion refers to rotation of one or both uterine horns. The condition is uncommon and can occur in the gravid or non-gravid uterus. Uterine torsion occurs more often during pregnancy and is more common in the queen than the bitch. Clinical signs are abdominal pain and shock. Acute abdominal enlargement may be seen in the non-pregnant female and signs of dystocia in the pregnant female. A high degree of suspicion of uterine torsion is made in the bitch or queen experiencing abdominal pain, enlarged uterus, and radiographic signs of uterine gas or acute distention of the abdomen. Definitive diagnosis is made by exploratory laparotomy. An immediate ovariohysterectomy is required. Appropriate fluid therapy should be administered to combat shock and broad-spectrum antibiotic should be administered for infection. Saving the life of the queen or bitch is more important than preservation of their reproductive potential.

PYOMETRA

Pyometra and cystic endometrial hyperplasia are common illnesses in older nulliparous bitches and queens. During diestrus, the endometrial glands of the uterus are stimulated, which causes hyperplasia and hypersecretion leading to cystic endometrial hyperplasia. Pyometra is uterine inflammation and bacterial infection that leads to an accumulation of pus in the uterine lumen. Most bitches with pyometra are seen

during diestrus, whereas queens are brought to veterinarians post estrus. The pathophysiology is not completely understood but is considered due to multiple exposure of the uterus to progesterone. Pathophysiology has been reviewed elsewhere.

The disease has been further divided into open and closed cervix distinctions based on the degree of cervical patency. Usually the bitch has a history of predisposing factors such as multiple estrous cycles, use of exogenous estrogen, or use of progestins. Clinical signs, often more severe in animals with closed cervix pyometra, include anorexia, fever, vomiting, polyuria, and polydipsia. Animals with "open-cervix" pyometra have a purulent vaginal discharge. Sepsis, endotoxemia, and renal failure can occur in some bitches with pyometra. Vaginal discharge with systemic signs and history of estrus 1 to 12 weeks prior to development of clinical signs leads to the suspicions of pyometra. Blood work abnormalities consist of a neutrophilia with a left shift and non-regenerative anemia. Azotemia, the raised serum protein concentrations (both albumin and globulin) and elevated liver enzymes are seen. These changes are caused by dehydration and endotoxemia. Urinalysis reveals normal to low urine specific gravity and sometimes proteinuria. Urinary tract infection occurs in some cases. The most common bacteria associated with pyometra are *E. coli*, although streptococci, staphylococci, and *Proteus* and *Klebsiella* spp. have also been reported. Diagnosis, based on history and clinical signs, is usually confirmed by radiography and/or ultrasound. Lateral radiographic views of the abdomen are most helpful. An enlarged sacculated uterus can be seen, especially in animals with closed-cervix pyometra. This cannot be distinguished from a pregnant uterus less than 42 days into gestation. Abdominal ultrasound is valuable for the diagnosis of pyometra. A fluid filled uterus can be visualized and differentiated from fetal sacs. Medical and surgical treatment options exist but surgery is usually recommended. Dehydration and sepsis is addressed first with fluid therapy and broad-spectrum antibiotics. Medical treatment with prostaglandin can be used if the cervix is open. Treatment protocols with natural prostaglandin have been reviewed elsewhere. Surgical treatment consists of ovariohysterectomy. Stabilization of the dog or cat with fluids and antibiotics is required before any treatment medical or surgical. Antibiotic therapy should be continued for 1 month.

In summary gynecologic emergencies may be challenging. Knowledge of clinical signs and reproductive history is critical to diagnosis. A complete physical examination and laboratory workup is necessary to determine complications associated with each emergency.

CHAPTER 123

Sepsis and the Systemic Inflammatory Response Syndrome

Linda Barton

Stedman's Medical Dictionary defines sepsis as "the presence of various pus-forming and other pathogenic organisms, or their toxins, in the blood or tissues." However, increased understanding of the pathogenesis of sepsis has shifted the focus from the microorganisms causing infection to the host's response to that infection. The clinical syndrome of sepsis represents the body's systemic response to infection, characterized by signs of inflammation, particularly when that response becomes deleterious to the host.

The human and veterinary medical literature has used a variety of terms interchangeably to describe patients with adverse systemic manifestations of infection. In an attempt to standardize the literature and to identify homogeneous patient populations for clinical trials, a consensus conference was sponsored in 1991 by the American College of Chest Physicians and the Society of Critical Care Medicine. The consensus conference agreed on definitions for the terms *bacteremia*, *sepsis*, *severe sepsis*, *septic shock*, and *multiple organ dysfunction syndrome* (MODS) (Box 123-1). Conference attendees recognized the clinical course of sepsis as a continuum. *Sepsis* is the term used to describe patients with infection-induced systemic inflammation. The occurrence of organ dysfunction secondary to sepsis is defined as *severe sepsis*. The development of hypotension, not responsive to IV fluid administration, is defined as *septic shock*.

Recognizing that severe insults other than infection can produce a generalized systemic reaction, organ dysfunction, and shock indistinguishable from those induced by sepsis, conference attendees created the term *systemic inflammatory response syndrome* (SIRS). SIRS can be used to describe evidence of systemic inflammation due to either an infectious or noninfectious process. Only when SIRS is associated with infection is it defined as sepsis. The SIRS criteria have been modified for the cat and dog (Table 123-1). Noninfectious processes associated with SIRS in animals include pancreatitis, tissue trauma, heat stroke, ischemia, burns, and pansystemic neoplasia.

PATHOGENESIS

Infection or tissue injury triggers a local immune response. Toxic effects from infecting organisms, components of infecting organisms (such as endotoxin, the lipopolysaccharide associated with the membrane of gram-negative bacteria), exotoxins, or aminophospholipids from damaged cell membranes stimulate the release of a variety of pro-inflammatory and anti-inflammatory mediators into the local environment. This local immune response is a desired host defense. In some individuals, inflammatory mediators spill over into the systemic circulation, which triggers a more generalized reaction. A systemic inflammatory reaction is more likely to develop with a severe insult or when a patient receives sequential insults. The "second-hit" theory proposes that patients with a controlled inflammatory process may develop SIRS if they sustain a second infectious or inflammatory insult.

The clinical manifestation of this generalized reaction depends on the balance between pro-inflammatory and

Box • 123-1

1991 ACCP/SCCM Consensus Conference Definitions

Bacteremia: The presence of viable bacteria in the blood.
Systemic Inflammatory Response Syndrome (SIRS): The systemic inflammatory response to a variety of infectious or non-infectious insults. The response is manifested by two or more of the following criteria:
- Temperature >38° C or <36° C
- Heart rate >90 beats/minute
- Respiratory rate >20 breaths/minute or Pa_{CO2} <32 torr
- WBC >12,000 cells/mm³, <4000 cells/mm³, or >10% immature (band) forms

Sepsis: The systemic response to infection. SIRS as a result of infection.
Severe sepsis: Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Clinical manifestations include lactic acidosis, oliguria and altered mentation.
Septic shock: Sepsis with hypotension, despite adequate fluid resuscitation.
Multiple Organ Dysfunction Syndrome (MODS): The presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

anti-inflammatory mediators. In a controlled response, pro-inflammatory and anti-inflammatory cascades are balanced and homeostasis is restored. An imbalance in favor of anti-inflammatory cytokines results in relative immunosuppression. SIRS/sepsis and the progression to severe sepsis and septic shock result from an imbalance in favor of the pro-inflammatory mediators.

The clinical signs of SIRS, organ dysfunction, and septic shock are produced by the pathophysiologic effects of inflammatory mediators. The effects on the cardiovascular system are characterized by peripheral vasodilation, which results in decreased systemic vascular resistance and myocardial dysfunction manifest as ventricular dilation, a decreased ejection fraction, impaired contractile response to volume loading, and decreased left ventricular compliance. Vascular endothelial injury occurs secondary to enhanced neutrophil activation and adhesion, which leads to increased vascular permeability.

Interactions between inflammatory and coagulation cascades during sepsis have become increasingly apparent. Large quantities of tissue factor (TF), the important trigger of the extrinsic coagulation cascade, are expressed by injured endothelial cells, and cytokine-stimulated neutrophils and macrophages. The procoagulatory state created by increased TF is further amplified by consumption of naturally occurring anticoagulants such as activated protein C, tissue factor pathway inhibitor, and antithrombin. Enhanced thrombin formation leads to deposition of fibrin in the microvasculature, which obstructs blood flow and exacerbates tissue hypoxia. This condition may progress to fulminant disseminated intravascular coagulation (DIC).

Table • 123-1

Criteria for Systemic Inflammatory Response Syndrome

CLINICAL PARAMETERS	DOGS	CATS
Heart rate	>120 bpm	<140 bpm or >225 bpm
Respiratory rate	>40 bpm or Pa_{CO_2} <30 mm Hg	>40 bpm
Temperature	<100.4° F or >104.0° F	<100.0° F or >104.0° F
Leukogram	>18,000 or <5000 WBC/μL	>19,000 or <5000 WBC/μL

From Otto CM: Sepsis. In Wingfield WE, editor: *The Veterinary ICU Book*, Jackson Teton NewMedia, 2002, p 694.

CLINICAL PRESENTATION AND DIAGNOSIS

Recognizing SIRS/sepsis and its sequelae as a continuum, clinical signs vary from animals with mild abnormalities to those with signs of organ dysfunction and septic shock. No single set of clinical, laboratory, and hemodynamic parameters can describe all situations. In addition to the SIRS-related changes in body temperature, heart rate, respiratory rate, and white blood cell count, affected animals may have decreased mentation, hypotension, bounding or hypodynamic peripheral pulses, thrombocytopenia, hypoalbuminemia, hypoglycemia, prolonged clotting times, increased fibrin split products, increased D-dimer, decreased antithrombin, increased bilirubin, increased liver enzymes, increased BUN/creatinine, oliguria, lactic acidosis, and/or hypoxemia.

The animal may have signs related to the underlying infection (i.e., coughing and dyspnea associated with bacterial pneumonia). Alternatively, the systemic inflammatory response may manifest before signs of the infection and should alert the clinician to search for an infectious cause. When animals have unexplained shock (no history or physical exam findings consistent with trauma, blood or fluid loss, or cardiac disease) sepsis should be suspected as the underlying cause.

Suspicion of sepsis demands an "infection hunt." Common causes of sepsis in dogs and cats include peritonitis, pyometra, prostatitis, prostatic abscess, pyelonephritis, pneumonia, pyothorax, and endocarditis. In hospitalized animals, nosocomial infections should be considered. IV catheters, urinary catheters, and other invasive devices should be carefully inspected and removed, as required. Translocation of bacteria from a diseased or unused GI tract is another possible source of infection. Signalment, history, and physical exam are useful in localizing the nidus of infection. Samples should be collected for CBC, serum biochemical profile, and urinalysis to assist in the localization of infection and to detect evidence of organ dysfunction. Additional information may be provided by evaluation of an arterial blood gas or coagulation profile.

Radiographs and ultrasound of the thorax and abdomen may also be indicated.

TREATMENT

Therapy of sepsis has three major components: first to identify and eradicate the infection, second is supportive care to maintain adequate tissue perfusion and minimize organ dysfunction, and finally therapy to alter the pathologic inflammatory cascade. The prognosis declines as SIRS/sepsis progresses to septic shock and MODS, which emphasizes the importance of early recognition and treatment.

Rapid institution of appropriate antibiotic therapy has been shown to improve survival in humans with sepsis. Empiric parenteral broad-spectrum antibiotic therapy should be initiated following collection of appropriate culture specimens (bronchoalveolar fluid, urine, blood, wound drainage, loculated fluid, or IV catheter tip) and can be modified when results of culture and sensitivity are available. In animals with an unknown infection source, blood and urine cultures should be obtained. The agent chosen depends on the host status and the suspected causative organism. Important factors to consider include the suspected source of infection, nature of the pathogen most likely responsible (community-acquired or nosocomial), local resistance patterns, and underlying immune status. Sepsis in dogs and cats is most often associated with gram-negative enteric bacteria. Prevalence of common bacterial isolates based on site of infection in dogs and cats has been reported. In addition to antibiotic therapy, surgical drainage of abscesses, and debridement of infected or devitalized tissue may be necessary to remove the nidus of infection/inflammation.

As the infection/inflammation resolves, animals must be aggressively monitored and supported to ensure adequate organ and tissue perfusion. Hypoperfusion can be detected by changes in physical exam parameters (decreased mentation, tachycardia [or bradycardia in cats], prolonged CRT, decreased pulse quality, decreased extremity temperature), decreased arterial blood pressure, oliguria, or development of hyperlactemia. Most affected animals have decreased preload caused by fluid leakage secondary to increased vascular permeability. Vasodilation of peripheral vessels and maldistribution of blood flow cause a relative hypovolemia. Therefore volume resuscitation is the best initial therapy for hypoperfusion. Aggressive volume administration is best guided by measurement of central venous pressure (CVP) or ideally pulmonary capillary wedge pressure (PCWP). IV fluid boluses (15 to 20 mL/kg isotonic crystalloid, or 5 mL/kg colloid) should be administered until normal perfusion has been restored or until risk of volume overload and pulmonary edema are evident (CVP >8 cm H_2O or PCWP > 18 mm Hg). Use of colloids is thought to prevent the development of interstitial edema in patients with increased vascular permeability, although there is no proven advantage of colloid over crystalloid fluid therapy. The type of fluid administered is probably less important than the rapidity with which resuscitation is achieved and the use of physiologic end points to evaluate the response to therapy.

If fluid therapy alone fails to restore adequate blood pressure and perfusion, vasopressor agents should be added. Dopamine (5 to 20 μg/kg/min) increases systemic blood pressure through both improved cardiac performance (β-agonist effect) and increased systemic vascular resistance (α-agonist effect). The vasopressor effect predominates at the higher end of the dose range. Therefore to prevent excessive vasoconstriction of peripheral and splanchnic vessels, dopamine should be started at 5 μg/kg/min and the dose titrated to effect. Evidence in human patients suggests that norepinephrine (0.25 to 2.0 μg/kg/min) is superior to dopamine in the treatment of hypotension associated with septic shock.

Oxygen delivery to tissues depends not only on the volume of blood delivered but also on the oxygen content of the arterial blood. To ensure normal oxygen delivery, factors that affect blood oxygen content should be monitored. Hemoglobin concentration should be maintained at at least 8 g/dL (PCV ≥24%) and hemoglobin saturation at at least 90%. Transfusions of pRBCs, Oxyglobin, supplemental oxygen, and/or mechanical ventilation should be used as needed to optimize oxygen delivery to the tissues.

Serial monitoring of key organ systems (the cardiovascular, pulmonary, coagulation renal gastrointestinal and central nervous systems are commonly affected in sepsis) is necessary to detect early derangements in function. Electrolytes and blood glucose should be monitored and supplemented as needed. Enteral nutrition is important to support host defenses and bowel integrity.

The final goal of therapy is to control or inhibit the actions of the inflammatory cascade. Clinical trials of a number of specific anti-inflammatory therapies, including antibody to endotoxin, IL-1 receptor antibody, antibradykinin, antiplatelet activacting factor, anti-TNF, and high-dose glucocorticoids, have been conducted in humans, and with the exception of activated protein C (APC) have not demonstrated a significant reduction in mortality. Drotrecogin alfa (activated), a human recombinant APC with antithrombotic, profibrinolytic, and anti-inflammatory properties, demonstrated a significant reduction in mortality in humans with severe sepsis and received FDA approval in 2001. The cost of the drug (approximately $6,800/person) will prohibit its use in veterinary medicine.

Until cost-effective specific anti-inflammatory therapies become available, optimal management of the septic veterinary patient will depend on rapid recognition, eradication of the source of infection/inflammation, and meticulous supportive care directed at restoring normal oxygen delivery to tissues.

CHAPTER 124

Shock

Cynthia M. Otto

Shock is not a disease but a complex physiologic state. Historically, shock was described as the effect of generalized circulatory abnormalities that led to inadequate tissue perfusion. Although this classic description still holds important clinical relevance, the complexity of shock states result not from the initial insult per se, but the systemic response to that insult. This is most clearly demonstrated in septic shock, in which the cascade of events that leads to irreversible cardiovascular collapse is the systemic inflammatory response initiated by products of infectious agents. This systemic inflammatory response syndrome (SIRS) can also be triggered by noninfectious insults including tissue hypoxia, tissue acidosis, pancreatitis, trauma, and major surgery. Similarly, although hypovolemia can be reversed, reperfusion of ischemic tissues leads to inflammation, and production and release of mediators. These complex cascades confound the treatment of shock; reversing the perfusion abnormalities may not stop the progression once the inflammatory cascade has been initiated. Treatment directed at the downstream cellular mediators of shock has not proven beneficial either. Whether the cause is infection, blood loss, or tissue hypoxia, one of the most successful approaches to the treatment of shock is early recognition and correction of the inciting cause before the cascade of inflammation is triggered.

Shock is a dynamic state and the clinical condition can change in a matter of minutes, hours, or even days. Early stages of shock may not be clinically obvious, as the compensatory mechanisms are recruited to maintain cardiac output and tissue perfusion. In late stages of shock, compensatory mechanisms fail; systemic inflammation leads to multiple organ dysfunction and death. In these late stages of shock, successful clinical intervention is uncommon. This chapter focuses on the clinical presentations associated with the three major types of shock in the early and intermediate stages of shock. Shock is classically divided into three main categories based on the mechanisms of impaired perfusion: cardiogenic, hypovolemic, and distributive.

TYPES OF SHOCK

Cardiogenic shock results predominantly from failure of adequate forward flow. The dysfunction can occur in either the diastolic or systolic phase or can result from an obstruction of flow. Systolic or forward flow failure results from overt heart failure or severe tachyarrhythmias. Diastolic or filling failure can result from pericardial tamponade, tension pneumothorax, or hypertrophic cardiomyopathy. Obstructive shock can be the result of thromboembolic disease, tumors, or distended organs (e.g., gastric dilatation and volvulus; GDV) occluding either forward flow or venous return. The location, degree of obstruction, and resulting compromise to systemic perfusion are important determinants of whether flow occlusion will lead to shock.

Hypovolemic shock leads to inadequate delivery of oxygen and nutrients to tissues and accumulation of byproducts of cellular metabolism due to insufficient circulating blood volume. Intravascular volume depletion can result from acute or chronic fluid loss or sequestration of fluids into third spaces.

Distributive shock is a condition in which the effective circulating volume is inadequate to provide tissue perfusion. The classic example of distributive shock is septic shock. However, other vasodilatory states can also lead to distributive shock such as heat stroke, anaphylaxis, neurogenic shock, and SIRS. The common defect in distributive shock is inappropriate vasodilation, which leads to a relative hypovolemia. Sepsis and heat stroke are both complicated by a vigorous systemic inflammatory response and further compromised tissue oxygenation due to maldistribution of blood flow and mitochondrial dysfunction.

The types of shock vary in their etiology, clinical signs, and treatment. The categories of shock are not mutually exclusive and many animals with distributive shock will also have some degree of hypovolemia, particularly as SIRS leads to increased vascular permeability and fluid loss. Mediators of SIRS and ischemia reperfusion injury include substances that contribute to cardiac dysfunction. Thus progression of both distributive and hypovolemic shock can lead to cardiogenic shock. Cardiac patients are frequently volume-depleted. Any animal with inadequate intestinal perfusion may develop bacterial translocation and sepsis. Unrecognized, untreated shock initiates a cascade of doom. Therefore early recognition based on index of suspicion, aggressive monitoring in patients at risk, and appropriate interventions are essential in the successful treatment of shock states.

CLINICAL SIGNS OF SHOCK

The normal physiologic response to poor tissue perfusion is to increase sympathetic tone, which results in increased heart rate, respiratory rate, and vasoconstriction. In the early (sometimes called *compensated*) stages, tachycardia may be the only clinical sign. With time and progression to the intermediate stages (also referred to as *early decompensated*), profound vasoconstriction results from the attempt to increase venous return and maintain stroke volume. In the intermediate stages, additional compensatory mechanisms trigger an increase in salt and water retention (angiotensin-aldosterone and ADH) and release of vasoconstrictors (e.g., vasopressin), that contribute to an increase in stroke volume. Clinically these compensatory mechanisms result in signs typically seen in cardiogenic and hypovolemic shock, including pale to white mucous membranes, a prolonged capillary refill time (>2 sec), cool extremities, a normal to decreased rectal temperature, decreased mentation, tachypnea, and hypotension. Although the overall compensatory response is consistent regardless of the etiology, the hallmark of distributive shock is the failure of effective vasoconstriction. The circulating mediators released in response to sepsis or SIRS result in vasodilation that leads to an effective hypovolemia. The clinical signs associated with distributive shock include red mucous membranes, rapid capillary refill time (<1 sec), and normal or increased rectal temperature.

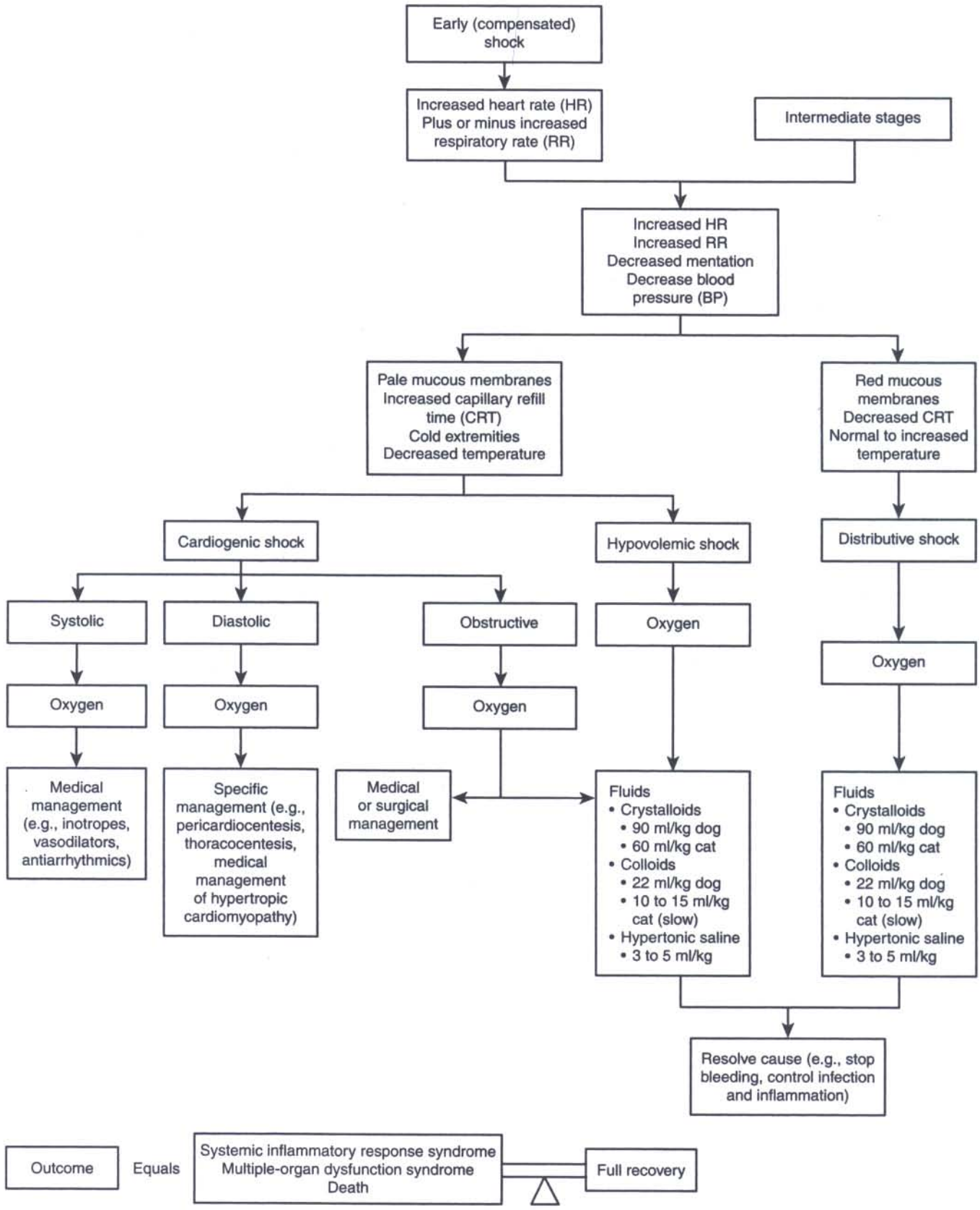

Figure 124-1 Algorithm for assessment and treatment of shock. *HR*, Heart rate; *RR*, respiratory rate; *mm*, mucous membranes; *CRT*, capillary refill time; *T*, rectal temperature; *BP*, blood pressure; *mgt*, management; *HCM*, hypertrophic cardiomyopathy; *SIRS*, systemic inflammatory response syndrome; *MODS*, multiple organ dysfunction syndrome.

Distributive shock also leads to dysregulation of the normal stress response, and although hyperglycemia may be seen early, classically it is hypoglycemia that is associated with distributive (septic) shock. One other unique feature of distributive shock is that cats frequently become bradycardic rather than tachycardic.

In order to differentiate cardiogenic shock from hypovolemic shock, a thorough cardiac evaluation and complete history are beneficial. Unfortunately, animals in shock are frequently not stable enough to obtain extensive diagnostic tests and therapy needs to be initiated based on physical examination and historical findings. Distributive shock that is complicated by concurrent fluid loss (due to changes in vascular permeability and fluid compartment shifts or the underlying etiology) may initially demonstrate clinical signs more typical of hypovolemic shock, but upon resuscitation, develop clinical signs of distributive shock.

TREATMENT OF SHOCK

The goal of treatment in early shock is to restore effective tissue perfusion and oxygenation (Figure 124-1). In later stages of shock, restoration of perfusion alone is usually insufficient to halt the progression of the inflammatory cascade. Aggressive support of organ function and prevention of additional pro-inflammatory complications (including hypotension, hypoxia, and infection) are critical. At all stages, correction of the inciting cause is necessary.

Oxygen is universally administered in patients regardless of the type of shock. Additional therapy depends on the etiology of the shock. For both hypovolemic and distributive shock, fluid therapy is essential (see Chapter 114). The goal is to increase the effective circulating volume. The choice of fluids depends on the cause of shock; however, initial treatment is typically provided by crystalloids (balanced electrolyte solutions) at volumes of approximately 90 mL/kg in the dog and 60 mL/kg in the cat. The fluid rate and the actual volume given should be tailored to each individual animal. Typically, one fourth of the bolus is provided within the first 5 to 15 minutes, with repeated evaluation of the cardiovascular response (e.g., heart rate, mucous membrane color, pulse quality, and capillary refill time). Colloids can be used for shock resuscitation (22 mL/kg bolus in dogs, and 10 to 15 mL/kg infusion in cats) of hypoproteinemic animals and in conjunction with (reducing the volumes of both fluid types) or instead of crystalloids. Due to potential anticoagulant effects, colloid administration generally should not exceed 22 mL/kg per day. (For a more extensive discussion of fluid therapy see Chapter 114). The resuscitative fluid of choice for hemorrhagic hypovolemic shock is blood. Typical recommendations limit blood transfusions to 22 mL/kg; however, massive transfusions (greater than one blood volume) may be required in some cases (see Chapter 127). Hypertonic saline (HTS) is typically mixed with a colloid (to a final concentration of 7% saline) and may be considered for resuscitation at 3 to 5 mL/kg over 5 to 20 minutes. The small volumes required may be particularly beneficial in larger animals in which volumes of crystalloid are rate limiting. The hypertonic nature may also be beneficial in animals with shock and concurrent head injury. It has been demonstrated, however, that HTS, and other therapies that rapidly increase blood pressure may predispose to excessive bleeding in uncontrolled hemorrhage.

In cardiogenic shock, aggressive fluid therapy may be fatal. Treatment of cardiogenic shock relies on correction of the underlying cause. For systolic dysfunction, treatment of arrhythmias, diuretics, vasodilators, or inotropes may be required (see Chapter 199). Pericardiocentesis is necessary for treatment of tamponade and thoracocentesis/chest tube placement for tension pneumothorax. Diastolic dysfunction resulting from cardiac hypertrophy can be a challenge to treat (see Chapter 204). Resolution of obstruction to flow may require surgical intervention (e.g., tumors, GDV) or medical management (e.g., thromboembolic disease). Prior to surgery, adequate circulatory volume and optimal perfusion should be established.

Specific therapy should be directed at the cause of shock, such as in hemorrhagic hypovolemia, bleeding must be controlled and in septic shock the source of infection must be eliminated. Vasopressors may be required in distributive shock when hypotension persists despite adequate volume repletion. Detailed discussion of sepsis can be found in Chapters 123 and 124. Despite over 30 years of investigation, specific anti-inflammatory therapies have generally failed in clinical trials of shock and sepsis (see sepsis chapter). Although long touted for beneficial effects in shock, there is no clinical evidence to support pharmacologic doses of glucocorticoids in the treatment of any form of shock.

Monitoring is critical during the resuscitation of shock. In addition to routine cardiovascular parameters (e.g., heart rate, mucous membrane color, pulse quality, and capillary refill time), respiratory rate, temperature, mentation, blood pressure monitoring (see Chapter 124), hematocrit, electrolytes, blood gases, base excess and lactate may help direct therapy. Central venous pressure monitoring is invaluable in shock to aid in determination of volume status and guide fluid resuscitation. More advanced monitoring that may be beneficial in managing the shock patient include cardiac output, oxygen delivery, oxygen extraction, and pulmonary capillary wedge pressure.

CHAPTER • 125

Systemic Anaphylaxis

Lori S. Waddell

Systemic anaphylaxis is an acute, life-threatening allergic reaction resulting from massive, generalized release of mast cell mediators, including histamine. Anaphylaxis can be triggered by venoms from insects and reptiles; medications, including hormones, antibiotics, nonsteroidal anti-inflammatory drugs, anesthetics, and sedatives; parasiticides; and other miscellaneous drugs and foods (Box 125-1). Immediate recognition and treatment of the veterinary patient with anaphylaxis is essential for a successful outcome.

PATHOGENESIS

Anaphylaxis can be caused by either an anaphylactic or anaphylactoid reaction. Anaphylactic reactions are mediated by

Box • 125-1

Causes of Anaphylaxis

Venoms
Insects of the Hymenoptera order—bees, wasps, ants
Spiders—black widow, brown recluse
Lizards—Gila monster, Mexican beaded lizard
Snakes—pit vipers (rattlesnakes, copperheads, water moccasins), coral snakes

Hormones
Insulin
Corticotropin
Vasopressin
Parathyroid hormone
Betamethasone
Triamcinolone

Antibiotics
Penicillins—amoxicillin, ampicillin, procaine penicillin
Chloramphenicol
Lincomycin
Gentamicin
Tetracycline
Sulfonamides
Cephalosporins
Polymixin B
Doxorubicin hydrochloride

Nonsteroidal Anti-Inflammatory Drugs
Aspirin
Ibuprofen

Anesthetics and Sedatives
Acepromazine maleate
Ketamine hydrochloride
Barbituates
Lidocaine and other local anesthetics
Narcotics
Diazepam

Parasiticides
Dicholophen
Levamisole hydrochloride
Piperazine
Dichlorvos
Diethylcarbamazine
Thiacetarsamide

Miscellaneous
Blood products
Aminophylline
Asparaginase
Calcium disodium edetate
Iodinated contrast media
Neostigmine
Amphotericin B
Vaccines
Allergen extracts—pollens, molds, foods
Enzymes—chymotrypsin and trypsin
Vitamins—vitamin K, thiamine, and folic acid
Dextrans and gelatins

Foods
Milk
Egg white
Shellfish
Legumes
Fruits—citrus
Chocolate
Grains

Physical Factors
Cold
Heat
Exercise

an interaction of antigen and IgE antibody on the surface of sensitized mast cells, which causes the release of histamine and other inflammatory mediators. This is defined as a type I, IgE mediated, hypersensitivity reaction. Sensitization requires previous exposure to an antigen or hapten, which can range in size from a protein to a small, low molecular weight drug. Proteins act directly as an antigen, while the smaller drugs will bind to cells and act as haptens. IgE is produced by and bound on the surface of mast cells and basophils by high-affinity receptors (FcεRI) for the Fc portion of the immunoglobulin. When an antigen causes cross-linkage of two surface IgE molecules, the mast cell is activated and primary and secondary mediators are released (Box 125-2). The cross-linking of the FcεRI receptors activates tyrosine kinases, which cause activation of phospholipase C, leading to production of diacylglycerol and inositiol triphosphate. These mediators increase intracellular calcium concentrations and activate multiple protein kinases. Phosphorylation of myosin, found in intracellular filaments, causes granules to move to the cell surface, fuse, and release the primary mediators of anaphylaxis: histamine, heparin, tryptase, kallikreins, proteases, proteoglycans, eosinophilic chemotactic factor of anaphylaxis (ECF-A), and neutrophil chemotactic factor of anaphylaxis (NCF-A). Cross-linking of the FcεRI receptors also activates phospholipase A_2, which produces arachadonic acid from membrane phospolipids, which results in release of the secondary mediators: leukotrienes, prostaglandins, thromboxanes, and platelet-activating factor. The protein kinases also change gene expression, which results in synthesis and secretion of other cytokines (IL-4, IL-5, IL-6, IL-13, TNF-α, MIP-1α), which are responsible for the late-phase inflammatory response. Release of the inflammatory mediators is rapid: granule exocytosis occurs within seconds to minutes, activation of the arachadonic acid cascade in minutes, and cytokine synthesis and secretion within 2 to 24 hours.

Anaphylactoid reactions cause anaphylaxis without IgE, either through directly activating mast cells to release histamine, or more commonly, by activating the complement pathway. They do not require previous exposure and sensitization. Activation of complement results in production of C3a and C5a, the anaphylotoxins, which cause degranulation of mast cells and release of histamine and other primary mediators, activation of the arachidonic acid cascade, and gene expression and synthesis of the inflammatory mediators. Anaphylactoid and anaphylactic reactions have exactly the same clinical appearance and are treated identically.

CLINICAL MANIFESTATIONS

Anaphylaxis can result in hypotension, bronchospasm, urticaria, erythema, pruritis, pharyngeal and laryngeal edema, arrhythmias, vomiting, and hyperperistalsis. Clinical signs are dependent on species and method of exposure. In dogs, the liver is considered the shock organ, and clinical signs result from hepatic vein congestion and portal hypertension. Initial signs may include excitement, vomiting, defecation (often diarrhea), then progress to respiratory distress, collapse secondary to hypovolemic shock, and death within one hour if not treated. A dog with anaphylaxis may have generalized wheals, angioedema (particularly of the face), pruritis, pale mucous membranes, poor capillary refill time, tachycardia, poor pulse quality, and appear depressed or even collapsed. Severe cases may result in respiratory distress secondary to upper airway obstruction from laryngeal and pharyngeal edema.

In cats, the lungs are considered the shock organ, and respiratory distress is the first sign in cats with systemic anaphylaxis. Respiratory distress results from airway obstruction secondary to laryngeal edema, bronchoconstriction, and increased mucus production. Other signs in cats include severe pruritis, vomiting, diarrhea, depression, and death. A cat with anaphylaxis usually has severe respiratory distress, some wheezes on auscultation, pale mucous membranes, poor capillary refill time, and poor pulse quality.

The most severe anaphylactic reactions are generally seen if the antigen is given by parental injection. Oral ingestion often causes vomiting, diarrhea, urticaria, and angioedema. Inhalation can result in rhinitis and bronchospasm. Topical administrations can cause conjunctivitis and urticaria with or without systemic signs.

Box • 125-2

Mediators of Inflammation in Anaphylaxis

Mediators	*Effects*
Primary	
Histamine	Increased vascular permeability, vasodilation, constriction of smooth muscle of bronchi and GI tract, increased mucus production
Proteases	Kinin production, activation of complement, initiation of disseminated intravascular coagulation
Heparin	Anticoagulation, urticaria, immune modulation
ECF-A	Eosinophil chemotaxis
NCF-A	Neutrophil chemotaxis
Secondary	
Prostaglandin E_2	Vasodilation, increased vascular permeability
Prostaglandin D_2	Bronchoconstriction, increased vascular permeability, pulmonary vasconstriction, peripheral vasodilation
Prostacyclin	Vasodilation, inhibition of platelet aggregation
Leukotrienes	Bronchoconstriction, increased vascular permeability, vasodilation, increased WBC chemotaxis
Thromboxane A_2	Increased platelet aggregation, smooth muscle contraction
Platelet activating factor	Platelet aggregation, platelet sequestration, increased platelet thromboxane production, increased vascular permeability, vasoconstriction, and bronchoconstriction

DIAGNOSIS

Diagnosis of systemic anaphylaxis is based on the history of exposure and peracute onset of clinical signs. Clinical signs often occur within seconds to minutes of exposure. Oral exposure can cause a delay of up to 30 minutes or longer before clinical signs appear.

TREATMENT

Initial treatment of a dog or cat presenting with anaphylaxis consists of the basics of emergency medicine. These include ensuring that the patient has a patent airway, is effectively breathing/ventilating, addressing cardiovascular dysfunction, and drugs and fluids as indicated. Dogs or cats having an anaphylactic reaction may have respiratory distress resulting from upper airway obstruction. The clinician should be prepared to intubate with an endotracheal tube or perform a tracheostomy if intubation is not possible. If respiratory distress without airway obstruction is present, oxygen should be administered by mask or flow-by during initial assessment and stabilization, and then by nasal catheter or oxygen cage. Vascular access is essential for treatment of these patients, both for fluid therapy and medications. Hypovolemic shock is a significant contributor to morbidity and mortality in anaphylaxis. Hypovolemia occurs secondary to increased vascular permeability and venous pooling. Fluid therapy, often starting with a shock bolus of crystalloids at a rate of 90 mL/kg/hr in dogs and 60 mL/kg/hr in cats, is indicated. Ongoing crystalloid therapy will be necessary at rates higher than maintenance to keep up with ongoing losses and will need to be tailored to the individual patient. Additional fluid therapy may include synthetic colloids, such as dextran or hetatstarch, given in small incremental boluses of 10 mL/kg/hr in dogs and 6 mL/kg/hr in cats. A constant rate infusion of synthetic colloids of 1 mL/kg/hr may also be used once the patient has been resuscitated. If a coagulopathy is present, blood products, especially fresh frozen plasma, may be necessary. This should be given at a dose of 10 to 20 mL/kg over several hours (or faster if needed for volume resuscitation). Fluid therapy is guided by clinical parameters inlcuding heart rate, pulse quality, mucous membrane color, capillary refill time, respiratory rate and effort, and packed cell volume and total solids.

Epinephrine is essential therapy for treatment of systemic anaphylaxis and should be administered immediately. A dose of 0.01mg/kg of the 1:10,000 solution given slowly IV is most effective, although 0.02 mg/kg can be given into the trachea if the patient is intubated and IV access cannot be obtained. Epinephrine can also be administered SQ or IM at a dose of 0.01 mg/kg in less severe cases. Epinephrine is useful because of its inotropic and chronotropic effects on the heart, bronchodilation, and increased intracellular concentrations of cyclic adenosine monophasphate, which decreases synthesis and release of inflammatory mediators of anaphylaxis. Heart rate, rhythm, and blood pressure should be monitored when giving epinephrine, especially when given intravenously because of its ability to cause arrhythmias and hypertension (at high doses). Epinephrine and fluid therapy should begin to improve clinical signs within minutes. Dogs and cats ideally will be fully stabilized within an hour.

Other medications that may be useful in the treatment of systemic anaphylaxis include pressors, glucocorticoids, antihistamines, aminophylline, and atropine. Dopamine at a dose of 4 to 10 mcg/kg/min or other pressors may be used if refractory hypotension is present. Aminophylline may be used if bronchoconstriction is refractory to epinephrine. It will cause bronchodilation, increase respiratory drive, and increase contractility of the muscles of respiration. A dose of 10 mg/kg IV for dogs and 5 mg/kg IV for cats is recommended. Atropine at a dose of 0.02 to 0.04 IV or IM should be used if bradycardia is present despite epinephrine administration. Glucocorticoids are useful in blocking the arachadonic acid cascade and reducing the severity of the late-phase anaphylactic reactions. Doses of 1 to 2 mg/kg IV for dexamethasone have been recommended. It is essential that glucocorticoids not be used in place of epinephrine in the emergency situation as they have little effect on the immediate stages of anaphylaxis. Antihistamines competitively bind at the histamine receptors and block its effects. Diphenhydramine, a H_1 blocker, should be administered at 0.5 to 1.0 mg/kg slow IV or IM to reduce pruritis and angioedema. The H_2 blockers, cimetidine, ranitidine, and famotidine, can be used to decrease gastric acid secretion stimulated by histamine. Dose varies with each of the H_2 blockers. Antihistamines are also not very useful in the acute, life-threatening stage of anaphylaxis, but may be helpful after the patient has been stabilized.

Intense monitoring of the patient for at least 12 to 24 hours after the anaphylactic episode is essential. This should include respiratory rate and effort, heart rate and rhythm, blood pressure, pulse oximetry and/or arterial blood gases, coagulation parameters, renal and hepatic function, and PCV, total solids, and glucose. Other supportive care, such as ventilatory support, should be provided as needed. Avoidance of the trigger for anaphylaxis is prudent in the future. Careful questioning of the owner about recent exposure to insects, reptiles, foods, topical therapies, and medications is essential. Prognosis for a patient presenting with systemic anaphylaxis is variable. The earlier the patient receives appropriate therapy, the better the prognosis. This is especially important since death can ensue in 1 hour or less from time of exposure.

CHAPTER • 126

Thoracic Trauma

Matthew W. Beal

Trauma to the thorax can be classified as blunt or penetrating. Blunt thoracic trauma commonly occurs after motor vehicle accidents, falls from a height, human-animal interactions, and dog bites. Dog bites are also a commonly recognized cause of penetrating thoracic trauma along with gunshot wounds and impalement injuries. Independent of the cause of the trauma, it is critical for veterinarians to recognize that trauma is most commonly a multisystemic problem (polytrauma). This necessitates attention to the entire animal. Similarly, injuries to the thorax are rarely isolated and more commonly are identified in combination (e.g., pneumothorax and pulmonary contusion). Keys to maximizing the likelihood of a positive outcome in dogs and cats with thoracic trauma include thorough physical examinations, anticipation of common injuries, understanding the pathophysiology of those injuries, and a proactive method to their identification and treatment.

TRAUMA-ASSOCIATED PLEURAL SPACE PATHOLOGY

Trauma associated pleural space pathology includes pneumothorax, hemothorax, and diaphragmatic hernia. As a group, these injuries are most likely to manifest with varying degrees of dyspnea accompanied by muffled lung and heart sounds on auscultation of the thorax. Differentiating these injuries will be largely based on a thorough physical examination and aided by thoracocentesis and diagnostic imaging techniques.

Pneumothorax

Pneumothorax is the accumulation of air in the pleural space between the parietal and visceral pleurae and is one of the two most commonly recognized results of traumatic injury to the thorax. Traumatic pneumothorax is classified as "closed" or "open." Closed pneumothorax may result from rapid compression of the thorax (and lungs) against a closed glottis, which causes alveolar disruption, laceration of the lung by a broken rib, rupture of bullae or blebs, or from pneumomediastinum. Air enters the pleural space from an injury to the thoracic wall in cases of open pneumothorax. Tension pneumothorax occurs due to a one-way-valve effect, in which air enters the pleural space during inspiration and cannot be evacuated during expiration. The resultant increase in intrapleural pressure results in hypoventilation and decreased venous return, manifesting with signs of severe respiratory and cardiovascular compromise.

Appropriate management of the traumatized small animal patient necessitates the assumption that *pneumothorax is present until proven otherwise.* That assumption will remind the veterinarian to pay particular attention to those physical examination findings that will identify the problem. *Clinically significant pneumothorax is a physical examination diagnosis.* Most animals with pneumothorax prefer to stand or to position themselves in sternal recumbency. In this position, on auscultation, decreased lung sounds are most likely to be noted dorsally and most often are noted in both hemithoraces. Temporary relief and definitive diagnosis of pneumothorax is based on oxygen administration and bilateral thoracocentesis (see Chapter 103). Radiography for the diagnosis of clinically significant pneumothorax may jeopardize the stability of a dog or cat and should be avoided. When pneumothorax is noted on radiographs of a dog or cat that is not in distress after trauma, findings will include retraction of the lung from the chest wall (loss of vascular markings in this space), consolidation of lung lobes, and on lateral radiographs, the appearance of the heart "floating" on a cushion of air (Figure 126-1). The latter radiographic finding is due to collapse of the heart to the side of the atelectatic lung lobe. Often, a single thoracocentesis is sufficient treatment for traumatic closed pneumothorax. However, if pneumothorax recurs (sometimes rapidly), thoracostomy tube placement and continuous pleural space drainage are recommended. Closed traumatic pneumothorax is rarely a condition that requires surgical correction. Open pneumothorax warrants immediate covering of the wound with an occlusive dressing and evacuation of the thorax by thoracocentesis or thoracostomy tube placement. Once stability has been achieved, open pneumothorax is *always* managed surgically (see Penetrating Thoracic Injury).

Hemothorax

Hemothorax is the accumulation of blood in the pleural space. Hemothorax results from disruption of pulmonary, thoracic wall, or mediastinal blood vessels. Hemothorax can also be seen in dogs and cats with diaphragmatic hernia and concurrent hemoabdomen. *Clinically significant hemothorax (although uncommon) is a physical examination diagnosis.* Hemothorax results in decreased lung and heart sounds ventrally to diffusely and concurrent signs of hypovolemic shock

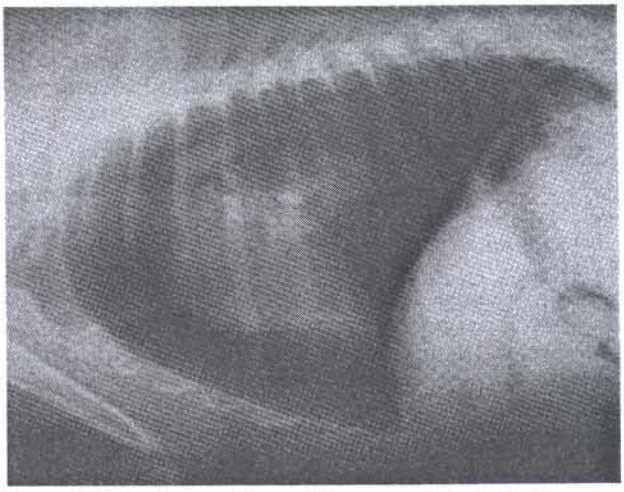

Figure 126-1 Pneumothorax. Note retraction of the lung from the chest wall, consolidation of lung lobes, and the appearance of the heart falling to the side of the atelectatic lobes.

(pale mucous membranes, slow CRT, high heart rate, weak pulses) and dyspnea. The volume of blood loss necessary to cause signs of hypovolemia is less than the volume that causes signs of dyspnea in dogs and cats with hemothorax. Diagnosis of a clinically significant hemothorax, much like pneumothorax, is based on thoracocentesis. Oxygen support and vigorous volume expansion techniques are always indicated as part of the initial treatment strategy for dogs and cats with hemothorax. Thoracostomy tube placement and continuous pleural drainage is indicated when greater than 5 mL/kg of blood is retrieved from the pleural space. Continuous drainage allows quantification of ongoing blood loss, prevention of atelectasis, and autotransfusion of shed blood.

Diaphragmatic Hernia

Diaphragmatic hernia is most common after blunt thoracic trauma and is thought to result from rapid compression of the abdomen with the majority of the force directed cranially against an open glottis. Penetrating thoracic and abdominal injuries can also cause diaphragmatic hernia. The dog or cat with diaphragmatic hernia may not show clinical signs or may have dyspnea, decreased lungs sounds ventrally to diffusely, borborygmi on auscultation of the thorax, an "empty" abdominal palpation, or a combination thereof. Diaphragmatic hernia is commonly associated with pleural effusion. Some dogs and cats may develop clinical signs of diaphragmatic hernia months to years after the initial trauma. Oxygen support will be beneficial in the initial stabilization of animals with diaphragmatic hernia. In addition, positioning the pet with the chest slightly higher than the abdomen may promote movement of mobile abdominal viscera back into the abdomen. Diaphragmatic hernia may be suspected on physical examination but is confirmed through diagnostic imaging techniques (survey radiographs, positional radiographs, positive contrast peritoneography, upper gastrointestinal contrast study, ultrasound, or computed tomography). Diaphragmatic hernia is a surgical problem that necessitates elective repair as soon as the respiratory and cardiovascular systems have been stabilized. Indications for immediate surgical intervention include fever, small bowel obstruction, biliary obstruction, protracted vomiting or a distended stomach within the pleural space. In the latter clinical syndrome, transthoracic gastrocentesis or orogastric intubation are indicated prior to anesthesia to relieve signs of dyspnea. Prognosis for survival of dogs and cats with diaphragmatic hernia ranges from 50% to 90%.

TRAUMA-ASSOCIATED PULMONARY INJURIES

Pulmonary Contusion

Pulmonary contusion (PC) refers to lung lesions that occur after a compression-decompression injury. Subsequent hemorrhage and edema lead to alveolar collapse and lung consolidation. Hypoxemia results from ventilation: perfusion mismatch, shunt, diffusion impairment, and in severe cases, hypoventilation. Much like pneumothorax, pulmonary contusion is common after trauma. *All dogs that have sustained trauma have PC until proven otherwise.* If the veterinarian makes this assumption, they are more likely to identify important physical examination findings and make treatment decisions that will improve outcome. *The presence of clinically significant PC (severe enough to cause clinical signs) is a physical examination diagnosis.* On auscultation of the thorax, increased lung sounds distributed unevenly between the hemithoraces is most commonly recognized. However, exceptions include the presence of concurrent pleural space disease and complete lobar consolidation, both of which may result in decreased lung sounds. Coughing and hemoptysis may be seen in dogs with moderate to severe PC. Small animals with rib fractures or flail chest often have concurrent PC. Radiographic evidence of PC includes interstitial to alveolar infiltrates and lobar consolidation. Initial therapy for PC is oxygen support to maintain oxygen saturation >92%. Severity of PC can be quantified through arterial blood gas analysis and calculation of alveolar-arterial oxygen gradient and the PaO_2:FiO_2.

Treatment of PC is largely supportive. The cornerstones of therapy include oxygen delivery by cage, hood, or nasal cannulae to maintain SpO_2 greater than 92% on FiO_2<0.60 without severe increases in respiratory effort. Often overlooked is the importance of frequent changes in position of the animal. Standing and short walks may prevent and combat atelectasis. Positive pressure ventilation (PPV) is indicated if oxygenation or ventilation requirements cannot be met or if they can only be met with severe increases in respiration efforts. Fluid therapy in the animal with PC is challenging. Basic guidelines include maintainance of euvolemia in light of concurrent injuries, maintainance of hydration, and efforts to avoid fluid overload. Despite numerous opinions, there is no clear answer to the question of whether crystalloid or colloid therapy is most appropriate for dogs with PC. In a 1999 study by Powell et al, corticosteroids were not shown to decrease duration of hospitalization or need for oxygen support. Because PC is associated with increased vascular permeability, furosemide is unlikely to be of benefit unless iatrogenic fluid overload has taken place. Bronchodilators are unlikely to be of benefit because PC is not a reactive small airway disease, and antibiotics are not indicated because of the exceedingly low incidence of bacterial pneumonia in dogs with PC. Prognosis for dogs with PC is based on severity of pulmonary injury but is generally good. Dogs that require positive pressure ventilation to maintain oxygenation and adequate ventilation have a more guarded prognosis.

TRAUMA-ASSOCIATED THORACIC WALL INJURIES

Thoracic wall trauma is most often associated with a host of concurrent thoracic injuries such as pneumothorax and pulmonary contusion.

Penetrating Thoracic Injury

Wounds to the thorax should be immediately covered with an occlusive sterile dressing. Following stabilization and management of concurrent injuries (pneumothorax) and radiography, the dog or cat should be placed under general anesthesia and the wounds explored. Simple probing is *not* adequate to determine whether or not wounds have penetrated the pleural space. Penetrating thoracic wounds should be explored, debrided, lavaged, cultured, and reconstructed with use of appropriate drainage techniques. Broad-spectrum antibiotic therapy is indicated to combat bacterial infection. Antibiotic therapy should be empirical based on likely contaminants while culture is pending. The external wound in animals with penetrating thoracic injury is often the "tip of the iceberg" and necessitates an aggressive, proactive approach to maximize the likelihood of a favorable outcome.

Rib Fractures and Flail Chest

Rib fractures happen with variable frequency after trauma and are diagnosed based on physical examination and/or thoracic radiography. Pain is the primary problem induced by rib fractures; however, penetration of the visceral pleura by a broken rib could result in pneumothorax and/or hemothorax. The chest wall is a resilient structure that requires significant force to cause a fracture. When such forces are applied across the thorax, intrathoracic injury is common. *Rib fractures are commonly associated with pulmonary contusion.* Pain associated

with rib fractures can be controlled with regional anesthesia (narcotic epidural), systemic analgesics, or local intercostal blockade with bupivicaine (dogs: 0.75% solution diluted to 0.25% infiltrated as a small bleb caudal to the rib and dorsal and ventral to rib fractures; block single nerves cranial and caudal to the injured rib or segment; total dose should not exceed 1.5 mg/kg and extreme caution should be exercised so as not to compromise ventilation by blocking too many intercostal nerves). Flail chest refers to the fracture of multiple adjacent ribs in multiple locations, which creates a floating thoracic segment that moves paradoxically to the remainder of the chest wall. Flail chest is a diagnosis based on physical examination. The combination of pendulous airflow, underlying pulmonary trauma, concurrent pleural space injuries, and pain predispose to hypoxemia and hypoventilation. Treatment of flail chest should initially be directed towards pain control and management of concurrent thoracic injury (e.g., pulmonary contusion, pneumothorax, etc.). Surgical fixation of flail chest is frequently unnecessary. When needed, it should be performed after the animal is stable.

TRAUMA-ASSOCIATED MYOCARDIAL INJURY

Arrhythmias

Cardiac arrhythmias, most commonly of ventricular origin, are often diagnosed 12-36 hours after trauma. These arrhythmias, often referred to as "traumatic myocarditis" and "myocardial contusion," may result from direct injury to the heart but are more likely a result of transient decreased myocardial oxygen delivery resulting from shock, with subsequent ischemia and later reperfusion injury. Physical examination may reveal pulse deficits, high pulse rate, and/or weak pulses. Severe arrhythmias may cause signs of shock. Common arrhythmias include isolated premature ventricular contractions, accelerated idioventricular rhythms, and ventricular tachycardia. Much debate exists as to when or if trauma associated ventricular arrhythmias need to be treated. Definite indications for treatment of ventricular arrhythmias include heart rate greater than 180 bpm, R on T phenomena, and any arrhythmia that is causing signs of decreased tissue perfusion. It is recommended that treatment be based on heart rates greater than 140 bpm, to decrease myocardial (and thus whole body) oxygen consumption. Prior to use of antiarrhythmic agents, blood pressure should be normalized (if possible), SpO_2 should be greater than 93%, and electrolyte and acid base status should be normalized. Subsequent treatment with lidocaine (2 to 4 mg/kg bolus followed by 50 to 80 µg/kg/min CRI in dogs) will abolish most ventricular arrhythmias. Refractory arrhythmias causing clinical signs of decreased perfusion of the tissues may be treated with procainamide. Most trauma-associated arrhythmias will resolve over 2 to 4 days.

Pericardial Effusion

Pericardial effusion is a rare complication of trauma in the dog and cat; however, it should be considered as a differential diagnosis in animals with clinical signs of shock. Clinically significant pericardial effusion should be suspected from physical examination findings and confirmed through echocardiographic assessment. Physical examination findings consistent with pericardial effusion include pale mucous membranes, slow capillary refill time, and muffled heart sounds, pulsus paradoxus (waxing and waning pulse pressure with respiratory cycle), and distended jugular veins. In the trauma situation, however, these physical examination findings may be complicated by concurrent injuries and hypovolemia. In this situation echocardiography is the most appropriate diagnostic test. Thoracic radiography may be helpful, but in acute pericardial effusion, the cardiac silhouette may not appear significantly enlarged although it may be more round than normal. Pericardial effusion should be relieved by pericardiocentesis.

TRAUMA-ASSOCIATED MEDIASTINAL INJURY

Pneumomediastinum

Pneumomediastinum is defined as an accumulation of air within the mediastinal space and, like rib fractures, should serve as a "flag" for concurrent injuries. Pneumomediastinum may result from injury to the large airways (see below), esophagus, alveoli (with subsequent tracking of air back into the mediastinum), and the cervical region. In the cervical region, air can track along the trachea and vascular structures of the neck into the mediastinum. Pneumomediastinum is rarely of clinical consequence but may be suspected in animals with subcutaneous emphysema in the cervical region. Pneumomediastinum can be definitively diagnosed on thoracic radiographs. An effort should be made to identify and definitively treat concurrent injuries.

Tracheal Avulsion

Tracheal avulsion is thought to occur due to a rapid and extreme hyperextension injury to the head or neck and is more common in cats than in dogs. Tracheal avulsion may affect the intrathoracic or extrathoracic trachea. Both intrathoracic and extrathoracic tracheal avulsion can be associated with subcutaneous emphysema, signs of respiratory distress, and airway obstruction on initial physical examination. Radiographic examination will illustrate pneumomediastinum and may or may not reveal discontinuity of the tracheal silhouette. Frequently, clinical signs will abate as the airway is maintained by a thin mediastinal reflection. However, within the following 1 to 2 weeks, dyspnea usually develops secondary to fixed airway obstruction as the ends of the avulsed trachea begin to stenose. Subsequent radiographic evaluation will better illustrate lack of continuity of the tracheal silhouette. Treatment is surgical repair and reconstruction of the trachea.

CHAPTER • 127

Blood Transfusions, Component Therapy, and Oxygen-Carrying Solutions

Ann E. Hohenhaus

Important advances have occurred in veterinary transfusion medicine over the past 10 years due to an increased knowledge and expertise. The major innovation has been the advent of component therapy. Component therapy is considered the optimal method of transfusion since it allows specific transfusion therapy: red blood cells for anemia and plasma to provide deficient coagulation factors. The use of whole blood in anemic patients wastes the plasma, which could be used to control hemorrhage in a dog with anticoagulant rodenticide toxicity. A dog with anemia secondary to chronic renal failure does not require coagulation factor replacement and needs only a red blood cell transfusion. The plasma from this unit of blood can be used for a different dog with a bleeding disorder. By transfusing only the component required to treat the disorder, the risk of adverse reaction is decreased while efficacy is maintained.

Blood for the production of components is collected as whole blood in an anticoagulant preservative solution. The collection bag is sterilely manufactured and comprises multiple bags interconnected via sterile tubing. The whole blood collected into this system is processed through one or more centrifugation steps to produce the various blood components. Each component has a specific composition, storage requirement, and clinical use (Table 127-1). Blood components are the products typically available from veterinary blood banks (Table 127-2).

To improve the ability of veterinarians to use blood components effectively, this chapter discusses the various components available for use in veterinary patients regarding their composition, clinical use, dosage, and most common adverse reactions. Although there have been many advances in veterinary transfusion medicine, there is currently not a consensus regarding the size of a "unit" of blood. For the purposes of this chapter, a unit of canine whole blood will be defined as the American Association of Blood Banks defines a unit of human blood (see Table 127-2). A unit of whole blood will be the blood (450 mL +/–45 mL) plus the anticoagulant (63 mL) collected from one dog into a standard blood bag. A "unit" of

Table • 127-1

Blood Products Available from Veterinary Blood Banks

PRODUCT	CONTAINS	USES	DOSAGE*	REACTIONS
Whole blood	RBCs, WBCs, plasma, platelets, anticoagulant	Feline transfusions Hypovolemic anemia Pediatric transfusions	10-20 mL/kg	Fever, acute hemolytic Volume overload
Packed red blood cells	RBCs	Clinically symptomatic anemia	6-10 mL/kg	Acute hemolytic, fever
Fresh frozen plasma	Plasma, anticoagulant	Coagulation factor deficiency	6-10 mL/kg	Volume overload, allergic, fever
	All clotting factors, immunoglobulins	Failure of passive transfer		
Frozen plasma	Plasma, anticoagulant	Failure of passive transfer	6-10 mL/kg	Volume overload, allergic, fever
	Low levels of clotting factors, immunoglobulins			
Cryoprecipitate	Factors VIII, XIII, vWF, fibrinogen	Deficiency of factors VIII, XIII, vWF, fibrinogen	1 unit/10 kg	Allergic, fever
Cryo-poor plasma	Factors II, IV, IX, X	Rodenticide intoxication	6-10 mL/kg	Allergic, fever
Platelet rich plasma	Platelets, plasma	Decreased platelet production	1 unit/10 kg	Allergic, fever
Frozen platelets	1×10^{11} platelets DMSO, plasma	Undefined ITP?	1 unit/10 kg	Bradycardia

*The dosage of any blood product is simply a guideline for the initial transfusion. All transfusions are given "to effect," which means that until the RBC count is high enough to adequately improve the recipient's oxygenation or adequate coagulation factors have been transfused to correct the hemorrhagic process. *NA*, Not applicable.

Table • 127-2

Volume in Various Units of Canine Blood Products

COMPONENT	VOLUME OF BLOOD OR PLASMA	VOLUME OF ANTICOAGULANT	TOTAL VOLUME IN ONE UNIT
Whole blood in standard anticoagulant	405-495 mL	63 mL	468-558 mL
Packed red blood cells in additive solution	200-240 mL	100-mL additive solution	300-350 mL
Packed red blood cells	200-240 mL	NA	200-240 mL
Fresh frozen plasma	200-240 mL	NA	200-240 mL
Cryoprecipitate	60-70 mL	NA	60-70 mL
Cryo-poor plasma	~100 mL	NA	~100 mL
Platelet rich plasma	200-240 mL	NA	200-240 mL

a component is the volume of product, for example, packed red blood cells or fresh frozen plasma obtained from 1 unit of whole blood. This information will not apply to blood from all blood banks, and the reader is referred to the specific product inserts for information regarding a particular blood bank's products. Because feline blood is collected in such a small volume (40 to 50 mL of whole blood per cat) and there is a lack of appropriate sized multi-bag systems, feline blood is not routinely processed into components, but it is possible to do so and feline components can be purchased from some veterinary blood banks.

When deciding to transfuse a patient with either a red blood cell product or a plasma product, the veterinarian must have in mind the goal of administering the transfusion. The veterinarian must recognize that transfusions do not cure any disease but merely supplements an absent or deficient component of blood on a temporary basis while the underlying disease is treated and the deficiency resolves. The decision to transfuse should always weigh the expected benefit to the patient against the risk of adverse effects of the therapy. To ensure safe administration of a transfusion, each patient who receives a transfusion will require pretransfusion testing, and monitoring during and after administration to prevent or recognize the side effects of that particular blood component.

RED BLOOD CELL PRODUCTS

Blood products that contain red blood cells include whole blood, packed red blood cells (pRBCs), pRBCs in additive solution, and leukoreduced pRBCs. The only indication for transfusion of a red blood cell containing component is a clinically symptomatic anemia (Table 127-3). Packed red blood cells, pRBC in additive solution, and leukoreduced pRBCs are appropriate products to treat anemia caused by blood loss, hemolysis, or bone marrow failure (see Table 127-3). Patients who are assymptomatic for their anemia do not need to be transfused, but an exact hemoglobin concentration or hematocrit level at which a red blood cell transfusion should be given has not been determined. Clinical signs of anemia that indicate red blood cell transfusion should be considered are tachycardia, weakness, tachypnea, and collapse. However, these clinical signs can also be attributed to many underlying diseases associated with anemia. The ability for physiologic mechanisms to compensate for a lack of red blood cells and the body's ability to produce red blood cells should be considered in the decision to transfuse. Because full compensation for anemia requires several days, a rapid onset of anemia from traumatic hemorrhage will require transfusion at a higher hemoglobin concentration or hematocrit than an anemia with a slow onset, such as pure red cell aplasia. Dogs or cats with pulmonary disease may require a transfusion at a higher hematocrit than those without, since the compromise of the respiratory system will decrease oxygenation of hemoglobin. Concurrent cardiac disease may limit the compensatory increase in cardiac output in response to anemia and dogs and cats with significant cardiac disease may require a transfusion at a higher hemoglobin or hematocrit than those without cardiac disease. When the hemoglobin reaches 3 g/dL or the hematocrit 12%, the major organs have reached the limit in their ability to compensate for a lack of red blood cells and the need for red blood cell transfusion is urgent. Above that level of hemoglobin concentration or hematocrit, the requirement for transfusion becomes less urgent and the clinical status of the patient, the rapidity of decline of red blood cells and the ability of the bone marrow to replace the red blood cells must be weighed against the likelihood of adverse effects from transfusion.

Table • 127-3

Suggested Blood Components for Treatment of Various Anemias

TYPE OF ANEMIA	OPTIMAL COMPONENT	ALTERNATE COMPONENT	ALTERNATE COMPONENT
Blood loss anemia (hypovolemic)	Packed red blood cells and crystalloid or colloid solutions	HBOC	Whole blood
Blood loss anemia (normovolemic)	Packed red blood cells	HBOC	Whole blood
Anemia of chronic renal failure	Packed red blood cells	Whole blood	
Anemia of bone marrow failure	Packed red blood cells	Whole blood	HBOC
Hemolytic anemia	Packed red blood cells	HBOC	Whole blood

HBOC, Hemoglobin based oxygen carrier.

Pretransfusion testing prior to transfusion of a red blood cell containing component should include a blood type in every cat receiving a red blood cell transfusion. If a cat has not previously been transfused, a blood type is sufficient pretransfusion testing. Blood typing or cross matching a dog prior to the first transfusion is not necessary. In subsequent transfusions in both, dogs and cats, a cross match should be performed to determine compatibility of the red blood cells to be transfused.

The most serious adverse effect of administration of any red blood cell containing component is acute hemolytic transfusion reaction due to recipient antibodies against the donor red blood cells. The most common reaction, fever, is believed to be due to cytokines contained in the transfused blood or from antibodies against RBC, WBC, or platelets. As with any transfusion, there is a risk of volume overload, Type I hypersensitivity reactions causing facial edema, allergic reactions, vomiting, and fever.

Whole blood (WB) is blood collected from the donor, plus the anticoagulant. A standard blood bag contains 63 mL of anticoagulant. It is probably the most commonly used product in veterinary practice since it can be produced without any expensive equipment. Whole blood is typically used to transfuse cats. Feline units of blood are usually 40 to 50 mL of blood plus 5 to 9 mL of anticoagulant preservative solution. Ideally, WB should rarely be used in the dog since component therapy conserves blood and allows more dogs to be transfused from one unit of donated blood. WB would be most appropriate in pediatric transfusions when it would waste an entire unit of blood to open it for 10 or 20 mL to transfuse a small puppy. Whole blood would also be appropriate for exchange transfusions, in which the patient's blood is removed and replaced. In addition to supplying red blood cells, whole blood would replace clotting factors and albumin, which are removed in the exchange process. Whole blood could be used for patients who are experiencing hypovolemic anemia from hemorrhage, but packed red blood cells and crystalloid or colloid solutions will achieve the same effect.

Whole blood should not be used in normovolemic anemia because of the risk of volume overload from the additional volume plasma adds to the transfusion.

The initial dosage of WB is 10 to 20 mL/kg.

Packed red blood cells are the cells and a small amount of plasma remaining after the plasma and anticoagulant is removed. The PCV is approximately 80%, which makes pRBC very viscous. Normal (0.9%) saline is the only solution that should be added to any blood product and can be done with pRBC to improve flow.

The initial dosage of packed red blood cells is 6 to 10 mL/kg.

Packed red blood cells in additive solution are processed similarly to pRBCs, but after the red blood cells are separated from the plasma, 100 mL of an additive solution are added to the red blood cells. PCV is 55% to 60%. Additive solution contains dextrose, adenine, mannitol, and sodium chloride preserving the red blood cell function longer than the traditional anticoagulants ACD or CPDA (35 to 37 versus 21 days). It eliminates the need to add saline to the pRBC to decrease viscosity and improve flow. The fresh frozen plasma obtained from this process is identical to FFP produced from standard anticoagulant bags. This blood product is administered exactly the same as pRBCs.

The initial dosage of pRBCs in additive solutions would be 10 to 15 mL/kg.

Leukocyte-reduced packed red blood cells are produced from whole blood via centrifugation in the same manner as standard packed red blood cells, but an additional processing step is used to remove the white blood cells. Removal of 99.9% of white blood cells is accomplished by passing the blood between the collection bag and an accessory bag via an integral filter. Filtration can be performed at the time of blood collection or immediately prior to transfusion. White blood cells are removed because they have been implicated as a cause of certain types of transfusion reactions. Filters are designed to remove white blood cells without decreasing red blood cell biochemical characteristics, viability, storage time, or PCV.

The major reaction to leukocyte reduced pRBCs is an acute hemolytic transfusion reaction. The risks of nonhemolytic fever, transfusion transmitted infections, immunosuppression, and alloimmunization should be decreased with leukocyte reduction. This blood product is administered exactly the same as pRBC.

The initial dosage of leukocyte reduced pRBC would be 15 mL/kg.

PLASMA COMPONENTS

Fresh frozen plasma (FFP) is the plasma obtained from WB, which has been centrifuged, and the red cells removed within 6 hours of collection (Table 127-4). The anticoagulant remains in the plasma fraction during processing. When it is frozen at –20° C, the clotting factors maintain activity for 1 year. FFP is an excellent source of clotting factors and can be used to treat a wide variety of hemorrhagic disorders, including hemophilia, von Willebrand's disease, rodenticide intoxication, and disseminated intravascular coagulation. It is not a good source of albumin or nutrition, and calculations indicate 45 mL/kg would be required to increase the serum albumin concentration by 1 g/dL. FFP may be used in puppies or kittens with failure of passive transfer. Plasma transfusions may cause volume overload or allergic reactions. Blood typing before administration of a plasma transfusion is required in cats because antibodies contained in the plasma will cause a transfusion reaction if plasma incompatible with the recipient's red blood cells is administered.

The initial dosage of FFP is 6 to 10 mL/kg one to three times daily. The dosage depends on the condition being treated. In kittens with failure of passive transfer, a dose of 150 mL/kg of serum SC or IP has raised serum IgG to normal levels. A dose of 22 to 40 mL/kg of serum has been recommended in puppies with passive transfer, but normalization of IgG levels was not attained. Plasma can be used in place of serum.

Frozen plasma (FP) is plasma that has not been processed and frozen within 6 hours of collection or fresh frozen plasma stored at –20° C for more than 1 year. Both contain reduced levels of labile coagulation factors V and VIII. It may also be produced from WB stored more than 6 hours. Frozen plasma may be used in puppies or kittens with failure of passive transfer. Albumin is preserved at that temperature for 5 years and frozen plasma may be used as a source of albumin.

The initial dosage of FP is 6 to 10 mL/kg one to three times daily depending on the condition being treated.

Cryoprecipitate is a concentrated source of von Willebrand's factor, fibrinogen (factor I), and factor VIII prepared from 1 unit of FFP. Fresh frozen plasma is thawed at 4° C. During thawing, a white precipitate (cryoprecipitate) forms in the plasma and this precipitate contains vWf, factors VIII and I. The cryoprecipitate is separated from the liquid plasma by centrifugation. The liquid plasma is termed cryo-poor plasma. Cryoprecipitate is used to treat von Willebrand's disease, hemophilia A, and fibrinogen deficiency. Storage and handling of cryoprecipitate is similar to fresh frozen plasma. It can be stored at –20° C for 1 year. Like any plasma component, cryoprecipitate may cause allergic reactions. One unit of cryoprecipitate is the amount produced from 1 unit of FFP.

The initial dosage of cryoprecipitate is 1 unit per 10 kg of body weight.

Cryo-poor plasma is the plasma that remains after the cryoprecipitate is removed. Cryo-poor plasma contains factors II,

Table • 127-4

Suggested Blood Components for Treatment of Various Coagulopathies

TYPE OF COAGULOPATHY	OPTIMAL COMPONENT	ALTERNATE COMPONENT
Anticoagulant rodenticide intoxication	Fresh frozen plasma	Cryo-poor plasma
Disseminated intravascular coagulation	Fresh frozen plasma	
Von Willebrand's disease	Cryoprecipitate	Fresh frozen plasma
Hemophilia A Factor VIII deficiency	Cryoprecipitate	Fresh frozen plasma
Hemophilia B Factor IX deficiency	Fresh frozen plasma	
Liver disease coagulapathy	Fresh frozen plasma	

VII, IX, and X, which make it useful for the treatment of rodenticide intoxication. Storage and handling of cryo-poor plasma is similar to fresh frozen plasma. Like any plasma component, cryo-poor plasma may cause allergic reactions.

The initial dosage of cryo-poor plasma is 1 unit per 10 kg of body weight.

Platelet-rich plasma (PRP) is prepared from fresh whole blood by centrifugation at a slower centrifuge rate than for production of pRBC and plasma. The platelets are suspended in plasma to facilitate transfusion and transfused within hours of collection. PRP should not be refrigerated as it inactivates platelet function. Allogeneic platelet transfusions should be most useful in cases of decreased platelet production rather than cases of increased consumption or destruction of platelets. Unfortunately, increased destruction of platelets is the most common cause of thrombocytopenia in the dog. Platelet transfusions may cause allergic reactions or fever. Multiple platelet transfusions may result in alloimmunization and refractory thrombocytopenia.

The dosage is 1 unit of platelets via PRP per 10 kg of body weight.

Other Blood Components

Frozen platelets are collected through plateletpheresis. Platelets are preserved by DMSO and also contain a small amount of fresh frozen plasma. Efficacy data on this product has not been published, but immune-mediated thrombocytopenia is the recommended target disease for this product. Because the product contains DMSO, it must be infused slowly or bradycardia will result. The dosage is 1 unit of platelets per 10 kg of body weight. The product insert indicates this dose should increase the platelet count 20,000/μL when measured 1 to 2 hours post transfusion.

Human immunoglobulin is a concentrated source of immunoglobulin produced from the plasma of more than 1000 human donors via ethanol cold fractionation technique. In a limited number of cases, it has been used to treat acute canine immune-mediated hemolytic anemia (IMHA). Human immunoglobulin has also been used to treat immune-mediated thrombocytopenia in humans and cutaneous drug reactions in a dog and a cat. It is believed that providing the large number of immunoglobulin molecules overwhelms the reticuloendothelial system and prevents it from destroying additional red blood cells. Immunoglobulin may also neutralize or modulate pathogenic autoantibodies and modulate activation and cytokine production. Immunoglobulin therapy of dogs with IMHA has been associated with thrombosis and thrombocytopenia, but these abnormalities may be a result of the primary disease not the immunoglobulin infusion. Theoretically, repeat administration could cause severe anaphylactic shock, but no reports of a second infusion have been published. The recommended dosage is 0.5 to 1 g/kg and the reconstituted product is infused over 6 to 8 hours.

OXYGEN-CARRYING SOLUTIONS

The term *blood substitute* is a poor description of intravenous solutions designed to deliver oxygen to the tissues as an alternative to homologous red blood cells. These solutions substitute for only one function of blood, the ability to carry oxygen; therefore they are used to treat patients with anemia from blood loss, hemolysis, or bone marrow failure. They do not contain coagulation factors, platelets, or white blood cells and consequently cannot perform the functions associated with those elements of blood. There are 2 major types of oxygen-carrying solutions: perflurocarbon emulsion-based carriers, and hemoglobin-based oxygen carriers (HBOC). Currently, the majority of the products are under clinical investigation in humans and the only product approved for use in veterinary patients is an HBOC.

HBOC-201 (Oxyglobin, Biopure Corporation, Cambridge, MA) differs from red blood cells in several ways. It is an acellular hemoglobin clear, dark purple solution with a pH of 7.8, produced from purified bovine hemoglobin. Oxyglobin contains 13 g/dL polymerized hemoglobin in a modified lactated Ringer's solution. It has an osmolality of 300 mOsm/kg.

Because Oxyglobin contains no red blood cells, the hemoglobin polymers transport oxygen in the plasma. Oxyglobin increases oxygen carrying capacity without increasing red blood cells; consequently, the PCV does not rise in patients who receive Oxyglobin and patient monitoring must include a measurement of total (RBC + plasma) hemoglobin to fully assess oxygen carrying capacity. Not all hematology analyzers measure hemoglobin concentration and only those that measure hemoglobin should be used to assess the effect of Oxyglobin. Hemoglobin can readily be measured using a hemoglobin meter, HemoCue, (HemoCue, Inc., Mission Viejo, CA), which has been validated in veterinary patients and uses a modified azide methemoglobin reaction to measure hemoglobin. The Hemavet multispecies analyzer (CDC Technologies, Oxford, CT), impedance analyzers and flow cytometric analyzers measure hemoglobin. I-Stat (Sensor Devices, Inc., Waukesha, WI) and IRMA Blood Analysis System (Diametrics Medical, Saint Paul, MN) calculate hemoglobin and should not be used to measure the effect of Oxyglobin.

Although polymerization of hemoglobin molecules prolongs the half-life in the plasma over that of native hemoglobin ($t_{1/2}$ = 18 to 43 hr, at a dose of 10 to 30 mL/kg), the half-life of Oxyglobin is shorter than that of transfused

allogeneic red blood cells, (days to weeks). Oxyglobin is labeled to increase oxygen-carrying capacity when compatible canine blood is not available due to inadequate supply or serologic incompatibility. It has a 36-month shelf life without refrigeration, and there is no requirement for preinfusion blood typing or crossmatching since antigenic red blood cell membranes are removed during ultrapurification.

Adverse effects differ from red blood cell–containing components. The intense purple color of the solution temporarily imparts an abnormal color to mucous membranes and urine. Fortunately, the discoloration does not affect oxygen saturation monitoring via pulse oximetry. The presence of Oxyglobin in plasma also limits laboratory testing, especially when colorimetric methodology is used. Tests most commonly affected are bilirubin, liver enzymes, creatinine, glucose, urine dipstick measurements, but the effect varies with the equipment used and the concentration of Oxyglobin in the plasma or urine. Oxyglobin is currently labeled as a single dose product, because there are concerns about the antigenicity of bovine hemoglobin in non-bovine species, but to date, antibodies do not appear to result in anaphylactic or anaphylactoid reactions in dogs administered multiple doses of the product. The large polymers of hemoglobin exert an oncotic effect in the plasma, which results in volume expansion. Parameters such as central venous pressure, respiratory rate, and respiratory sounds should be monitored during and following an Oxyglobin infusion to prevent volume overload, pulmonary edema, and pleural effusion.

The manufacturer's recommended dosage is 10 to 30 mL/kg administered as a continuous intravenous solution in dogs. Typically, the low end of the dose range is used for the initial infusion. If required, the remaining dose can be infused. Oxyglobin has not been approved for use in cats and the optimal dose and rate of infusion have not been determined in cats, although Oxyglobin has been administered safely to cats.

SECTION V

Blood Pressure

CHAPTER 128

Blood Pressure Assessment

Rebecca L. Stepien

Routine assessment of blood pressure (BP) in clinical veterinary patients is a relatively recent development, and the volume of published literature regarding what is normal and abnormal in pet dogs and cats is growing rapidly. In contrast to human hypertension (HT), hypertension in veterinary patients most often is associated with a causative underlying disease[1-4] (Table 128-1). BP values obtained during diagnostic evaluation are assessed in conjunction with other clinical findings (e.g., evidence of retinal detachment, a history of polyuria and polydipsia), because these associated findings may point to the cause of the HT or indicate HT-associated end-organ damage. A single high BP value should never be used to diagnose systemic HT in the absence of other clinical information.

BP measurements that exceed published normal ranges are not always indicative of disease. Patient distress[5] or physical manipulations, such as fluid administration, may elevate BP acutely. The degree of clinical concern associated with elevated BP is proportional to the degree of elevation in combination with the clinical signs and clinical condition of the patient.

DEFINITION OF NORMAL

Normal ranges for BP in dogs[6-9] and cats[4,10-12] are often expressed as a mean value for a normal population ±2 standard deviations; animals with BP values outside this range are considered abnormal. The drawbacks to this approach to diagnosis of HT include inadvertent inclusion of normal animals with a BP value outside the "95% range" (leading to unnecessary diagnostic testing or therapy) or exclusion of HT as a diagnosis in an affected animal with mild or moderately elevated values (increasing the risk of end-organ damage). In addition, a dichotomous "normal" versus "too high" diagnostic result cannot take into account the differing risk of end-organ damage with increasing BP values.

Another approach to the diagnosis of HT is based on establishing diagnostic "cutoff" values at the level usually associated with clinically detectable disease. Clinical information regarding the BP typically associated with ophthalmologic[13] and renal[2,4,11] abnormalities in spontaneous canine and feline HT is available, but there is no information about threshold BP values for end-organ damage in this group of patients. Furthermore, the "trigger point" at which elevated BP results in clinical signs likely differs from patient to patient and may be affected by the rapidity with which the HT develops.[14]

Previous definitions of the high end of normal for dogs varied between 160 and 180 mm Hg and between 160 and 200 mm Hg in cats, but progression of renal damage in dogs is already enhanced with systolic BP (SBP) values in this range,[15] and clinical studies have documented end-organ damage at SBP values as low as 170 mm Hg.[13] Accordingly, current recommendations consider a SBP greater than or equal to 160 mm Hg (as measured by oscillometric or Doppler ultrasonographic methods) worthy of further diagnostic concern in both dogs[16] and cats,[17] although the use of antihypertensive medications may not be warranted (Table 128-2). The prevalence and importance of diastolic HT in dogs and cats are not well defined, therefore most recommendations for BP assessment relate to systolic BP measurement.

Table 128-1

Diseases/Clinical Findings Commonly Associated with Systemic Hypertension in Dogs and Cats*

DOGS	CATS
Ocular findings consistent with hypertensive choroidopathy, hypertensive retinopathy or intraocular hemorrhage	Ocular findings consistent with hypertensive choroidopathy, hypertensive retinopathy or intraocular hemorrhage
Chronic or acute renal failure	Chronic or acute renal failure
Hyperadrenocorticism	Hyperthyroidism
Diabetes mellitus	Diabetes mellitus
Neurologic signs unexplained by other causes	Any neurologic signs
Pheochromocytoma	Age ≥10 years
Unexplained left ventricular hypertrophy	Murmurs gallop rhythm
	NOTE: Idiopathic hypertrophic cardiomyopathy cannot be diagnosed without excluding hypertension.

*A complete funduscopic examination and BP measurement are indicated in animals known to have or suspected of having these disease conditions. Conditions that are rare in the species (e.g., hyperthyroidism in dogs) are not included. BP measurement is often included in routine cardiac evaluations.

Table • 128-2

Recommended Approach to Assessment of Abnormal Blood Pressure Values

PATIENT STATUS	BLOOD PRESSURE (mm Hg)	RISK OF END-ORGAN DAMAGE	RECOMMENDED ACTION*
Clinical signs of hypertension (HT): Known underlying disease	≥180/120	High	Begin anti-HT medication prior to full evaluation of underlying disease conditions. Treat underlying disease.
	160-179/100-120	Moderate	Begin anti-HT medication prior to full evaluation of underlying disease conditions. Treat underlying disease.
	150-159/95-100	Low	Begin anti-HT medication prior to full evaluation of underlying disease conditions. Treat underlying disease.
	<150/95	Minimal	Treat underlying disease. Search for other causes of clinical signs (e.g., coagulopathy). If no other cause of signs is found, monitor BP over time.
Clinical signs of HT present No known underlying disease present	≥180/120	High	Begin anti-HT medication prior to full evaluation of underlying disease conditions. Perform diagnostic evaluation for underlying disease.
	160-179/100-120	Moderate	Begin anti-HT medication prior to full evaluation of underlying disease conditions. Perform diagnostic evaluation for underlying disease.
	150-159/95-100	Low	Consider anti-HT medication prior to full evaluation of underlying disease conditions. Perform diagnostic evaluation for underlying disease. Search for other causes of clinical signs (e.g., coagulopathy).
	<150/95	Minimal	Search for other causes of clinical signs (e.g., coagulopathy), If no other cause of signs is found, monitor BP over time.
No clinical signs of HT present	≥180/120	High	Treat underlying disease. Begin anti-HT medication.
At risk due to concurrent disease	160-179/100-120	Moderate	Treat underlying disease. Consider anti-HT medication if rapid resolution of underlying disease is not anticipated.
	150-159/95-100	Low	Treat underlying disease. Monitor BP every 3-6 months for progression.
	<150/95	Minimal	Treat underlying disease. Monitor BP every 3-6 months for progression.
Clinically healthy	≥180/120	High	Confirm BP value by repeated testing. If values are consistent, consider therapeutic trial of anti-HT medication.†
	160-179/100-120	Moderate	Confirm BP value by repeated testing. If values are consistent, monitor BP every 3-6 months for progression or development of clinical signs or compatible disease.
	150-159/95-100	Low	Confirm BP value by repeated testing. If values are consistent, monitor BP every 3-6 months for progression.
	<150/95	Minimal	Normal No further testing is indicated.

*The clinical course of action should be tailored to the individual patient's circumstances. Recommendations may change as more clinical information becomes available.
†The normal BP range for healthy sight hounds may be higher than for other breeds.[20]

APPROACH TO PATIENT GROUPS

The goals of detection of HT in cats and dogs are to alleviate clinical signs and to prevent future clinical signs or subclinical deterioration of organ function. Veterinary clinicians are at a disadvantage in the early detection of clinical signs of HT. In humans, stage 1 and stage 2 HT (BP values of 140-179/90-109 mm Hg) are frequently asymptomatic. When symptoms are reported, they often include patient perceptions that would be difficult to assess in veterinary patients, including morning headaches, a sense of fullness in the head, or "general unease"[18]. Similar BP, however, values have been associated with progression of renal damage in dogs with renal failure.[15] Because the first clinical sign of HT in dogs and cats may be catastrophic (e.g., retinal detachment), detection of BP elevations below the level likely to produce clinical signs is preferable. Therefore, except for in patient with overt clinical signs, detection of HT is a preventive measure. BP values are obtained using accurate and repeatable methodology (see Diagnostic Blood Pressure Measurement, Chapter 76). Persistent elevation of BP is a clinical finding that leads to further clinical investigation and to consideration of therapy.

PATIENTS WITH CLINICAL SIGNS OF HYPERTENSION

Hypertension has been documented in association with clinical abnormalities of the ocular, neurologic, cardiovascular, and renal systems,[13,19,20] and effective therapy of HT in these circumstances typically eases, if not resolves, clinical signs.[13] Animals with clinical signs of HT and elevated BP should receive immediate antihypertensive therapy to decrease BP and thereby alleviate clinical signs. A detailed evaluation for known causes of HT in the species in question follows acute antihypertensive therapy. In some cases, gaining control of the underlying disease (e.g., pheochromocytoma, hyperadrenocorticism) may result in lowering or normalization of BP.

PATIENTS AT RISK FOR HYPERTENSION

Patients considered at risk for HT are those with no clinical signs of HT that have a disease condition or clinical signs of a disease known to be associated with HT in that species. Even though little reliable information is available on the effect of the duration of BP elevation and the extent of end-organ damage in spontaneous canine and feline HT, it is likely that with the exception of acute, extreme BP elevations, chronic BP elevations are more damaging to end-organ vascular beds than short-term elevations. Therefore early detection of elevated BP in dogs and cats at risk is aimed at detecting and managing any treatable underlying conditions and at attempting to maintain BP within a range less likely to lead to end-organ damage (see Table 128-2).

APPARENTLY HEALTHY PATIENTS

The prevalence of HT in apparently healthy dogs is low,[21] and oscillometric and Doppler ultrasonographic test methods are moderately sensitive and specific at a diagnostic SBP cutoff value of 160 mm Hg.[16] These test characteristics result in a low positive predictive value for abnormal test results in healthy dogs. Therefore, based on current information, routine screening of BP in this population is not recommended. The prevalence of HT in the healthy feline population is also low,[10] but the prevalence of renal disease and hyperthyroidism (both diseases commonly associated with feline HT) in older cats is high enough to prompt consideration of routine screening of cats over the age of 10 years.[13,17]

BP assessment is a diagnostic test indicated in patients likely to have HT and as part of preventive medical care in patients at risk. Aspects of BP assessment that may change over time include the degree of BP elevation leading to clinical concern and possibly intervention, the importance placed on systolic versus diastolic HT, and the selection of patient groups to be included in screening procedures.

CHAPTER 129

Pathophysiology of Systemic Hypertension

Scott A. Brown

Systemic arterial blood pressure (BP) is the product of cardiac output and total peripheral resistance. Cardiac output may be further factored as the product of heart rate and stroke volume, yielding the following relationship:

$$BP = (\text{Heart rate} \times \text{Stroke volume}) \times \text{Total peripheral vascular resistance}$$

Thus any factor or process that persistently elevates one or more of these three determinants of BP can cause systemic hypertension. Similarly, to be effective, antihypertensive therapy must target one of the three determinants of BP.

Systemic hypertension can be simply defined as persistently elevated BP. Systemic hypertension is often defined on the basis of BP measurements in human beings as a systolic BP (SBP) greater than 140 mm Hg and/or a diastolic BP (DBP) greater than 90 mm Hg. In dogs and cats the definition of systemic hypertension is controversial, although one definition that applies to cats and most breeds of dogs is a SBP greater than 160 mm Hg and/or a DBP greater than 100 mm Hg in repeated, reliable measurements of BP in a calm animal.

The term *isolated systolic* (and *diastolic*) *hypertension* refers to a condition in which only the SBP (or DBP) persistently exceeds the corresponding normal range. In the past physicians were more concerned about elevation of the DBP, but recent studies suggest that end-organ damage, particularly renal, is better correlated with the degree of SBP elevation.

Isolated systolic hypertension is common in elderly people as the result of a loss of arterial compliance, which develops as arterial walls stiffen with age. Although isolated systolic and diastolic hypertension is observed in dogs and cats, the prevalence and importance of these findings have yet to be well studied in veterinary medicine.

CLASSIFICATION SYSTEM

Systemic hypertension is often classified on the basis of causation as either primary (essential) or secondary. *Essential hypertension* exists when BP is persistently elevated even though a careful diagnostic evaluation fails to identify a cause of the hypertension. *Secondary hypertension* occurs when there is a known cause, generally a disease process that alters renal or neurohormonal functions. A clinical definition of essential hypertension is persistent elevation of BP in an animal with no clinical or biochemical evidence of a renal or endocrinologic abnormality that could cause hypertension (e.g., hypercorticism, hyperthyroidism, pheochromocytoma, hyperaldosteronism, or diabetes mellitus). Because of the broad normal ranges for creatinine and blood urea nitrogen (BUN) levels, the absence of azotemia is a necessary, but not sufficient, condition to eliminate renal disease as a cause of secondary hypertension in a dog or cat. Only a normal urinalysis, normal glomerular filtration rate (GFR), and normal renal biopsy can achieve this purpose. Essential hypertension accounts for 95% of cases of hypertension in human beings but has rarely been identified in dogs and has not been conclusively reported in cats.

Although used for decades in human beings, this primary (essential) versus secondary terminology is overly simplistic and misleading. As noted above, the BP cannot be elevated unless stroke volume, heart rate, and/or peripheral vascular resistance are increased (i.e., something must be abnormal). More important, the normal long-term renal response to systemic hypertension is natriuresis and diuresis, which should normalize the BP by reducing extracellular fluid volume and cardiac output. Therefore BP cannot remain persistently elevated without an abnormality in renal sodium handling. Indeed, the kidney must play a causal or permissive role in any animal with systemic hypertension. At the very least, a functional kidney "disease" exists in every chronically hypertensive animal, regardless of whether the animal has essential or secondary hypertension. Nonetheless, it is important in the clinical evaluation of every hypertensive animal that an exhaustive search be made for an inciting cause of the increase in BP. This distinction between primary (essential) and secondary hypertension suggests and facilitates that search; for this reason, this terminology remains useful for clinical purposes.

GENESIS OF HIGH BLOOD PRESSURE

Because essential hypertension is rare in veterinary medicine, yet accounts for 95% of cases of identified hypertension in human beings, it might be expected that systemic hypertension is uncommon in veterinary medicine. To the contrary, diseases associated with secondary hypertension are quite common in certain veterinary species. In particular, chronic renal disease is frequently observed in geriatric cats and dogs, with the prevalence reaching nearly one in three cats in select populations. Because kidney disease is often associated with disturbances of neuroendocrine factors and body fluid balance, it is not surprising that most, although not all, surveys have identified systemic hypertension in a significant proportion of cats and dogs affected with kidney disease. Other examples of conditions associated with the development of secondary hypertension in dogs and cats include diabetes mellitus, hyperadrenocorticism, pheochromocytoma, and hyperthyroidism.

Systemic hypertension can arise from an excess of circulating glucocorticoids, caused by adrenocortical overproduction or exogenous administration. These compounds have a variety of effects, including a mineralocorticoid type, which stimulates renal retention of salt and water and resultant increases in blood volume and cardiac output. These animals also may suffer from overproduction of renin, which elevates peripheral vascular resistance, contributing further to the development of hypertension. Animals with diabetes mellitus similarly may develop systemic hypertension as a result of overproduction of renin and blood volume expansion associated with hyperglycemia.

Hyperthyroidism is relatively common in geriatric cats and is associated with increases in BP. Thyroid hormone enhances cardiac function and sensitivity of the myocardium to catecholamines. The result is tachycardia and increased stroke volume, resulting in systemic hypertension. It remains unclear whether hyperthyroid cats with systemic hypertension often, or always, have kidney disease as a contributing factor to the high BP.

Pheochromocytomas are rare tumors of the neuroendocrine cells of the adrenal medulla in which overproduction of epinephrine and norepinephrine leads to peripheral vasoconstriction, tachycardia, and an increase in stroke volume. Often the release of hormones is episodic, causing periodic "attacks" of tachycardia and hypertension.

A variety of medications may also produce secondary hypertension. Examples include corticosteroids (as noted above), cyclosporin A (vasoconstriction leading to increased peripheral vascular resistance), phenylpropanolamine (increased peripheral vascular resistance from alpha adrenergic effects), and erythropoietin (increased blood viscosity, which enhances peripheral vascular resistance).

The role of dietary factors in the causation of secondary hypertension is unclear in veterinary medicine. A segment of the human population and certain strains of rats exhibit sensitivity of BP to changes in dietary salt intake. However, most studies indicate that the BP of dogs and cats is salt insensitive unless the salt intake is massive or there is a pre-existing cause of secondary hypertension. However, sodium chloride (NaCl)-rich therapeutic agents can raise BP, particularly intravenous fluid and electrolyte solutions. Maintenance fluid administration with isotonic electrolyte solutions generally provides 250 to 500 mg NaCl/kg body weight/day, compared with a typical dietary intake of 25 to 50 mg NaCl/kg body weight/day. Overzealous fluid therapy, therefore, can contribute to or cause systemic hypertension in susceptible patients. Any animal with systemic hypertension or a condition known as a possible secondary cause of hypertension (e.g., renal disease) should be considered potentially salt sensitive.

Ingestion of dietary omega-3 polyunsaturated fatty acids appears to be antihypertensive in human beings, but this may not be the case in dogs, in which these fatty acids' vascular effects appear to be intrarenal rather than systemic. Little is known about the vascular or intrarenal effects of dietary omega-3 polyunsaturated fatty acids in cats.

CONSEQUENCES OF SYSTEMIC HYPERTENSION

Unfortunately, systemic hypertension is usually asymptomatic initially and may go unrecognized for months or years until irreversible tissue damage becomes evident as organ failure ensues. Systemic hypertension in human beings is associated

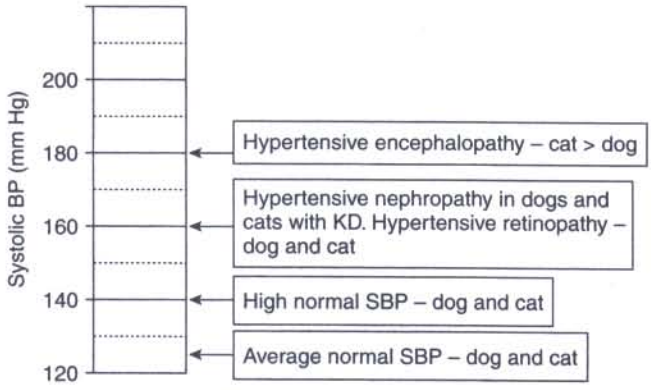

Figure 129-1 Proposed thresholds for end-organ damage in dogs and cats with systemic hypertension (see text for details).

with complications in the cardiovascular system (e.g., myocardial infarctions, "strokes"), central nervous system (e.g., hypertensive encephalopathy, "strokes"), urinary system (e.g., progressive renal damage) and eyes (e.g., retinal and choroidal injury). In veterinary medicine, hypertension is recognized with increasing frequency in cats and dogs, where it has been linked to damage in these same tissues. Although this remains somewhat speculative, and some breeds of dogs (especially sight hounds) have unusually high normal ranges for BP, data are accumulating that suggest that cats and most breeds of dogs with systemic hypertension (systolic BP equal to or greater than 160 mm Hg) are at risk for adverse effects (Figure 129-1). The most commonly identified adverse effects of marked systemic hypertension occur when the systolic BP exceeds 180 mm Hg, especially if an acute rise in the SBP of 30 mm Hg or more occurs within 48 hours; these complications include hypertensive retinopathy (intraocular hemorrhage, retinal edema, and/or retinal detachment in cats and dogs), hypertensive encephalopathy (progressive stupor, coma, and seizures associated with intracranial edema), and central nervous system (CNS) "stroke" (uncommon in dogs and cats). At a somewhat lower BP (SBP of 160 to 180 mm Hg), chronic changes induced by hypertensive damage to the kidney, eye, and cardiovascular system are also recognized in dogs and cats; the threshold for this injury is not certain but lies at approximately 160 mm Hg in cats and most breeds of dogs.

CARDIOVASCULAR EFFECTS OF HYPERTENSION

The most commonly observed effect of hypertension in the cardiovascular system is left ventricular hypertrophy. Cardiac muscle responds to chronically increased afterload by concentric hypertrophy (increased wall thickness without dilatation). Although left ventricular stiffness and reduced diastolic filling can elevate left ventricular diastolic pressure, leading to pulmonary congestion, this is uncommon. Functional failure (congestive heart failure) is also uncommon as a sequela of hypertension in dogs and cats unless a pre-existing or additional cardiovascular abnormality is present. Left ventricular hypertrophy may be documented clinically by thoracic radiography or cardiac ultrasonography. Effective antihypertensive therapy may reverse some of these changes.

A variety of vascular changes are observed in people with chronic hypertension. High pressures in small arteries and arterioles leads to extravasation of plasma into the vessel wall, producing a thickening referred to as *hyaline arteriosclerosis*. Chronic hypertension also induces vascular smooth muscle hypertrophy. Elderly human beings develop arteriosclerosis with a loss of large artery compliance and elasticity with aging. However, these vascular changes are seemingly absent or mild in dogs and cats, because they are seldom documented in these species.

Central Nervous System Effects of Hypertension

Circulation to the brain is generally well regulated locally, resulting in the property of *autoregulation*. This autoregulatory control of blood flow across a range of BP is mediated primarily by arteriolar smooth muscle, which constricts in response to a rise in BP (Figure 129-2). This protects the central nervous system from many of the adverse effects of systemic hypertension across a broad range of BP. However, there is a limit to the ability of these arterioles to prevent the transmission of elevated BP to the local microcirculation (i.e., arterioles, capillaries, and venules). Further rises in BP above this autoregulatory limit lead to increases in pressure and flow within the microcirculation, which alters Starling forces across the capillary wall. The subsequent rise in intracapillary hydrostatic pressure, in particular, tends to increase transcapillary fluid filtration, promoting the development of interstitial edema within the brain parenchyma. Because the brain is "compartmentalized" within the bony cranium, this increase in interstitial volume can lead to a rise in intracranial pressure, causing neurologic dysfunction referred to as *hypertensive encephalopathy*. Clinical signs caused by brain edema may include disorientation, head pressing, ataxia, stupor, coma, and seizures. If severe, edema-induced increases in intracranial pressure can lead to cerebral herniation under the tentorium or cerebellar herniation through the foramen magnum. Brain herniation is generally a fatal complication of hypertensive encephalopathy. Although this condition occurs in both species, for poorly understood reasons, cats are particularly susceptible to the development of hypertensive encephalopathy.

Hypertension may also lead to small artery rupture and resultant localized ischemia ("stroke" or cerebrovascular accident [CVA]), but this is uncommon in veterinary species, perhaps because medium and large vessel disease (atherosclerosis and arteriosclerosis, respectively) are relatively uncommon. A CVA can occur as a result of small artery rupture within the cerebral vasculature (hemorrhagic CVA) or from vessel thrombosis (thrombotic CVA). In both cases, affected portions of the brain suffer infarction, and the animal may exhibit clinical signs such as ataxia, disorientation, seizure, stupor, or coma. These occur in hypertensive patients in veterinary medicine but seem to be less common than hypertensive encephalopathy, particularly in cats.

OCULAR EFFECTS OF HYPERTENSION

Perhaps because routine screening of animals for hypertension by BP measurement is uncommon, sudden onset of blindness from hypertensive retinopathy is one of the most common presenting complaints for animals with systemic hypertension. As with other microvascular beds (see Figure 129-2), once the upper limit of autoregulation has been reached, any subsequent rise in choroidal arteriolar and capillary flows and pressures leads to plasma leakage with associated abnormalities, including edema, hemorrhage, and detachment of the retina.

RENAL EFFECTS OF HYPERTENSION

Hypertension and kidney disease are integrally linked in human beings, with hypertension serving as a leading cause of renal failure and renal failure frequently contributing to the genesis and maintenance of systemic hypertension. This applies to any type of kidney disease, be it acute or chronic; vascular, tubulointerstitial, or glomerular; or mild, moderate, or severe. It has

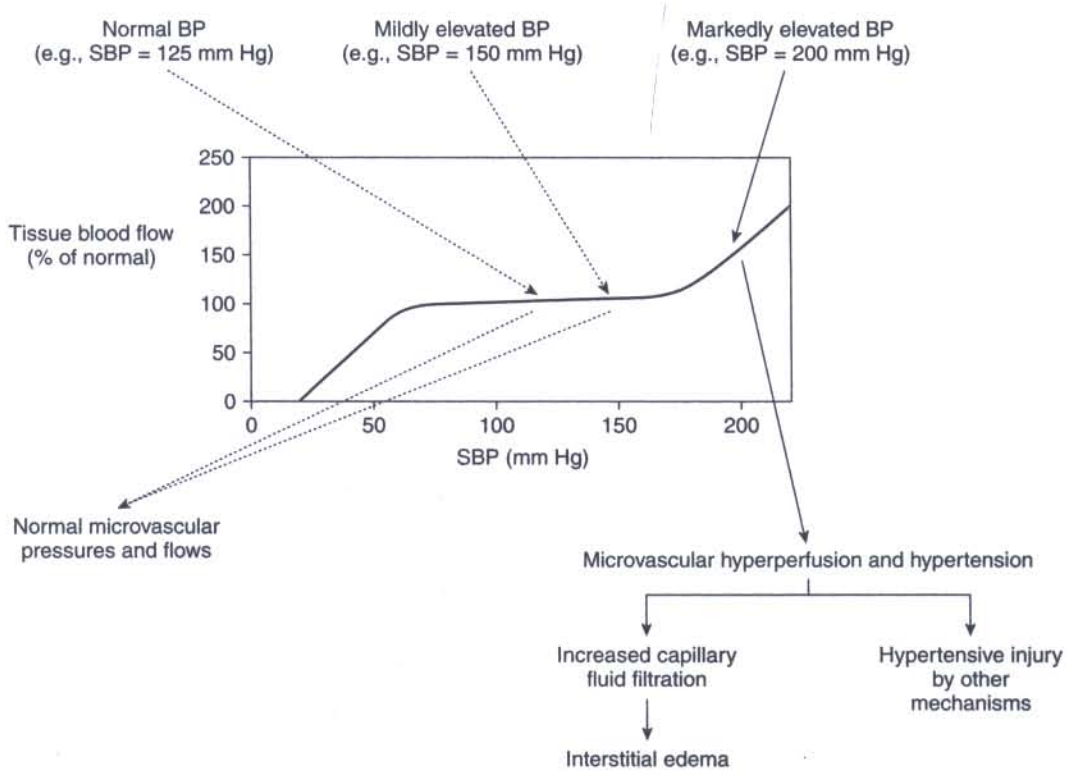

Figure 129-2 The relationship between systolic blood pressure (SBP) and tissue blood flow demonstrates a range of pressures wherein tissue blood flow is maintained constant (autoregulated) by the local vasculature. When SBP exceeds this range, tissue hyperperfusion and hypertension, and subsequent injury, ensue (see text for details).

been argued that high BP and kidney disease are a complex cause-effect dilemma (i.e., a "chicken and egg" issue), but this is probably not the case in dogs and cats. There is no evidence that a persistent elevation of BP in the absence of a pre-existing primary renal disease can produce structural renal damage in dogs and cats. Indeed, there is evidence to the contrary. The more common scenario is the initial presence of a kidney disease, with activation of the renin-angiotensin system and/or interference with renal sodium handling, which produces systemic hypertension, which then is capable of damaging the diseased kidney.

Systemic hypertension can contribute to renal injury in dogs with kidney disease, and the same is likely to be the case in cats. The renal microcirculation is unique in that the glomerular capillary bed is both preceded and followed by an arteriole. In kidney disease of any type, patchy areas of ischemia may result in overproduction of renin, with resultant increases in circulating and/or local concentrations of angiotensin II (Figure 129-3). Systemic generation of angiotensin II raises cardiac output and peripheral vascular resistance, exacerbating systemic hypertension. Critically, if kidney disease is present, the afferent arteriole is dilated. This site-specific dilatation represents an adaptive (perhaps maladaptive) response to the presence of a kidney disease. Constriction of the efferent arteriole by angiotensin II, coupled with this afferent dilatation, dramatically raises glomerular capillary pressure. The affected glomerular capillary bed and its associated nephron and interstitium are susceptible to hypertensive injury. Chronically sustained, hypertension in a dog or cat with kidney disease and a SBP greater than 160 mm Hg can lead to nephron destruction and can contribute to progressive renal failure.

RENOPROTECTIVE ROLE OF ANTIHYPERTENSIVE AGENTS

Kidney function (i.e., GFR and microvascular pressures and flows) is generally preserved during variations in BP as a result of the intrinsic property of renal vasculature referred to as autoregulation (see Figure 129-2). The normal kidney autoregulates, or maintains stability of, its own blood flow and GFR and is capable of achieving this effect despite variations in mean BP from 60 to 160 mm Hg. Unfortunately, studies have shown that animals with acute and chronic renal insufficiency lose the ability to autoregulate renal blood flow and GFR, making them more susceptible to renal damage from increases in BP.

In animals with systemic hypertension and chronic kidney disease, the most frequently recommended antihypertensive agents are vasodilators because they tend to produce renal vasodilatation, preserving GFR. Two classes of vasodilatory agents have proved to have renoprotective effects in rodents and human beings; these are the angiotensin-converting enzyme inhibitors (ACEIs) and the calcium channel antagonists (CCAs). As noted above, glomerular capillary pressure, the largest driving force for GFR and a site for the initiation of the deleterious effects of hypertension in the kidney, depends on afferent and efferent arteriolar tone. Dilatation of the afferent arterioles or constriction of the efferent arterioles increases glomerular capillary pressure (undesirable) and GFR (desirable).

An antihypertensive with a vasodilating effect at the efferent arteriole, such as an ACEI (e.g., benazepril, enalapril, ramipril, or spirapril), lowers BP by producing systemic vasodilatation and may have other beneficial effects in hypertensive dogs with kidney disease. In cats, the role of the renin-angiotensin

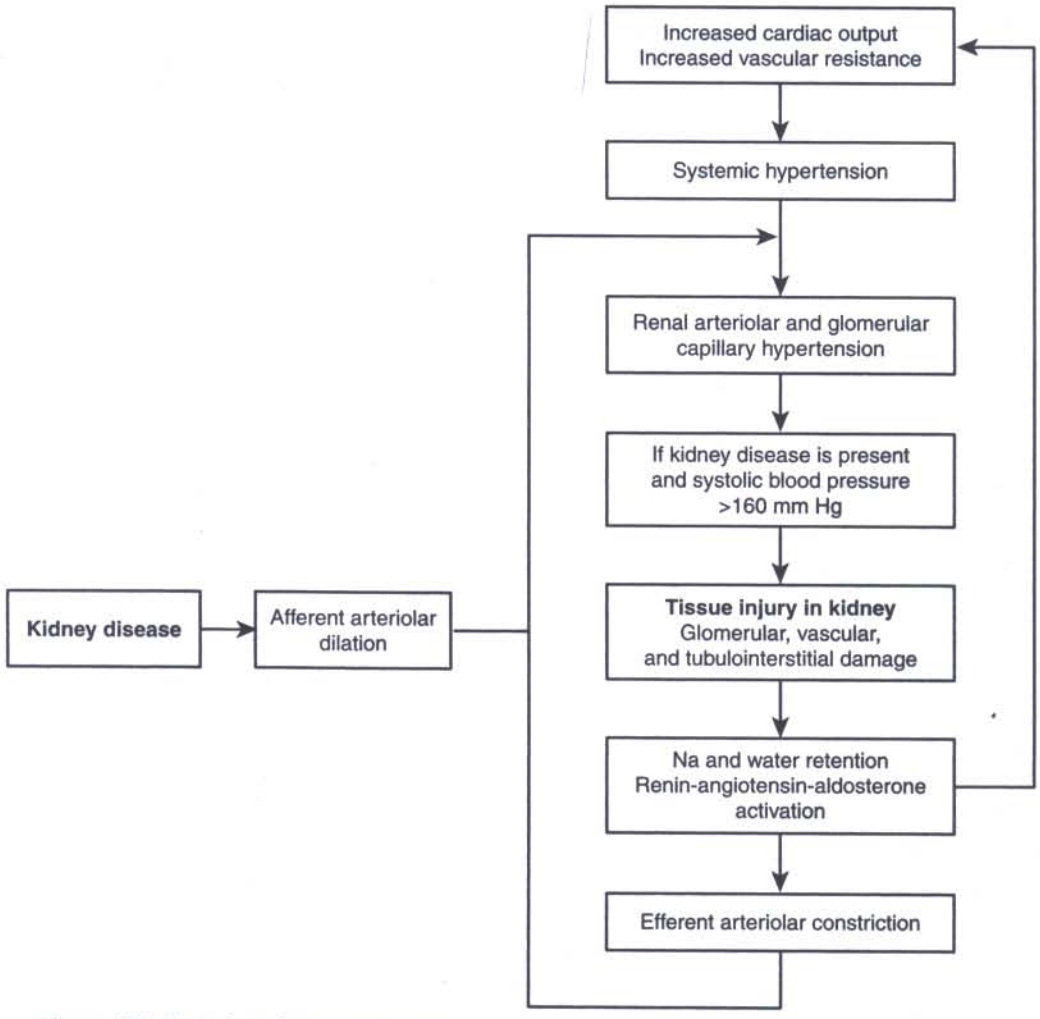

Figure 129-3 Kidney disease and systemic hypertension are closely linked in a series of complex processes that are self-perpetuating (see text for details).

system in the maintenance of systemic hypertension has been questioned. However, these agents may prove efficacious, because they lower intraglomerular pressure, presumably through inhibition of intrarenal formation of angiotensin II. Alternative methods of interfering with the renin-angiotensin-aldosterone system have not been fully evaluated in veterinary medicine (e.g., aldosterone and angiotensin receptor antagonists).

Some drugs classified as CCAs reduce total peripheral vascular resistance, leading to a decrease in BP. Amlodipine besylate is a long-acting dihydropyridine calcium antagonist that has been used effectively in hypertensive cats. The CCAs preferentially dilate the afferent arteriole. Vasodilatation at this site tends to raise intraglomerular pressure and could promote renal injury and/or proteinuria. However, these agents are most frequently used in cats, in which they are quite effective at lowering BP. The overall effect on intraglomerular pressure of reducing BP coupled with afferent arteriolar vasodilatation is hard to predict. Furthermore, the calcium channel antagonists have nonhemodynamic effects that may offer renoprotection. In dogs, in which CCAs seem less effective at lowering BP, use of these drugs as sole agents could predispose the animal to renal damage by allowing the high BP to be transmitted unimpeded through a dilated afferent arteriole to the susceptible glomerular capillary tuft.

Currently, co-administration of a CCA and an ACEI is advocated for hypertensive human beings with chronic kidney disease, because this therapy may reduce BP while equally dilating both the afferent and efferent arterioles, producing a balanced effect on the GFR and glomerular capillary pressure.

CHAPTER • 130

Management of Hypertension

Patti S. Snyder
Kirsten L. Cooke

Once a diagnosis of hypertension has been made, the decision to treat and the choice of antihypertensive medication depend on numerous factors, including the presumed cause of the hypertension, the presence of target organ damage, and the severity of the blood pressure elevation. The goals of antihypertensive therapy should be to reduce blood pressure and slow the progression of target organ damage caused by long-standing hypertension.

If an underlying cause of the hypertension can be identified, this condition should be addressed in the overall treatment plan for the hypertension. However, even if the presumed cause of the hypertension is controlled, antihypertensive treatment is usually continued indefinitely. If target organ damage is present, treatment of hypertension is usually initiated at systolic blood pressures greater than 160 mm Hg (Table 130-1). If target organ damage is not observed, documentation of a systolic blood pressure greater than 180 mm Hg on three separate occasions is considered sufficient evidence to begin treatment to lower blood pressure. There is less agreement among clinical researchers regarding treatment decisions based on diastolic blood pressure measurements.

Hypertensive animals that show neurologic signs are seen infrequently; however, if neurologic signs are observed, immediate intervention is necessary, using an antihypertensive agent that exerts gradual but effective blood pressure control. The more typical presentation is the pet with severe hypertension without life-threatening signs; these animals often exhibit such signs as blindness due to retinal hemorrhage or detachment. Because the stress of hospitalization could contribute further to elevations in blood pressure, most hypertensive animals are not hospitalized unless neurologic signs are seen. However, animals with severe hypertension deserve close monitoring, which may necessitate frequent visits for evaluation and blood pressure measurement until the hypertension improves.

DIET

Salt restriction has been the foundation of antihypertensive therapy in human beings. The goal of sodium restriction is to decrease total body sodium and extracellular fluid volume. Unfortunately, with the exception of a small population of dogs with essential hypertension, sodium restriction alone has not been shown to ameliorate hypertension in naturally hypertensive dogs and cats. Although one recent study showed that feeding a food with a moderately increased sodium level (1.0% sodium) to normotensive cats did not cause an elevation in systolic blood pressure, it should be noted that these were young cats with normal blood pressure. It is currently recommended that diets high in sodium (1.3% or higher) be discontinued if possible.

Although an obesity-induced hypertension dog model exists, and overweight dogs have slightly higher blood pressures than dogs with normal body weights, the feeding of calorie-restricted diets has not been shown to lower blood pressure in obese, spontaneously hypertensive dogs and cats.

DIURETICS

By contracting the extracellular fluid volume, diuretics decrease blood pressure. Although still commonly used in hypertensive humans, diuretics in general have not been of

Table • 130-1

Drugs Used to Treat Hypertension in Cats and Dogs

DRUG	DOSAGE	
	CATS	DOGS
Furosemide (Lasix, generic)	1-4 mg/kg PO, IV q12-48h	2-4 mg/kg PO, IV q8-24h
Atenolol (Tenormin, generic)	2 mg/kg PO q12-24h	0.25-1 mg/kg PO q12-24h
Propranolol (Inderal, generic)	2.5-5 mg total dose PO q8-12h	0.2-1.0 mg/kg PO q8-12h
Enalapril (Enacard, Vasotec, generic)	0.25-0.5 mg/kg PO q12-24h	0.5 mg/kg PO q12-24h
Benazepril (Lotensin, Fortekor)	0.25-0.5 mg/kg PO q24h	0.25-1.0 mg/kg PO q24h
Ramipril (Altace, Vasotop)	None Available	0.125-0.25 mg/kg q24h
Nitroprusside (Nitropress)	None Available	2-10 µg/kg/min IV CRI
Phenoxybenzamine (Dibenzyline)	0.25-0.5 mg/kg PO q12h	0.25-1.5 mg/kg PO q8-12h
Prazosin (Minipress, generic)	None	0.5-2 mg total dose PO q8-12h
Amlodipine (Norvasc, Istin)	0.18-0.3 mg/kg PO q24h	0.2-0.4 mg/kg PO q24h
Acepromazine (Promace, generic)	0.05-0.1 mg/kg SC, IV	0.05-0.1 mg/kg SC, IV
Hydralazine (Apresoline, generic)	2.5-5 mg total dose PO q12-24h	0.5-3 mg/kg PO q12h

benefit in spontaneously hypertensive dogs or cats; however, some clinical researchers suggest that furosemide may be useful on an acute basis when used in conjunction with other antihypertensive agents. Diuretics should not be used in dehydrated, hypertensive patients or those with metabolic imbalances such as hypokalemia.

ADRENERGIC BLOCKING AGENTS

Beta-adrenergic receptor blockers are thought to decrease blood pressure by reducing the heart rate and cardiac contractility, thereby decreasing cardiac output (an important component of blood pressure). No difference is apparent in the antihypertensive effects of the cardioselective beta blocker atenolol and the nonselective beta blocker propranolol. The advantages of atenolol are that less frequent dosing is required, and fewer $beta_2$-blocking effects (e.g., bronchoconstriction) are seen. Propranolol, when used as a single antihypertensive agent, has not been effective in hypertensive cats. Even when it is combined with enalapril and phenoxybenzamine, few cats show substantial improvement in blood pressure. Recently, propranolol and atenolol have been used in conjunction with the calcium channel blocker amlodipine in cats with refractory hypertension.

Beta blockers are considered the treatment of choice in hypertensive, hyperthyroid cats, because excess thyroid hormone causes an exaggerated response to catecholamines. If the hypertension fails to respond to beta blocker therapy, amlodipine can also be used in hyperthyroid cats. There is limited experience with the antihypertensive effects of beta blockers in hypertensive dogs. Beta blockers should not be used as an antihypertensive agent in dogs suspected of having hypertension due to a pheochromocytoma.

Blocking of postsynaptic $alpha_1$-receptors in blood vessels results in vasodilatation. Phenoxybenzamine, an alpha-adrenergic blocking agent, has been used with mixed results alone and in combination with ACEIs or amlodipine in hypertensive cats. Phenoxybenzamine is considered the antihypertensive drug of choice in dogs with pheochromocytomas. Another alpha-adrenergic blocker, prazosin, has been reportedly used in hypertensive dogs.

Labetalol, a beta- and alpha-receptor blocker, has received attention in human medicine as an antihypertensive agent for which the primary antihypertensive effect is vasodilatation by alpha-receptor blockade. Because of its fast onset of action, it may be useful in emergency settings; however, experience with the drug in veterinary medicine currently is limited.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Angiotensin-converting enzyme inhibitors (ACEIs) control blood pressure by blocking the conversion of angiotensin I to angiotensin II, thereby reducing circulating angiotensin II, a potent vasoconstrictor. Reducing angiotensin II concentrations also decreases the secretion of antidiuretic hormone and aldosterone, which promote sodium secretion and therefore water excretion, effectively decreasing extracellular fluid volume and lowering blood pressure. Plasma renin activity and angiotensin I concentrations were not elevated but aldosterone concentrations were increased in hypertensive cats with chronic renal failure, compared with normotensive control cats. However, in a study of 16 hypertensive cats, plasma aldosterone did not change significantly with the administration of the ACEI benazepril or enalapril, and hypertension remained uncontrolled in 14 of 16 cats. In contrast, Brown and others showed that benazepril decreased both glomerular capillary pressure and systemic arterial blood pressure in an experimental feline model of chronic renal insufficiency.[1]

No one has compared the antihypertensive effects of the various ACEIs currently available in hypertensive dogs or cats, and most veterinary experience with ACEIs stems from their use in animals with congestive heart failure. The ACEI dosage used to treat hypertension appears to be similar to that used for congestive heart failure, although for hypertension some clinicians have used slightly higher doses if the animal did not have renal compromise and was not receiving concomitant diuretic therapy.

The number of dogs that require antihypertensive therapy is small compared to the number of cats that are hypertensive, and our experience in treating hypertensive dogs is considerably less, therefore minimal information is available on effective antihypertensive agents in dogs. Currently, the first-line therapy option for dogs with systemic hypertension is either an ACEI or a calcium channel blocker, usually amlodipine. When enalapril was given to dogs with idiopathic glomerulopathy, blood pressure decreased significantly (even in animals that were not hypertensive).

Even if control of hypertension is not optimal with an ACEI, the drug may have other beneficial actions, such as renoprotection. In refractory hypertension, ACEIs have been combined with other classes of antihypertensive agents, such as beta blockers and calcium channel blockers, to improve blood pressure control.

CALCIUM CHANNEL BLOCKERS

The calcium channel blockers decrease blood pressure by promoting vasodilatation and preventing an increase in the cytosolic calcium in vascular endothelial cells that is necessary for vasoconstriction.

Amlodipine besylate, a member of the dihydropyridine class of calcium channel blockers, is the treatment of choice in cats with systemic hypertension. Its long duration of action allows for once daily dosing, and it is safe to use in animals with renal compromise, a common finding in cats with hypertension.

Amlodipine is the only antihypertensive agent proven to be effective in a placebo-controlled clinical trial of naturally occurring systemic hypertension in cats. In this study, systolic blood pressure declined significantly after 1 week of therapy (pretreatment value, 212 mm Hg; post-treatment value, 160 mm Hg) and remained controlled when the cats were re-examined 4 months later.[2] Amlodipine was also effective in controlling hypertension in cats with surgically induced renal insufficiency and hypertension. Most recently, amlodipine was shown to lower systolic blood pressure from a mean of 202.5 mm Hg to 153 mm Hg in 20 hypertensive cats. In hypertensive cats with secondary ventricular hypertrophy, amlodipine administration resulted in resolution of the hypertrophy in 50% of the cats. Although amlodipine has been used safely in cats with renal dysfunction, there have been scattered reports of worsening azotemia in a small percentage of cats given the drug. For this reason, re-evaluation of a serum biochemistry panel is advised 1 to 2 weeks after initiation of amlodipine therapy.

Although there is less reported experience with amlodipine in hypertensive dogs, it is often prescribed as a first-line therapy for hypertension. If the drug is not effective at controlling hypertension in dogs, an ACEI can be combined with or substituted for the amlodipine.

COMBINATION THERAPY

Several clinical investigators have used ACEIs with beta blockers, or amlodipine combined with either beta blockers or ACEIs, in attempts to control blood pressure in cats with

particularly resistant hypertension. Unfortunately, because no clinical reports are available on large numbers of cats or dogs effectively treated with combination therapy, information is lacking regarding preferred combinations or efficacy.

OTHER THERAPIES

The phenothiazine derivative acepromazine maleate is a vasodilating agent commonly used in most veterinary practices. Its blood pressure–lowering effects are believed to be associated with alpha-adrenergic blocking effects. In the acute setting, when immediate blood pressure control is needed and other antihypertensive agents are not available, acepromazine can be administered. The vasodilator hydralazine has been used in cats receiving renal allograft that showed clinical signs of systemic hypertension. Administration of hydralazine reduced systolic blood pressure to the normal range within 15 minutes.

Sodium nitroprusside releases nitric oxide in vascular smooth muscle and causes vasodilatation (both arterial and venous). Its primary use has been in dogs with fulminant congestive heart failure. Nitroprusside should be administered as an intravenous constant-rate infusion, with an infusion pump used to improve the accuracy of dosing. However, it should be noted that because of vascular adaptations to long-standing, elevated blood pressure, abrupt decreases in blood pressure in chronically hypertensive animals can compromise cerebral perfusion and may not be in the patient's best interest.

ADDITIONAL TREATMENT RECOMMENDATIONS

Pet owners should be closely questioned about other drugs the hypertensive animal may be receiving that could affect blood pressure. The administration of corticosteroids, phenylpropanolamine, subcutaneous fluids, and even topical preparations such as ocular phenylephrine could make blood pressure control more difficult in some hypertensive patients. If possible, these drugs should be discontinued, or the lowest possible dose should be used.

Re-evaluation of the hypertensive patient should include appropriate biochemical evaluation (serum biochemistry panel, thyroid testing), funduscopic examination, and indirect blood pressure measurement. The frequency of the re-evaluations depends on the patient's clinical signs, the type and severity of end-organ damage, and the degree of blood pressure elevation. Re-examination may also be dictated by any potential underlying medical problems that could contribute to or cause the blood pressure elevation. Goals for successful control of hypertension are still being debated; however, a general guideline is a systolic blood pressure under 160 mm Hg in an awake, unstressed animal.

When hypertension is diagnosed, our initial response is a desire to lower blood pressure immediately to protect organs from further damage. In most of our patients, hypertension has been a long-standing condition when the diagnosis is made. Long-standing hypertension leads to adaptations in the cerebral vasculature such that a rapid drop in blood pressure may compromise cerebral perfusion. Rapid decreases in blood pressure are most often associated with administration of parenteral drug therapy, therefore these drugs should be reserved for cases in which the benefits of parenteral therapy outweigh the risk posed by the hypertension.

Because antihypertensive therapy is likely to be lifelong, administration of a single agent with a long duration of action (preferably an agent administered once daily) is ideal for improving owner compliance. If adverse effects are observed, another drug, usually from a different class, should be substituted. If the response to the initial agent is inadequate, the dose may be increased (if possible) or another agent, usually from another class, can be combined with the initial agent. If blood pressure control is still not achieved, monitoring of the blood pressure throughout the day to observe trends before and after drug administration may be useful. Owner and patient noncompliance and inadequate management of the underlying cause of the hypertension should also be considered if control of hypertension is difficult. A final consideration for inadequate control of hypertension is the concomitant use of other drugs that could contribute to the increased blood pressure.

Adverse Effects

Lowering of the blood pressure below normal is a potential complication of any antihypertensive agent and, as mentioned earlier, rapid lowering of blood pressure can lead to cerebral ischemia. These are less likely to occur with the commonly used oral antihypertensive therapies. Anorexia, vomiting, and diarrhea are the most common side effects seen with the antihypertensive agents, but the development of azotemia or worsening azotemia may also be seen once an antihypertensive agent is initiated. Monitoring of renal parameters on serial biochemistry panels is advised for any animal receiving chronic drug administration, including animals on long-term antihypertensive therapy.

CHAPTER 131

Hypotension

Lori S. Waddell

Hypotension is defined as a systolic arterial blood pressure of less than 80 mm Hg and/or a mean pressure of less than 60 mm Hg in either dogs or cats. Causes of hypotension include decreased preload to the heart, decreased vascular tone, and cardiac dysfunction. Untreated hypotension can lead to *shock*, which is defined as inadequate tissue perfusion and oxygen delivery to the tissues. Treatment of hypotension should always be aimed at correcting the underlying problem. Recognition and treatment of hypotension are essential to prevent the development of refractory shock, organ failure, and death (Figure 131-1).

Blood pressure provides a measurement of tissue perfusion. The two are not equivalent, but blood pressure monitoring is the simplest means of obtaining an objective parameter. Subjective measures of tissue perfusion are obtained by physical examination; they include pulse quality, mucous membrane color, capillary refill time, and heart rate and rhythm. Combined with blood pressure monitoring, these parameters provide the basis for a more accurate assessment of tissue perfusion. A normal blood pressure does not necessarily mean that the tissues are adequately perfused, as blood pressure may be maintained with severe peripheral vasoconstriction.

CLINICAL MANIFESTATIONS

The clinical signs associated with hypotension depend on the severity and cause of the condition. In dogs, hypotension is usually associated with tachycardia, bounding to weak pulses, pale mucous membranes, slow capillary refill time, mental dullness, and weakness. If the underlying cause is sepsis, the mucous membranes may be injected or red with a rapid capillary refill time. Cardiac causes of hypotension can also change the clinical picture, with arrhythmias; weak, irregular pulses; and even severe bradycardia possible. Hypotensive cats also usually have tachycardia, poor pulse quality, pale mucous membranes, slow capillary refill time, mental dullness, and weakness. However, unlike dogs, cats with sepsis or systemic inflammatory response syndrome (SIRS) often have bradycardia rather than tachycardia and rarely have injected mucous membranes. In both species, hypotension is often associated with decreased urine output, hyperventilation, hypothermia, and cold extremities.

Inability to palpate pulses peripherally can be useful in assessing blood pressure. When metatarsal pulses are palpable, the systolic blood pressure is above 70 to 80 mm Hg. Although measurement of blood pressure can confirm the presence of hypotension, the diagnosis can certainly be made on physical examination findings alone.

PATHOGENESIS

Blood pressure is dependent on cardiac output and peripheral vascular resistance. Cardiac output is determined by heart rate, contractility, preload, and afterload. The three main causes of hypotension are decreased preload, decreased cardiac function, and decreased vascular tone (Box 131-1). These may occur individually or in combination.

Multiple compensatory mechanisms are activated by hypotension. The baroreceptors in the carotid sinuses and aortic body sense a lack of stretch, resulting in increased sympathetic nervous system activation, increased release of antidiuretic hormone (ADH) and adrenocorticotropic hormone (ACTH) from the pituitary, and increased release of catecholamines and cortisol from the adrenal glands. These changes result in an increased heart rate, increased vasoconstriction, and increased water retention by the kidneys. Simultaneously, the macula densa in the glomeruli are affected, and the renin-angiotensin-aldosterone system is activated, resulting in sodium retention by the kidneys and further vasoconstriction. These mechanisms serve to increase blood volume by means of sodium and water retention and to preferentially perfuse the brain and heart while decreasing perfusion to the skin, muscles, and abdominal organs, including the kidneys. Recognition and treatment of hypotension are essential to prevent the development of refractory shock and organ failure. Acute renal failure is one of the most common consequences of hypotension, but others include decreased coronary artery perfusion due to the increased heart rate, increased risk of bacterial translocation from the gastrointestinal tract, impaired hepatic function, and activation of the coagulation cascade.

Hypovolemia results in decreased cardiac output secondary to decreased venous return to the heart, which results in decreased preload. Moderate to severe hypovolemia must be present to affect blood pressure due to the normal compensatory actions that occur, including increased heart rate to maintain cardiac output and increased peripheral vascular resistance secondary to vasoconstriction. The compensatory mechanisms maintain adequate blood pressure until more than 20% to 25% of the intravascular volume has been depleted. Hypovolemia can occur with blood loss or increased fluid losses secondary to vomiting, diarrhea, polyuria, or third spacing of fluid.

Restriction of filling of the heart also results in decreased preload, decreased cardiac output, and hypotension. Pericardial effusion with tamponade and restrictive pericarditis can result in hypotension by this mechanism. Severe pneumothorax and positive pressure ventilation can also reduce venous return to the heart. Hypertrophic cardiomyopathy in cats reduces left ventricular volume, thereby reducing preload and cardiac output.

Bradyarrhythmias can affect blood pressure by reducing cardiac output, especially when the heart rate is extremely slow. Although the pulses may be strong when the bradyarrhythmias occur, overall cardiac output can be drastically reduced by the infrequency of systole. The resulting low cardiac output may be severe enough to cause syncopal episodes secondary to hypotension and decreased perfusion of the brain. Tachyarrhythmias can result in hypotension by reducing preload to the heart. At very rapid heart rates, filling of the heart is limited by the relatively short time of diastole.

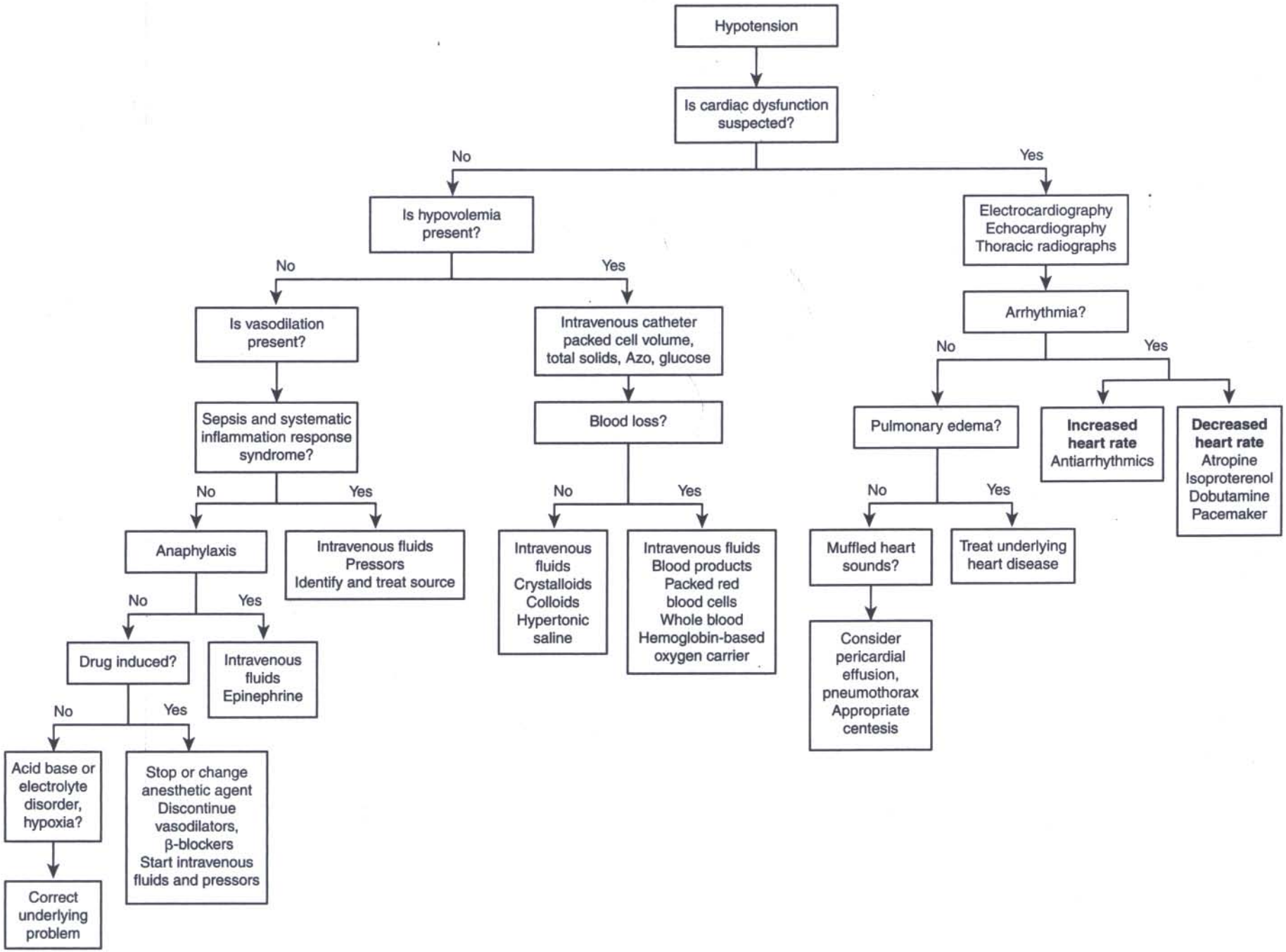

Figure 131-1 Algorithm for differential diagnoses and treatment of hypotension.

Box • 131-1

Causes of Hypotension

Decreased Preload
Hypovolemia
Hemorrhage
Trauma
Gastrointestinal losses
Polyuria
Hypoadrenocorticism
Effusions or third spacing of fluid
Burns
Heatstroke

Decreased venous return
Pericardial tamponade
Restrictive pericarditis
Severe pneumothorax
Positive pressure ventilation
Gastric dilatation and volvulus
Heartworm disease (caval syndrome)

Decreased Cardiac Function
Cardiomyopathy
Valvular disease
Bradyarrhythmias
Tachyarrhythmias
Electrolyte abnormalities
Acid-base disturbances
Severe hypoxia

Decreased Vascular Tone
Sepsis/systemic inflammatory response syndrome (SIRS)
Anaphylaxis
Neurogenic
Drug induced (anesthetic agent, vasodilators [e.g., beta blockers, calcium channel blockers])
Electrolyte abnormalities
Acid-base disturbances
Severe hypoxia

This results in reduced cardiac output despite an increased heart rate.

Decreased cardiac output can also occur due to primary cardiac disorders. Dilated cardiomyopathy is characterized by reduced stroke volume and reduced cardiac output caused by decreased contractility. Valvular incompetence, resulting in regurgitant flow, also causes decreased stroke volume. Other causes of decreased cardiac contractility include myocarditis, myocardial infarction, myocardial depression secondary to sepsis, SIRS, anesthetic drugs, beta blockers and calcium channel blockers, and acid-base and electrolyte abnormalities.

Decreased peripheral systemic resistance can also cause hypotension. Common causes of vasodilatation are sepsis/SIRS; anaphylaxis; anesthesia; use of vasodilators, including beta blockers and calcium channel blockers; electrolyte abnormalities; and acid-base disturbances. Many of these mechanisms also affect cardiac contractility, resulting in hypotension mediated by decreased cardiac output and vasodilatation simultaneously.

MEASUREMENT OF BLOOD PRESSURE

Blood pressure monitoring can be divided into two main types, noninvasive and invasive methods. The noninvasive methods are most commonly used, and in dogs and cats usually consist of either an oscillometric system (Cardell Monitor, Sharn Veterinary, Tampa, Florida or Dinamap, Critikon, Tampa, Florida) or Doppler methods (Parks Electronics, Aloha, Oregon). Invasive blood pressure monitoring is performed by direct arterial pressure measurement and is the most accurate method available.

TREATMENT

It is essential that the treatment of hypotension always be aimed at correction of the underlying physiologic problem: decreased preload, cardiac dysfunction, or peripheral vasodilatation. Differentiation of cardiac and noncardiac causes of hypotension is a critical first step (Figure 131-1). If the animal is hypovolemic, intravenous fluids should be administered until euvolemia has been attained. If hypovolemia is severe enough to cause hypotension, a shock bolus should be given. The standard doses of isotonic crystalloids are 60 to 90 mL/kg/hour for dogs and 45 to 60 mL/kg/hour for cats. If colloids are indicated in place of crystalloids, approximately one fourth of the crystalloid dose should be given. Hypertonic saline is a rapid intravascular volume expander and can be used when immediate resuscitation is needed. The dose for hypertonic saline is 5 mL/kg given over 5 to 10 minutes for dogs and 3 to 4 mL/kg given over the same time period for cats. After administration of hypertonic saline, it is essential to follow with one third to one half of a shock bolus of isotonic crystalloids to provide continued intravascular volume expansion and to replenish the interstitial space. If hypovolemia occurs secondary to blood loss, blood products, such as whole blood or packed red blood cells, or a hemoglobin-based oxygen-carrying solution should be administered to provide adequate oxygen-carrying capacity.

If the volume status is unknown or if there are concerns about overloading the animal with intravenous fluids, a central venous catheter can be placed for central venous pressure (CVP) monitoring. A low CVP (less than 0 cm H_2O) indicates hypovolemia due to fluid loss or vasodilatation secondary to decreased peripheral resistance. A high CVP (greater than 10 cm H_2O) indicates volume overload, right-sided heart failure, or increased pulmonary vascular resistance (afterload). If the significance of a CVP reading is questionable, a small test bolus of fluids can be given. A rapid bolus of 10 to 15 mL/kg of crystalloid or 3 to 5 mL/kg of colloid is used. The vascular bed is a compliant system, able to accommodate changes in volume with minimal changes in pressure. If the animal has a low CVP due to hypovolemia, the CVP will show either no change or a transient rise toward normal followed by a rapid decrease. The mean arterial pressure may also increase transiently. A bolus given to a dog or cat that is euvolemic usually causes a small increase in the CVP of 2 to 4 cm H_2O with a return to baseline within 15 minutes. A large increase (greater than 4 cm H_2O) and slow return to baseline (longer than 30 minutes) are seen with hypervolemia or reduced cardiac compliance.

If the animal remains hypotensive once euvolemia has been achieved, the use of pressors should be considered. Commonly used pressors include dopamine, epinephrine, and phenylephrine administered as constant-rate infusions. These drugs need to be titrated to effect, requiring frequent blood pressure monitoring. They should never be used in place of adequate volume expansion, because most dogs and cats with hypovolemia already have compensatory vasoconstriction.

Cardiac causes of hypotension must be addressed on a case by case basis. If tachyarrhythmias are the cause, antiarrhythmic therapy should be administered. Bradyarrhythmias may respond to medical therapy or may require placement of a pacemaker. Obstruction of cardiac filling by pericardial effusion or severe pneumothorax should be addressed by appropriate centesis. Positive inotropes should be administered when decreased cardiac contractility is suspected.

DIAGNOSTIC PLAN

Diagnosis of the underlying cause of the hypotension must often wait until after therapy has been initiated due to the critical nature of hypotension. History and physical examination abnormalities can often help in the determination of a tentative diagnosis, allowing therapy to be started. Initial diagnostics in an unstable hypotensive dog or cat should include packed cell volume, total solids, and glucose values and an estimate of the blood urea nitrogen level (Azostix, Bayer corporation, Elk-hart, IN). Electrolytes and acid-base status can also be helpful. Depending on the clinical signs, an electrocardiogram (ECG), abdominal and thoracic radiographs, abdominal ultrasonography, echocardiography, CVP and pulse oximetry determinations, and arterial blood gas analysis can be useful. A complete blood count, serum chemistry profile, and urinalysis should also be performed. If indicated, an ACTH stimulation test should be considered. If sepsis is suspected, blood and urine cultures should be done unless the source of sepsis can be directly cultured.

SECTION VI

Therapeutic Considerations in Medicine and Disease

CHAPTER 132

Clueing in Customers*

Leonard L. Berry
Neeli Bendapudi

Nobody likes going to the hospital. The experience is at best unnerving, often frightening, and, for most of us, a potent symbol of mortality. What's more, it's very hard for the average patient to judge the quality of the "product" based on direct evidence. You can't try it on, you can't return it if you don't like it, and you need an advanced degree to understand it—yet it's vitally important. Therefore when we're considering a doctor or a medical facility, most of us unconsciously turn detective, looking for evidence of competence, caring, and integrity—processing what we can see and understand to decipher what we cannot.

The Mayo Clinic doesn't leave the nature of that evidence to chance. By carefully managing a set of visual and experiential clues, Mayo tells a consistent and compelling story about its service to customers: At Mayo Clinic, the patient comes first. From the way it hires and trains employees, to the way it designs its facilities, to the way it approaches care, Mayo offers patients and their families concrete and convincing evidence of its strengths and values. The results are exceptionally positive word of mouth and abiding customer loyalty, which have allowed Mayo Clinic to build what is arguably the most powerful brand in health care—with very little advertising—in an industry where few institutions have any brand recognition beyond their local markets.

It's called "evidence management": an organized, explicit approach to presenting customers with coherent, honest evidence of your abilities. Evidence management is a lot like advertising, except that it turns a company into a living, breathing advertisement for itself. Other organizations manage evidence well, too. Ritz Carlton, for example, very effectively communicates outstanding personal service: Employees at all levels take note of customer preferences and are empowered to solve problems on the spot, continually tailoring the experience to each person. Mayo Clinic does not have all the answers; health care is a highly inventive industry, and many institutions could serve as fine examples to business. However, during our extensive study of the Mayo organization over a five-month period, we saw evidence—management practices that rival or surpass anything we've seen in the corporate sector, practices that are applicable outside of health care. As part of our research design, we interviewed approximately 1000 Mayo employees and patients, observed hundreds of doctor-patient visits at two of Mayo's three major campuses (Scottsdale, Arizona, and Rochester, Minnesota; the third is in Jacksonville, Florida), and stayed in the hospitals overnight as patients. In almost every experience and interaction, in subtle and not-so-subtle ways, we got the message that at Mayo Clinic, the patient comes first (Box 132-1).

Many businesses sell products that are intangible or technically complex—financial and legal services, software, and auto repair are just a few—and their customers naturally look for clues that can help explain what they don't understand or see. In fact, in just about any organization, the clues emitted by people and things (humanics and mechanics, respectively, as introduced to the management literature by Lewis Carbone and Stephan Haeckel) tell a story to customers or potential customers. The question for managers is whether the clues tell the intended story. Mayo Clinic's effectiveness at designing and managing evidence offers a lesson other service organizations would do well to heed: Understand the story you want to tell, and then make sure your people and your facilities provide evidence of that story to customers, day in and day out.

CLUES IN PEOPLE

When we interviewed Mayo patients, we were struck by how consistently they described their care as being organized around their needs rather than the doctors' schedules, the hospital's processes, or any other factor related to Mayo's internal operations. The actions of Mayo staff members, according to what we were told, clearly signal the patient-first focus. Here are representative remarks: "My doctor calls me at home to check on how I am doing. She wants to work with what is best for my schedule." "When I had a colonoscopy, [my doctor] waited to tell me personally that I had a polyp because he remembered that my husband died from small bowel cancer, and he knew that I would be worried I may have the same thing." "My oncologist is... the kindest man I have ever met. He related some of his personal life to me. I was more than my problem to him. He related to me as a person."

Such glowing praise isn't limited just to the doctors and nurses. One patient, for example, was "amazed" at how well the people at the registration desk handle requests: "People who come up to the desk are nervous, or angry, or abusive. These ladies at the registration desk just keep their cool. I wish they could train the customer service reps in department stores."

It's no accident that employees communicate a strong, consistent message to patients. Mayo explicitly and systematically hires people who genuinely embrace the organization's values. The clinic emphasizes the importance of those values through training and ongoing reinforcement in the workplace, a practice that began in the very early part of the twentieth century, when Drs. William and Charles Mayo started the organization. Indeed, William Mayo's credo—"The best interest of the patient is the only interest to be considered"—guides hiring decisions to this day.

It's difficult to get a job at Mayo Clinic because of intellect or technical skill alone. Demonstrated task competence is essential, of course, but the hiring managers are also trained in behavioral interview techniques, and they are expected to use them to elicit an applicant's values. A candidate may be asked, for instance, to discuss a time when he set a development goal for himself and how he met that goal or to describe the proudest moment in his career or even the moment he found

*Used by permission from *Harvard Business Review*, Feb 2003.

Box • 132-1

The Research

Mayo Clinic has three major campuses (Rochester, MN; Scottsdale, AZ; and Jacksonville, FL); primary care clinics in more than 60 communities; 21 owned or managed hospitals; more than 2800 staff physicians; medical technology, medical publishing, laboratory, and health care benefits-administration businesses; and revenue in excess of $4 billion. It serves more than 500,000 individual patients annually.

For this article, we conducted the largest service study ever done at Mayo Clinic. During a 5-month period, we interviewed approximately 1000 Mayo patients, physicians, nurses, allied health staff, and managers at the original Rochester campus and the Scottsdale campus. We also collected data as participant observers, checking into the hospitals as patients, observing surgeries in the operating room and more than 250 doctor-patient interactions in the examination room, making hospital rounds, and flying on the Mayo One emergency rescue helicopter service. We formally studied service delivery in 14 medical specialties selected to provide a cross-section of the practice: cardiac surgery, cardiology, dermatology, emergency medicine, endocrinology, family medicine, gastroenterology, medical and radiation oncology, neurology, orthopedic surgery, preventive medicine, thoracic surgery, transplant surgery, and urology. Mayo Clinic gave us complete access to study its service culture and processes, and the Mayo Clinic Institutional Review Board approved our study.

most frustrating. Interviewers avoid discussing hypothetical situations that allow candidates to figure out the "right" answer and instead probe for specific details that reflect true experiences and perspectives. For example, a candidate who identifies making a difference in a patient's life as his or her proudest moment may be more attuned to Mayo's values than one who mentions achieving a career milestone.

The people who make the cut—indeed, the people who are drawn to Mayo in the first place—are those who take pride in having the freedom to put patients first. We heard many doctors and nurses say that they appreciate being allowed to practice medicine as they feel it should be practiced. Those feelings of pride and the alignment of employees' attitudes with Mayo's values contribute to lower staff turnover across the board. Annual turnover among hospital nurses is only 4% at Mayo versus 20% for the industry as a whole—continuity that, in turn, helps boost the quality of care.

Once hired, all new employees go through an orientation process specifically designed to reinforce the patient-first mentality. The program for nonphysician employees—whether janitors, accountants, or nurses—is designed to help all staff people understand how their jobs affect patients' care and well-being. If housekeeping fails to maintain sanitary conditions, for instance, a patient's health may be compromised no matter how excellent the medical care received. Storytelling figures heavily in these programs, with the emphasis on how employees have used Mayo values to make difficult decisions on patients' behalf.

Storytelling continues in the workplace because, once people are away from the classroom, the idea of putting the patient first can seem distant and sometimes even unrealistic, given the stress and unpredictability of day-to-day work. Consider, for instance, one story featured at several orientation sessions and widely disseminated throughout the organization. A critically ill patient was admitted to the Scottsdale hospital shortly before her daughter was to be married, and she was unlikely to live to see the wedding. The bride told the hospital chaplain how much she wanted her mother to participate in the ceremony, and he conveyed this to the critical care manager. Within hours, the hospital atrium was transformed for the wedding service, complete with flowers, balloons, and confetti. Staff members provided a cake, and nurses arranged the patient's hair and makeup, dressed her, and wheeled her bed to the atrium. A volunteer played the piano and the chaplain performed the service. On every floor, hospital staff and visiting family and friends ringed the atrium balconies, "like angels from above," to quote the bride. The wedding scene provided not only evidence of caring to the patient and her family but also a strong reminder to the staff that the patient's needs come first. They got the message: We heard the story multiple times in our interviews with employees.

Another story was initially told at a leadership development program for rising Mayo administrators. In one session, Mayo staff members shared experiences that showed how the service philosophy affects care. An emergency room physician told of a patient who walked into the ER with severe shortness of breath. When told she had a bacterial infection requiring immediate surgery, the woman expressed concern about her sick dog, which was in her illegally parked truck. The attending nurse assured her that he would move the truck and take care of the dog, but when he walked outside, what he saw was not a pickup but a semi, which he wasn't licensed to drive. He was about to have it towed—for $700—when he stopped to consider ways he might save the patient the expense. In the end, the nurse took it upon himself to obtain permission to park the truck at a nearby shopping center for a few days and find a fellow nurse—a former trucker—to drive the truck there. He took the dog to a veterinarian and then cared for it in his own home while the patient recovered. When asked what prompted him to do this, the nurse replied, "At Mayo Clinic, the patient's needs come first."

Various events celebrating exceptional service on behalf of patients further reinforce employees' commitments. The Rochester campus hosts an annual Heritage Week, celebrating the clinic's history and values and reinforcing their relevance to Mayo's work today through historical presentations and displays, lectures, ecumenical and liturgical services, concerts, and social events. Employees, retirees, volunteers, patients, visitors, and members of the community are invited. Mayo Rochester also recognizes exceptional service with its quarterly campus-wide Karis Award (Karis is Greek for caring). All staff members are eligible and can be nominated by a coworker, patient, or family member; the identity of the nominator is not disclosed, which removes political considerations from the process. One 1999 winner, a world-renowned colorectal surgeon with numerous scientific recognitions, told his tablemates at the award luncheon that he cherished the Karis more than any other award he's received, calling it, "The only award I have for just being a really good doctor."

CLUES IN COLLABORATION

In 1910, William Mayo said, "In order that the sick may have the benefit of advancing knowledge, union of forces is necessary... It has become necessary to develop medicine as a cooperative science." Dr. Mayo's vision profoundly influences the organization's approach to care. Patients experience the Mayo Clinic as a team of experts who are focused on patients' needs above all else. They perceive an integrated, coordinated response to their medical conditions and, often, to related

psychological, social, spiritual, and financial needs. Elsewhere, doctors may be reluctant to admit to any gaps in their knowledge. Not so at Mayo. Mayo Clinic assembles the expertise and resources needed to solve the patient's problem. If a Mayo doctor can't answer a question and needs to bring someone else onto a team, she freely admits it to the patient. The doctors meet with one another and with the patient—visible evidence that they are collaborating to solve the patient's problem rather than passing it from one doctor to another. One patient we interviewed expressed a common sentiment when he said, "I have a lot of problems, and I like that I can go to Mayo and be seen by a team of specialists who work together to see the big picture." Collaboration is particularly important because the institution's reputation has become so well known that patients often come in looking for a miracle. Many have consulted several other doctors and consider Mayo the last resort, so the physicians there regularly see patients with complex problems and high expectations, a situation that puts the doctors under extra pressure to make the right diagnoses and treatment decisions and not miss often subtle medical distinctions.

Mayo Clinic encourages this type of collaboration through various organizational incentives. All physicians are salaried, so they don't lose income by referring patients to colleagues, and the organization explicitly shuns the star system, downplaying individual accomplishments in favor of organizational achievements. In the words of one cardiovascular surgeon, "By not having our economics tied to our cases, we are free to do what comes naturally... to help one another." Doctors who are focused on maximizing their incomes or who want to be the star of the show don't work for Mayo Clinic. A surgeon specializing in the liver explained, "The kind of people who are attracted to work for Mayo Clinic have a value system that places the care of those in need over personal issues such as salary, prestige, and power. There is little room for turf battles. It is never a problem to add [a new case] on to the workload of the day. It's simply the best thing to do for the patient."

Mayo also supports teamwork with its use of technology. Staff members partner via a combination of face-to-face and remote collaboration using a sophisticated internal paging, telephone, and videoconferencing system that connects people quickly and easily. Remote teamwork through voice or virtual interaction is just as common as in-person teamwork at hallway or bedside consults. One physician told us, "I never feel I am in a room by myself, even when I am." Recently, for example, a Mayo ENT specialist in Scottsdale called together 20 doctors from all three campuses to discuss a difficult case—a patient with skin cancer at risk for metastasis and, owing to the necessary surgery, nerve injury and disfigurement. The team, assembled in a day, met by videoconference for an hour and a half and reached a consensus for a course of treatment, including specific recommendations on how aggressively to sample the patient's lymph nodes and how best to reconstruct the surgical wound.

Mayo's electronic medical record (EMR) improves the clinic's ability to present a seamless, collaborative organization and manage the evidence that patients see. The EMR provides an up-to-date narrative of the patient's symptoms, diagnoses, test results, treatment plans, procedures, and other related data, connecting in- and outpatient information and communicating across disciplines in outpatient practices. This connection is critical to patient-first decisions in ways that patients don't necessarily see. One emergency room physician said it had prevented her from intubating a patient who had asked not to be resuscitated, for instance, and others told of the importance of the EMR in managing patient medications to avoid allergic reactions or dangerous drug interactions. However, patients also notice and appreciate the single source of information, as we heard repeatedly in our research. One patient told us, "On my last visit, the doctor pulled up all my test scores from the past five years on a computer and showed me the trends, and we discussed what to do. I thought that was excellent." In short, patients told us in numerous interviews that Mayo's team service gave them a sense that the organization was coordinating its resources to provide the best possible care, with the patients' needs foremost in employees' minds.

CLUES IN TANGIBLES

In health care, the visual clues about an institution's core values and the quality of care are particularly difficult to separate from the actual service because people spend significant time in the facility—some stay for days or even weeks. The physical environment is also connected to medical outcomes: The potential of design to promote healing through stress reduction has been documented in dozens of studies. For these reasons, more medical institutions are making an effort to create open, welcoming spaces with soft, natural light. Mayo Clinic goes further with its design philosophy, which is perhaps as well honed and articulated as that of any major service provider in America, and pays strict attention to how every detail affects the patient's experience.

From public spaces to exam rooms to laboratories, Mayo facilities have been designed explicitly to relieve stress, offer a place of refuge, create positive distractions, convey caring and respect, symbolize competence, minimize the impression of crowding, facilitate way finding, and accommodate families. In the words of the architect who designed Mayo Rochester's new 20-story Gonda Building, "I would like the patients to feel a little better before they see their doctors." A well-designed physical environment has a positive impact on employees as well, reducing physical and emotional stress—which is of value not only to employees but also to patients because visible employee stress sends negative signals. In our interviews, patients commented on the lack of apparent stress; one said, "It did not seem like a doctor's office when we went to Mayo. There was no tension."

The Gonda Building has spectacular wide-open spaces, a marble stairwell and floor, glasswork sculpture suspended above, and a multistory wall of windows looking onto a garden. The building's soaring lobby houses a cancer education center because, as one administrator put it, "The more visible the center, the more you remove the stigma of having cancer." The lobby of Mayo Clinic Hospital in Scottsdale is also visually stunning, with its atrium, indoor waterfall, stonework, and wall of windows overlooking a mountain range.

Mayo doesn't limit its facilities' clue management to public spaces. After all, the scary stuff in a medical facility happens elsewhere—in the catheterization lab, in diagnostic imaging, in the hospital room. At Mayo hospitals, staff members write the names of attending doctors and nurses on a white board in every patient's room, which helps stressed-out patients and families keep track of multiple caregivers and serves as a visible clue that there's a real person they can talk with about any concerns. In-hospital showers, microwave ovens, and chairs that convert to beds are available for family members because, as one staff member explained, "People don't come to the hospital alone." The pediatric section of Mayo's St. Mary's Hospital in Rochester transformed artwork by local schoolchildren into a colorful array of wall and ceiling tiles. The resuscitation equipment in pediatric examination rooms is hidden behind a large picture (which slides out of the way when the equipment is needed). While the hospital was under construction at the Scottsdale campus, officials arranged to have an automobile lifted into the building so

physical rehabilitation patients would be able to practice getting in and out of a car in the privacy of a hospital.

Environmental clues in the outpatient setting are orchestrated just as carefully. Mayo Clinic buildings include quiet, darkened private areas where patients can rest between appointments. Public spaces are purposely made softer with natural light, color, artwork, piano music, and the sights and sounds of fountains. In examination rooms, the physician's desk is adjacent to a sofa large enough for the patient and family members, a design that removes the desk as a barrier between doctors and their patients.

Mayo also understands that the way employees present themselves sends a signal to patients. Patients don't encounter doctors in casual attire or white coats. Instead, the more than 2800 staff physicians wear business attire, unless they are in surgical scrubs, to convey professionalism and expertise. It's a dress code that some outside Mayo have called "pretentious"; yet we'd argue that it's no more pretentious than, say, the dress code for airline pilots. Airline passengers don't want to see their pilot in a polo shirt, and patients feel the same way about doctors. In effect, Mayo Clinic doctors—just like service workers in many other industries—work in a uniform; it is a visible clue that communicates respect to patients and their families.

Such attention to visual clues extends to the minutest detail. Mayo Rochester employee Mary Ann Morris, the administrator of General Service and the Office of Patient Affairs, often tells a story about her early days with the organization. She was working in a laboratory—a job that required her to wear a white uniform and white shoes—and after a hectic morning getting her two small children to school, she arrived at work to find her supervisor staring at her shoes. The supervisor had noticed that the laces were dirty where they threaded through the eyelets of Morris's shoes and asked Morris to clean them. Offended, Morris said that she worked in a laboratory, not with patients, so why should it matter? Her boss replied that Morris had contact with patients in ways she didn't realize—going out on the street wearing her Mayo name tag, for instance, or passing patients and their families as she walked through the halls—and that she couldn't represent Mayo Clinic with dirty shoelaces. "Though I was initially offended, I realized over time [that] everything I do, down to my shoelaces, represents my commitment to our patients and visitors," Morris told us. "Twenty-eight years later, I still use the dirty shoelace story to set the standard for the service level I aspire to for myself and my coworkers."

A dirty shoelace might seem minor, given the important work of caring for the ill; but a shoelace is something a customer can see, whereas medical expertise and technical ability are not. It's a piece of evidence—a small but integral part of the story Mayo tells to its customers. We aren't arguing that "patients first" is the only story a medical institution might choose to tell patients. A hospital might instead choose to signal, "We hire the smartest doctors," and manage the evidence with prominent displays of academic credentials and awards, a lecture series, and heavy publicity about new research. What Mayo Clinic has done better than just about any organization we can think of, however, is clearly identify a simple, consistent message and then manage the evidence—the buildings, the approach to care, and yes, even the shoelaces—to support that message, day in and day out.

CHAPTER 133

Rational Use of Diagnostic Tests

Andrew S. Peregrine

Diagnostic tests are used routinely in veterinary practice for screening animals and for identification of a specific target disorder in a diseased animal. However, very few diagnostic tests are accurate all the time. Thus not all animals that test positive necessarily have the target disorder under investigation. To correctly interpret diagnostic data, information is required on (1) a diagnostic test's *sensitivity*, the proportion of animals with the target disorder that test positive; (2) the test's *specificity*, the proportion of animals without the target disorder that test negative; and (3) the prevalence of the target disorder in animals similar to the one you are testing, or the probability that the animal has the target disorder before the test is run. Without this information, interpretation of diagnostic data is not possible.

Because diagnostic tests for heartworm *(Dirofilaria immitis)* infection in dogs are used commonly by veterinary practitioners, the following text describes how sensitivity, specificity, and prevalence estimates should be used to interpret data generated by these tests. The principles described apply to all diagnostic tests, including the clinical history and physical examination.

Heartworm antigen tests are the most common type of diagnostic method used to examine dogs for heartworm infection and typically have a sensitivity and specificity of approximately 80% and 98%, respectively.[1,2] Table 133-1 summarizes data from 1000 dogs when examined with such a test. Since the prevalence of heartworm infection in this population of animals is 30%, the total number of dogs infected with heartworm is 300. Because the antigen test's sensitivity is 80%, 240 (0.80×300) of the 300 infected dogs will test positive (cell *a*). The remaining 60 (300-240) infected dogs will test negative (cell *c*). Animals in cell *a* are therefore *true-positives*, whereas those in cell *c* are *false-negatives*. In light of the test's specificity of 98%, 686 (0.98×700) of the 700 uninfected dogs will test negative (cell *d*). The remaining 14 dogs (700-686) will erroneously test positive (cell *b*). Dogs in cell *d* are therefore *true-negatives*, whereas those in cell *b* are *false-positives*. In summary, the test has classified correctly dogs in cells *a* and *d* (*true-positives* and *true-negatives*) but has classified incorrectly dogs in cells *b* and *c* (*false-positives* and *false-negatives*).[3,4]

A sensitivity of 100% for the heartworm antigen test would rule out heartworm infection in all dogs that test negative. Likewise, if the test had a specificity of 100% all dogs that test positive could be diagnosed with heartworm.[3] However, because both parameters are less than 100%, some

Table • 133-1

Performance of a Heartworm Antigen Test* When Applied to a Dog Population with a Prevalence of Heartworm Infection of 30%

		Heartworm infection			
		Present	Absent	Total	
Heartworm antigen test	Positive	a 240	b 14	$a+b$ 254	Positive - predictive value $=\frac{a}{a+b}=\frac{240}{254}=94.5\%$
	Negative	c 60	d 686	$c+d$ 746	Negative - predictive value $=\frac{d}{c+d}=\frac{686}{746}=92.0\%$
	Total	$a+c$ 300	$b+d$ 700	$a+b+c+d$ 1000	Prevalence $=\frac{a+c}{a+b+c+d}=\frac{300}{1000}=30\%$
		Sensitivity $=\frac{a}{a+c}$ $=\frac{240}{300}=80\%$	Specificity $=\frac{d}{b+d}$ $=\frac{686}{700}=98\%$		

*Sensitivity = 80%, specificity = 98%.

animals will be misclassified. *Predictive values* therefore need to be calculated. These indicate the likelihood that a test result has correctly classified the heartworm status of an animal. The *positive-predictive value* indicates the proportion of all animals that test positive for heartworm (cells $a + b$) that are truly infected with heartworm (cell a) and in Table 133-1 is 94.5%. Thus when one of the described dogs tests positive for heartworm antigen, the likelihood that the animal is truly infected with heartworm is 94.5%. Similarly, the *negative-predictive value* indicates the proportion of all animals that test negative for heartworm antigen (cells $c + d$) that are truly not infected with heartworm (cell d). In Table 133-1 this value is 92.0%. In other words, if a negative test result is obtained, it is 92% certain that the dog is not infected with heartworm.

Unlike sensitivity and specificity, *predictive values* are strongly influenced by the true prevalence of the target disorder and therefore are not stable characteristics for a test.[4,5] To illustrate this point, Table 133-2 describes the performance of the aforementioned heartworm antigen test when applied to a population of dogs with a prevalence of heartworm infection of 0.5%. Although the sensitivity and specificity of the test are unaltered, the *positive-predictive value* has dropped to 16.7%. Thus only one in approximately every five positive test results is a *true-positive*. Therefore in this situation, heartworm infection should not be diagnosed solely on the basis of one positive antigen test (unlike the situation in Table 133-1). Additional diagnostic information is required to determine whether the positive result is a *true-* or *false-positive*. In contrast to the *positive-predictive value*, the antigen test's *negative-predictive value* of 99.9% (see Table 133-2) is higher than the situation described in Table 133-1. A negative antigen test result can therefore be used to rule out heartworm infection with a high level of certainty when applied to dogs with a prevalence of heartworm infection of 0.5%.

An understanding of the impact of prevalence on predictive values is of fundamental importance in interpretation of diagnostic data. Table 133-3 indicates how the *positive-* and *negative-predictive values* for the heartworm antigen test alter as the prevalence of heartworm infection increases from 0.02% to 50%. The sensitivity and specificity remain unaltered. Over this range the *positive-predictive value* increases from 0.8% to 97.6%, whereas the *negative-predictive value* decreases from 100% to 83.1%. Thus as the prevalence increases, the *positive-predictive value* increases. By contrast, the *negative-predictive value* decreases.[3] At a prevalence of infection of 10% or less the *positive-predictive value* is less than 90%. An additional diagnostic test(s) should therefore be used to confirm or refute a positive test result when obtained from

Table 133-2

Performance of the Heartworm Antigen Test* Described in Table 133-1 When Applied to a Dog Population With a Prevalence of Heartworm Infection of 0.5%

		Heartworm infection			
		Present	Absent	Total	
Heartworm antigen test	Positive	*a* 4	*b* 20	*a+b* 24	Positive - predictive value $= \frac{4}{24} = 16.7\%$
	Negative	*c* 1	*d* 975	*c+d* 976	Negative - predictive value $= \frac{975}{976} = 99.9\%$
	Total	*a+c* 5	*b+d* 995	*a+b+c+d* 1000	Prevalence $= \frac{5}{1000} = 0.5\%$

*Sensitivity = 80%, specificity = 98%.

such populations of dogs. Finally, in light of the effect of prevalence on predictive values (particularly *positive-predictive values*)[3,5], it is important to appreciate that the prevalence of heartworm infection is dependent on both the geographic location of an animal and on whether or not an animal has been on heartworm-preventive medication. Thus in every veterinary practice, routine screening of healthy dogs with heartworm antigen tests is actually carried out on two distinct populations of animals: those that were not on preventive medication the previous year and those that were. Although the prevalence of heartworm infection in the former dogs may be as high as 45%, the prevalence in the latter is typically less than 1%, even in high-prevalence areas. Interpretation of an antigen test result is therefore dependent on which dog population is being examined. Both estimates can be obtained from dogs examined at a practice over the previous 1 to 2 years.

Table 133-3

Predictive Values for a Typical Heartworm Antigen Test* When Applied to Dog Populations With Various Prevalences of Heartworm Infection

PREVALENCE OF INFECTION†	POSITIVE-PREDICTIVE VALUE‡	NEGATIVE-PREDICTIVE VALUE	1-(NEGATIVE-PREDICTIVE VALUE)§
0.02%	0.8%	100%	0%
0.2%	7.4%	100%	0%
0.5%	16.7%	99.9%	0.1%
1.0%	28.8%	99.8%	0.2%
2.0%	44.9%	99.6%	0.4%
5.0%	67.8%	98.9%	1.1%
10.0%	81.6%	97.8%	2.2%
30.0%	94.5%	92.0%	8.0%
50.0%	97.6%	83.1%	16.9%

*Sensitivity = 80%, specificity = 98%.
†Pre-test probability of infection.
‡Probability of infection following a positive test.
§Probability of infection following a negative test.

If a diagnostic test is to be useful, it must have the potential to have a major effect on diagnosis, prognosis, or therapeutic decisions.[6] Thus, if the probability that an animal has a target disorder after application of a test is not significantly different from the probability prior to using the test (*the pre-test probability*), the diagnostic method does not have clinical utility. The *pre-test probability of the target disorder* is the proportion of animals with the target disorder among all animals tested and is the same as the true prevalence. In the case of the heartworm scenario described at a prevalence of 30% (see Tables 133-1 and 133-3) the *pre-test probability* of heartworm infection is 30%. Since the *probability of infection following a positive test* is indicated by the *positive-predictive value*, the probability of infection at this prevalence for a test-positive animal is 94.5%. The positive result has therefore increased the certainty of infection by 64.5%. To what extent does a negative test rule out heartworm infection? The *probability of infection following a negative test* indicates the proportion of animals testing negative that are infected with heartworm and is calculated as 1-(*negative-predictive value*). At a prevalence of heartworm infection of 30% a negative antigen test decreases the probability of infection to 8% (see Table 133-3). Thus when the *pre-test probability of infection* is 30%, both positive and negative tests provide useful diagnostic information. In contrast, when the *pre-test probability of heartworm infection* is 0.5%, the probability of infection following a positive antigen test is 16.7%, whereas the probability of infection following a negative test is 0.1% (see Table 133-3). A positive test has therefore increased the probability of infection by 16.2% (from 0.5% to 16.7%), whereas a negative test has decreased the probability of infection by 0.4% (from 0.5% to 0.1%). Very little information has therefore been learned from both positive and negative test results in this situation.[3]

CHAPTER 134

Principles of Drug Therapy

Dawn M. Boothe

DOSE-RESPONSE RELATIONSHIP

The intent of drug therapy is to induce a desired pharmacologic response for a sufficiently long period of time and avoid adverse drug events. Adverse events fall into two categories. Type A ("augmented"; Type I) generally are dose or duration dependent and result from plasma drug concentrations (PDC) that either are below (therapeutic failure) or exceed the maximum therapeutic range. As such, Type A events are largely predictable and potentially unavoidable if the clinician is sufficiently familiar with the drug and the patient.

DETERMINANTS OF DRUG DISPOSITION

Drug Movement

After administration of a fixed dose of a drug, several dynamic drug movements, largely dependent on passive diffusion, act in concert to determine PDC across time (Figure 134-1). The major movements include absorption from the site of administration to systemic circulation, defined as the major vessels and well-perfused organs; distribution of the drug from systemic circulation to tissues (target and non-target) and back again; and elimination of the drug from the body, accomplished by metabolism and excretion.

Plasma Drug Concentration Versus Time Curve: Clinical Pharmacokinetics

Pharmacokinetics scientifically (mathematically) describe the relationship of drug concentrations in a tissue across time such that dosing regimens and drug response can be predicted in animals. Because tissue samples cannot be collected easily, drug is most often measured in plasma. The four dynamic drug movements that affect PDC time most commonly follow first order, that is, a constant fraction rather than a constant amount of drug moves per unit time. As such, log drug concentrations are plotted across time (Figure 134-2, *A* and *B*). When the data is fit to the best line (based on sum of residuals), an equation is generated that allows prediction of drug behavior in a patient (or sample population). If the data can be accurately described by a single slope (as can occur only with intravenous [IV] administration [see Figure 134-2, *A*]), one drug movement (irreversible elimination) causes the change in PDC and the drug is described as following a one compartment (i.e., one component) open (i.e., the drug leaves the system) model. The slope of the PDC versus time curve describes the rate of elimination (k_{el}) of the drug and determines the time for 50% of the drug to be irreversibly eliminated from the body or the *elimination half-life*. The amount of tissue to which a drug is distributed is estimated by the volume of distribution (V_d), a theoretical and mathematically derived parameter that directly and inversely influences PDC after administration of a specific dose (see Figure 134-2). Calculation of V_d considers that concentrations of the drug occur throughout the body at the same concentration as that measured in the plasma. Clearance (volume/time) describes the fraction of the V_d from which drug is irreversibly eliminated and is calculated from V_d and k_{el}:

$$Cl = V_d \times k_{el}$$

Few drugs behave as a one compartment open model. If multiple drug movements influence the PDC (as occurs with any drug undergoing absorption from the site of administration; see Figure 134-2, *B*), two or more slopes may be necessary to describe the data, with each slope being influenced by one or more drug movements. Generally, computer-assisted linear regression "strips" each slope from the curve before the data is best fit to the multiple components. For multicompartment

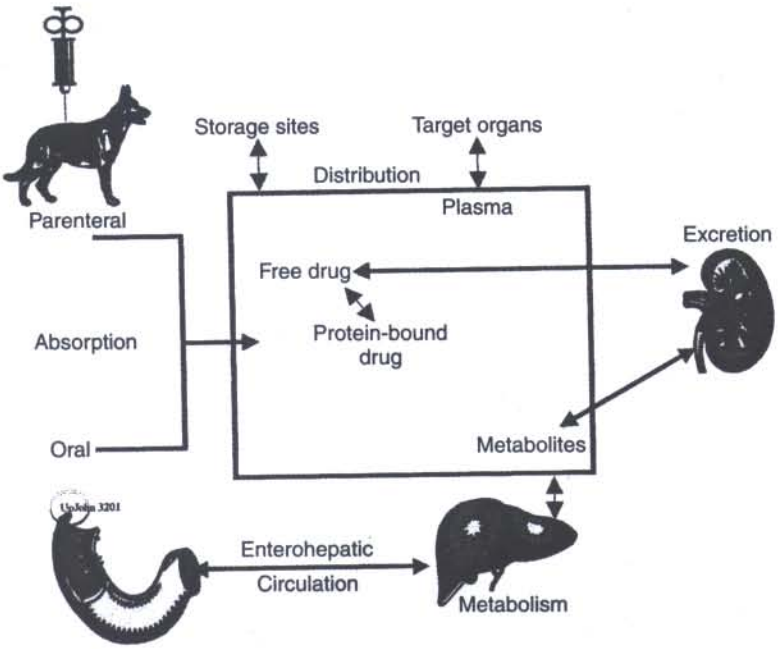

Figure 134-1 The determinants of plasma drug concentration act in concert following administration of a fixed dosing regimen. Each determinant can be influenced by patient (e.g., species, age, gender), pharmacologic (i.e., drug interactions), or disease factors.

open models, each component is described by a slope or rate (ki) and y intercept PDC (e.g., A, B) (see Figure 134-2, Plot B). The first component of the curve is generally considered to represent drug distribution (slope = α) and the terminal (in this case, second) component elimination (e.g., k_{el}, or β, γ, depending on the number of components that describe the curve). The distribution *half-life*, calculated from α, is the time necessary for 50% of drug to be distributed. The elimination half-life is determined from the terminal component of the curve. Two V_d can be calculated, which represent either the central or peripheral compartments, respectively (see Figure 134-2, Plot B). Oral administration results in at least

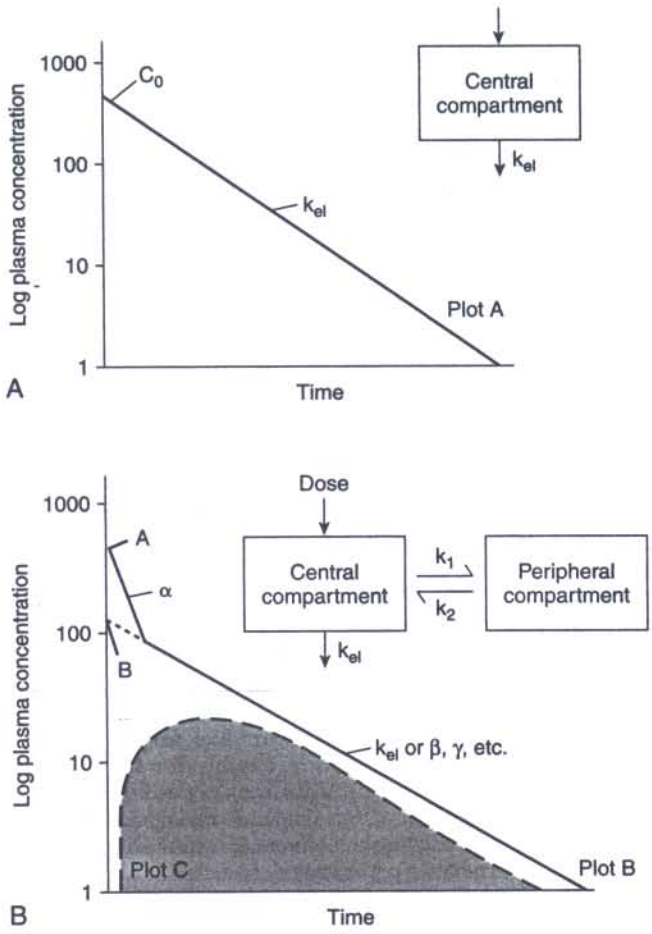

Figure 134-2 Log plasma drug concentration (PDC) versus time curves is subjected to linear regression. Following intravenous (IV) administration, a drug that fits a one-compartment open model will plot as a straight line. The equation $y = mx + b$ when plotted semilogarithmically becomes $C = C_o e^{-kt}$ where C is the predicted drug concentration (mass/volume) at any time, *t*, following drug administration, C_o is the concentration of drug at time *0*, which is extrapolated back from the first data point, and *k* is the elimination rate constant ($time^{-1}$). The rate also can be calculated from two data points (i.e., peak and trough samples collected as part of therapeutic drug monitoring (*inset*, Plot B). Distribution for A is either instantaneous or does not occur. The V_d (volume/mass) is calculated: $V_d = Dose/C_o$. For drugs distributed into peripheral tissues, at least two components are present (Plot B). PDC decline in the first phase due to both distribution into tissues and elimination. Once a distribution equilibrium has been reached, PDC decline only due to elimination (second component). Linear regression yields the equation for a two compartment open model: $C = Ae^{-\alpha t} + Be^{-\beta t}$. The slope ($\alpha$) is the distribution rate constant whereas the slope of the second (terminal) component is the elimination rate constant (β or k_{el}). The V_d of the central compartment for such a drug is calculated from PDC extrapolated to the y intercept from the first component prior to distribution (A) and the V_d of the peripheral compartment from the y intercept of the second component (B, after distribution equilibrium is reached). For oral administration (Plot C), absorption generally also follows first order, and the general equation becomes $C = Be^{-\alpha t} - Ae^{-kat}$ (the absorption component is subtracted from the remainder of the curve). The absorption rate constant (k_a) can be derived from the upswing of the curve, but only after the elimination component of the curve is stripped. Generally, the distribution phase of non-IV doses is masked by the absorptive phase. Bioavailability *(F)* of the drug would be determined from the ratio of area under the curve measured from data collected after administration of the extravascular dose *(dotted line)* and the IV dose. The AUC for each route must be adjusted for any dose differences: $F = AUC_{oral} \times Dose_{oral}/AUC_{IV} \times Dose_{IV}$.

a two component model, with input generally also following first order input (see Figure 134-2, Plot C). The *absorption half-life* derived from the slope of the upswing of the oral PDC curve (K_a) is the time necessary for 50% of a drug to be absorbed.

The dose of drugs not administered IV is based on the *bioavailability*, or the percent of administered drug that reaches systemic circulation *(F)*. Bioavailability is calculated by comparison of the area under the PDC versus time curve *(AUC)* generated from data collected following administration both IV (defined as 100% bioavailable) and the alternative route being studied (Figure 134-2, C). If the AUC for both curves are equal following adjustment for dose differences, bioavailability is 100% (F = 1.0). However, the pharmacologic response to a drug may vary even if bioavailabilities are equal. A drug whose rate of absorption is slower than another may be completely absorbed (i.e., bioavailability is 100%), but PDC may not reach the same magnitude or peak when in a different preparation.

Subjecting PDC across time may force the data to fit a model that is not appropriate. Non-compartmental (model independent) analysis describes drug behavior based on statistical moments, area under the time versus concentration curve (AUC), and area under the moment curve, which are generated from computer analysis. Elimination half-life is based on the slope of the terminal component of the curve. However, a comparable parameter, mean residence time (MRT), which describes the time needed for 63% of an IV dose to be eliminated, is more physiologically relevant.

Mechanisms of Drug Movement

Each drug movement is affected by a number of physiologic factors, the most important being the rate and extent of passive diffusion. Lipid solubility, molecular weight, and drug pK_a are major determinants of passive diffusion that reflect the chemical structure of the drug and thus cannot be modified. The concentration gradient of diffusible drug across the site of drug movement is the single most important determinant of passive drug diffusion; thus passive drug movement is most simply increased by increasing drug dose. However, the amount of diffusible drug can be influenced by many factors, particularly dissolution and ionization. In its ionized form, a drug cannot traverse lipid membranes and may be "trapped" in the environment. A weakly acidic drug is generally ionized when surrounded by an environmental pH that is greater than its pK_a (i.e., a basic environment) or, if a weak base, less than its pK_a (i.e., an acidic environment). Thus orally administered aminoglycosides (pk_a 9 to 10) are ionized and trapped in the acidic environment of the gastrointestinal tract, whereas as weak acids, such as the betalactam antibiotics (e.g., amoxicillin or cephalothin) will be predominantly unionized and more likely to be well absorbed (if not destroyed by gastric acidity). Likewise, aminoglycosides are less effective in an acidic urine compared with an alkaline urine, although they will be more rapidly eliminated. Beta lactams, however, will be unionized in an acidic urine, and as such, they not only will penetrate bacteria more easily but they are more likely to be passively reabsorbed from the renal tubular lumen and hence "recycled" before being eliminated in the urine. Other host determinants of passive diffusion include thickness of the membrane to be traversed (i.e., edematous compared with normal tissues); surface area (e.g., small intestine versus stomach); and temperature.

Determinants of Drug Disposition

Absorption Both rate and extent of absorption from the gastrointestinal tract are influenced by a number of host factors, most of which affect passive diffusion. These include gastrointestinal pH, which favors absorption of weak acids; surface area, which favors absorption in the small intestine instead of the stomach; motility, which mixes the drug, thus increases the concentration of diffusible drug at the site of movement; permeability and thickness of the mucosal epithelium, which can be negatively or positively impacted by disease; and, less commonly, intestinal blood flow, which maintains the concentration gradient across the mucosal epithelium. The latter factor is important only for drugs capable of rapid transfer across the epithelium. Other factors such as the impact of acidity on product stability or the presence of p-glycoprotein in intestinal epithelial cells (e.g., for cyclosporine) can also affect gastrointestinal drug absorption. Bioavailability of an orally administered drug also is decreased if the drug is metabolized by intestinal epithelial cells (e.g., again cyclosporine) or microbes, or the liver. Hepatic metabolism can profoundly affect systemic delivery of an orally administered drug because absorption into the portal vein exposes the drug to the liver prior to systemic circulation. Drugs characterized by a high hepatic extraction ratio (>70%) are almost completely removed from the blood by hepatocytes during the first passage of blood through the liver (first-pass metabolism). Oral doses of such drugs must be increased despite good to excellent oral absorption if PDC are to be therapeutic. The effects of first-pass metabolism may be reduced if drug metabolites are also pharmacologically active (i.e., propranolol and diazepam).

Novel routes of drug administration may overcome the detrimental effects of first pass metabolism of some drugs. Examples include transdermal delivery such as patches, ointments, or gels; buccal patches and iontophoresis; aerosolization; and rectal administration. However, before a novel route is accepted as an effective method of drug delivery by the medical community, it must be scientifically established for the drug, as is exemplified by the use of transdermal gels for systemic delivery of drugs in cats, which have been proven effective following single-dose administration of several days.

Distribution Once a drug reaches systemic circulation, it must be distributed from the central (blood) compartment to the site of drug action in peripheral tissues and then back into the central compartment to be eliminated (see Figure 134-2). Because C_{max} (Figure 134-3) is not achieved in tissues until distribution has reached equilibrium, peak drug monitoring samples should not be collected immediately after dosing. The major factors that determine drug distribution include lipid solubility of the drug (its ability to penetrate cell membranes); concentration of diffusible drug (thus not bound to proteins or other tissue components), and regional (organ) blood flow. The lipid solubility of the drug influences the extent of protein binding as well as the extent of drug distribution, and thus V_d and dose. Although V_d is useful for determination of doses and extent of distribution, it cannot confirm where the drug has been distributed. However, lipid soluble drugs distribute to total body water. As such, they are characterized by a $V_d \geq 0.6$/kg. A V_d of this magnitude suggests that the drug is distributed to total body water because it can penetrate cell membranes, which might be an important consideration in selection of some drugs (e.g., antibiotics, drugs active in the central nervous system). In contrast, the distribution of water-soluble drugs is limited to extracellular fluid (ECF) and V_d for such drugs generally is 0.3 L/kg or less. If the V_d of a drug changes due to disease (or varies among species), the dose of drug necessary to get the same PDC must similarly change. For lipid soluble drugs. as weight increases, the V_d of the drug will proportionately change with weight and dosing on a mg/kg basis is appropriate. However, predicting the effect on water-soluble drug is more difficult. Pediatric patients are characterized by an ECF compartment that is proportionately greater than that in adults. Thus doses of water-soluble drugs should be higher for them

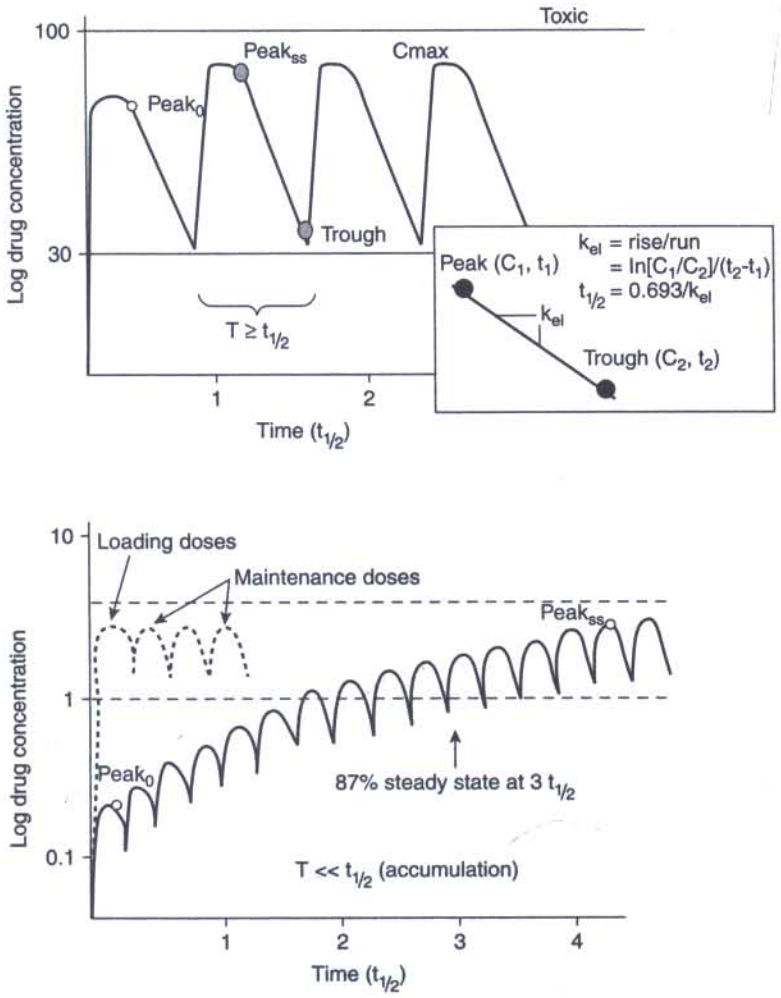

Figure 134-3 The goal of a fixed dosing regimen is to maintain PDC in the therapeutic range after multiple extravascular dosing. The therapeutic range of a drug is defined by a peak or maximum concentration (C_{max}) above which toxicity is more likely, and a trough or minimum concentration (C_{min}) below which therapeutic failure is more likely. A drug whose dosing interval is longer than its half-life *(A)* will be largely eliminated before the next dose is given. The fluctuation in PDC can be unacceptably large for such drugs. In contrast, a drug administered at an interval shorter than its half-life *(B)* will accumulate since most of the drug is still in the body by the next dose. At steady-state, which occurs at 3 to 5 drug half-lives, the fluctuation in drug concentrations during the dosing interval is small. For any drug, half-life can be determined from peak (C_{max}) and trough (C_{min}) P (*inset*, B). Since the PDC is plotted logarithmically, the equation for slope (rise over run) becomes: ln $[C_1/C_2]/t_2$-t_1. For example, if gentamicin samples collected at 2 hours and 12 hours after an IV dose were 10.5 and 2.0 µg/ml, the k_{el} for gentamicin in this animal would be 0.17 hr^{-1}, where C_{max} and C_{min} are the desired peak and trough concentrations, respectively. Since C1/C2 =2 at one $t_{1/2}$ (where t_2-t_1= $t_{1/2}$), $t_{1/2}$= 0.693/k (0.693 - natural log [Ln] of 2). For gentamicin in this example, the elimination half-life would be 0.693/0.17^{-1}hr or 4.2 hr. If a dosing interval is deemed inappropriate, a more appropriate interval (T_{max}) can be calculated: T_{max}= ln[C_{max}/C_{min}]k_{el}.

compared with adults. Diseases associated with fluid retention (ascites, edema) or intensive fluid therapy are likely to increase V_d of many water-soluble drugs (and thus decrease PDC), whereas obesity, dehydration, or weight loss is likely to decrease V_d and thus increase PDC of a water-soluble drug. Dosing based on body surface area (i.e., mg/m²) may also avoid increased risk of adverse events that occur in some patients due to differences in body size. This method of dosing also takes into account differences in excretion. However, this method may increase the risk of toxicity in very small animals (<10 kg).

Drug binding to proteins affects distribution. Plasma protein-binding renders a drug more water soluble, which facilitates movement in circulation. Weakly acidic, lipid-soluble drugs tend to bind to albumin, whereas basic drugs tend to bind to α_1 glycoproteins. Drugs also may bind to tissue proteins. However, the protein-bound drug cannot be distributed between plasma and tissues. Protein-bound drug is not pharmacologically active, cannot be renally excreted, and for many drugs, does not distribute into hepatocytes responsible for hepatic metabolism. Highly protein-bound (>80%) drugs are more likely to be involved in adverse drug events because displacement of only a small proportion of drug from the protein (i.e., due to competition with other protein-bound drugs, or hypoalbuminemia) can significantly increase the proportion of free, active drugs. For example, displacement of only 1% of a drug that is 99% protein-bound (e.g., nonsteroidal antiinflammatories) such that it becomes 98% bound doubles the concentration of pharmacologically active drug. However, increased renal and hepatic clearance of the unbound drug will increase such that PDC eventually return to normal as a new equilibrium is reached. Highly protein-bound drugs are characterized by a V_d of less than 5%, the volume of the plasma or blood central compartment. However, displacement from plasma proteins increases the V_d of the drug as free drug enters tissues. Protein-binding of drugs complicates extrapolation of dosing regimens among species because the proportion of bound drug often is not determined. Fortunately. the majority of drugs are not highly protein-bound.

Metabolism Irreversible drug elimination from the body is the final determinant of PDC. Most drugs are eliminated by hepatic metabolism and/or renal excretion. Lipid soluble drugs often require conversion to a water soluble form to facilitate renal elimination. Metabolism most commonly occurs in the liver in one or two phases. Phase I induces a chemical change that increases water solubility and renders the drug more susceptible to phase II metabolism. Reactions include oxidation, hydrolysis, or reduction and are mediated most commonly by cytochrome P450 (microsomal) enzymes. Phase I metabolites are often inactive (e.g., phenobarbital), but can be equally, more (i.e., a pro-drug, such as enalapril), or less active (e.g., diazepam) than the parent compound. Often, the drug becomes more toxic (e.g., acetaminophen). Multiple superfamilies of P450 enzymes exist and deficiencies or increases (e.g., drug induced, genetic) in one or more P450 enzymes are increasingly recognized for their role in selected

adverse drug events. Phase II is also referred to as *conjugation* because a large, water-soluble molecule is added to either the parent drug or phase I metabolite. Glucuronidation, a reaction in which the cat is deficient, is the most common phase II reaction. Addition of glutathione to a reactive metabolite is an important mechanism by which reactive metabolites can be scavenged before tissue damage occurs. Sulfonation and acetylation, the latter being a reaction in which the dog is deficient, are less common phase II reactions. With the exception of some acetylation reactions (e.g., procainamide), phase II metabolites are inactive. Metabolites are generally eliminated in the urine, or less commonly, in the bile. Drug metabolism also occurs in other tissues, including the kidney, lungs, skin, and intestines. Drug-induced toxicity in these organs may reflect their metabolic capacity.

Factors that can affect hepatic drug metabolism include the amount and activity of drug metabolizing enzymes, and if the drug is characterized by a high extraction ratio (>70%; "flow-limited" drug), hepatic blood flow. Changes in protein-binding of highly bound drugs can also affect the rate of hepatic metabolism of drugs characterized by a low (<70%: "capacity-limited" drug) extraction ratio. The rate of elimination of capacity-limited drugs is inversely proportional to their degree of protein binding. Disease, drug interactions, and species differences can have a profound impact on drug metabolism and thus duration of drug elimination. For example, drugs that induce (phenobarbital, rifampin) metabolism increase the clearance of other drugs metabolized by the liver and can cause therapeutic failure, or possibly increased toxicity (due to metabolite formation) with the other drug. Induction generally requires multiple days of therapy and reflects an increase in the synthesis of enzymes. In contrast, inhibition can occur immediately, often due to competition for the same enzymes. Inhibitors (e.g., chloramphenicol, cimetidine, ketoconazole) will prolong the half-life of other drugs and may result in drug toxicity. Inhibitors can be used therapeutically as is exemplified by the use of cimetidine to decrease the toxicity of acetaminophen or ketaconazole to prolong the half-life of cyclosporine.

Renal and Biliary Excretion *Renal* excretion is the most important route of drug elimination for both parent drugs and their metabolites. Host factors that determine renal excretion include glomerular blood flow, active tubular secretion, and tubular resorption, each of which is directly influenced by renal blood flow. The kidney is also capable of metabolizing some drugs, although this capacity is only occasionally of clinical importance.

Glomerular filtration is a passive process. Drugs enter the glomerulus by bulk flow, being excluded if too large (>60,000 MW), such as occurs if the drug is protein-bound. In contrast, active transport of drugs in the proximal tubules is very efficient, rapid, and independent of protein-binding. Separate transport proteins exist for acidic, basic, and neutral drugs. Transport is susceptible to competition among drugs, although drug interactions as a result of competition are not frequent and seldom clinically relevant. The prototypic example of competition is the use of probenecid to compete with and thus inhibit the renal excretion of expensive beta-lactam. Resorption of drugs from renal tubules into peritubular capillaries slows renal excretion and prolongs drug half-life. The extent to which a drug is reabsorbed depends upon its lipid solubility and its ionization. Weakly acidic drugs are more likely to be resorbed in acidic urine but are more likely to be trapped and excreted in alkaline urine. Changes in urinary pH (especially acidification) might be therapeutically altered to modify the rate of renal drug excretion. Because renally excreted drugs are concentrated in the kidney (urine), selection of antibiotics for treatment of bacterial cystitis (but not other urinary tract infections) based on minimum inhibitory concentrations (MIC) may markedly underestimate the efficacy of the drug because MIC generally are based on plasma, rather than urine, drug concentrations.

In contrast to renal excretion, biliary excretion is very slow and is much less clinically important. Drugs are eliminated in the bile by at least three active transport systems: one each for organic acids, bases, or neutral compounds. Characteristics that determine biliary excretion of drugs include chemical structure, polarity, and molecular weight (generally >600 MW); the latter is one of the major determinants. Drugs excreted in the bile are in greater contact with the intestine and its flora compared with other drugs and are thus more likely to cause adverse reactions in the gastrointestinal tract. Whereas a conjugated drug will not be resorbed from the intestinal tract, intestinal microbes can unconjugate drugs so that they are reabsorbed *(enterohepatic recirculation)*. The half-life and exposure of the drug to the intestinal tract is subsequently prolonged.

Elimination The combined effects of renal and biliary excretion, as well as other routes of elimination (i.e., pulmonary, sweat) irreversibly remove drug from the body. The elimination half-life of a drug is the time necessary for half the drug to be eliminated from the body and is derived from the terminal component of the PDC versus time curve. It is one of the most useful parameters for determining an appropriate dosing interval. At one drug elimination half-life, 50% of the dose has been eliminated; by 3 to 5 drug half-lives, 87 to 99% of the drug has been eliminated. Thus for a drug with a 4-hour half-life, approximately 12 to 20 hours must elapse before most of the drug has been eliminated. For drug intoxication, 1 to 2 elimination half-lives is generally sufficient for PDC to drop below the toxic range unless a massive overdose has occurred. An exception occurs if hepatic drug (or other) metabolizing enzymes become saturated. In such cases, elimination becomes zero order and half life is no longer an applicable parameter.

Plasma clearance (Cl) is the volume of plasma irreversibly cleared of the drug per unit time and represents the sum total of organ clearance. Unlike elimination (a rate), clearance is a volume per unit time. The volume of blood cleared per unit time by an organ is independent of PDC. The same volume of blood will be irreversibly cleared of drug by an organ regardless of how much drug is in the blood. If the drug is cleared exclusively by one organ (e.g., renal clearance of aminoglycosides or hepatic clearance of caffeine), then plasma clearance also represents clearance of the specific organ and can be used to evaluate the function of the organ. Although clearance is the physiologic activity responsible for drug elimination, it generally is not directly measured, but rather, is calculated from other parameters (see Figure 134-2). However, it can be determined only after IV administration. The impact of changes in clearance tends to be estimated by changes in elimination half-life. However, although half-life is the clinically useful estimate of how long a drug stays in the body, it is a "hybrid" parameter in that it is influenced by both distribution and clearance. The greater the volume of drug cleared per unit time, the shorter the drug half-life. However, the larger the V_d, the longer the half-life because the distributed drug cannot access the organs of clearance. Thus drug elimination half-life changes directly (and proportionately) with the volume of distribution of a drug but inversely (and proportionately) with the clearance of the drug. The clinical significance of these relationships might be exemplified in a patient that has become dehydrated as a result of uncompensated chronic renal disease. As tissue volume contracts with dehydration, the V_d decreases. Although PDC (and the risk of drug toxicity) increases, because the volume cleared per unit time does not change, and because more drug is in each milliliter of blood, the drug is actually eliminated more rapidly. If all else remains

normal, drug half-life will decrease. In the patient that is not dehydrated but suffers from significantly comprised renal function, renal clearance decreases and drug half-life thus also decreases. In the patient with both volume contraction due to dehydration and compromised renal function, the effects of the changes in clearance and volume of distribution balance one another. Drug elimination half-life may not change, even though renal function may be impaired. With successful volume replacement, half-life may increase unless renal function also improves.

FIXED DOSING REGIMENS

Dose

A fixed dosing regimen is comprised of a dose and interval. The dose necessary to achieve a specified target PDC (e.g., C_{max}) depends on the V_d:

$$\text{Dose} = [C_{max}][V_d]$$

The dose of drug must be increased or decreased proportionately with changes in V_d to achieve the same target PDC. The V_d of a drug is the sole determinant of PDC achieved after an IV dose is administered for drugs that do not accumulate (i.e., the dosing interval is sufficiently long that each dose is essentially eliminated before the next dose; see below). For drugs that do accumulate, the initial dose of the drug must also take into account the magnitude of accumulation, which is in turn dependent upon the elimination half-life of the drug in relation to the dosing interval.

Interval

The frequency of dosing or the dosing *interval* is determined by the time (T_{max}) it takes for maximum PDC (C_{max}) to drop to a point below which the desired response no longer occurs, C_{min} (Figure 134-3, *A*). Thus T_{max} depends on the amount of fluctuation in PDC desired during the dosing interval and the elimination rate constant (k_{el}). If C_{min} for a drug is close to half of C_{max}, then approximately 1 drug half-life (i.e., $T_{max} = t_{1/2}$) can elapse before the next dose must be administered. A more appropriate interval can be calculated using k_{el} if C_{min} does not approximate half of C_{max}. The longer the elimination half-life of a drug, the longer the interval (or T_{max}) can be between doses.

Decreasing a dosing interval is of no benefit for drugs whose half-life is long. For example, an 8-hour dosing interval for phenobarbital (drug half-life 50 to 100 hours average 72 hours) offers no advantage to a 12-hour interval since very little drug will be eliminated during the 12-hour period between doses. An exception is made if induction of drug metabolizing enzymes by phenobarbital has decreased drug half-life to less than 24 hours. In contrast, prolonging a dosing interval for convenience may be dangerous for drugs with a short half-life (e.g., many antibiotics). For example, if the drug half-life is two hours, a 4-hour increase in the dosing interval will result in a 75% decrease in C_{min} since 2 half-lives will elapse between the dosing interval. For drugs with a short half life, often adding an additional dose (i.e., shortening the dosing interval) is more effective (and cheaper) than doubling the dose. An example might be a time dependent (betalactam) antibiotic or cyclosporine. Some drugs remain effective despite dosing intervals that are longer than the elimination half-life of the drug. Examples include antimicrobials that exhibit a post antibiotic effect (e.g., aminoglycosides); drugs that accumulate in tissues (e.g., omeprazole); drugs whose metabolites are active (particularly if the metabolite half-life is longer than the parent compound [e.g., tepoxalin]); and drugs that destroy targets that must be resynthesized before the effect resolves (e.g., selected antiprostaglandins).

Drug half-lives can be as short as 2 minutes or less (e.g., epinephrine and dobutamine) or as long as several weeks (e.g., potassium bromide). Drugs with half-lives that are too short for convenient dosing are either given as constant IV infusion (e.g., lidocaine) or may be prepared as slow-release preparations (e.g., benzathine penicillin). Although the elimination half-life of the drug does not vary for slow release preparations compared with other preparations of the drug, the absorption of the drug is much slower. The intent, although not always successful, is to maintain constant therapeutic concentrations by ensuring continuous addition of drug into plasma. Note, however, that absorption may be so slow that therapeutic concentrations are never reached. Many oral drugs are prepared as slow- or continuous-release preparations (e.g., quinidine or theophylline). However, these preparations have been formulated for humans and the release kinetics may vary substantially in animals. Use of these preparations should be reserved for drugs that have been studied in animals. Alternatively, therapeutic drug monitoring for some drugs can be used to ensure that drug concentrations fall within the therapeutic range.

Accumulation

For drugs with very long half-lives, the dosing intervals can be correspondingly prolonged to allow for convenience. However, a dosing interval that is too long is also often inconvenient (e.g., phenobarbital and 3 days). In addition, for drugs with a narrow therapeutic range, fluctuation of PDC during the dosing interval must be minimized. In both situations, the recommended dosing interval (e.g., every 12 hours for phenobarbital) may be shorter than the drug elimination half-life. With each subsequent dose of drug administered at an interval *(T)* that is shorter than drug half-life, drug from the previous dose will remain in the body. The amount of drug remaining depends upon how much shorter the dosing interval is compared with the half-life. In such situations, the drug begins to accumulate with multiple doses (see Figure 134-3, *B*). Eventually, a steady-state is reached for the drugs such that the amount of drug administered with each dose equals the amount eliminated during the dosing interval. As with drug elimination, approximately 3 to 5 drug half-lives must elapse following a fixed dosing regimen before steady-state is reached. Steady-state is a relevant issue only for drugs that accumulate. The amount that a drug will accumulate as steady-state is reached depends on the difference between drug elimination half-life and the dosing interval. The greater the difference (the larger half-life is compared with the interval), the more the accumulation. For example, bromide (half-life 21 days) will accumulate more than phenobarbital (half-life 3 days) when both are administered twice daily. The amount of accumulation can be approximated. If the elimination half-life is equal to dosing interval, drug will accumulate twofold; if the elimination half-life is twice the interval, concentrations at steady state will accumulate fourfold. The relationship between elimination half-life and dosing interval also determines the amount that PDC may fluctuate during a dosing interval. The larger the elimination half-life compared to the dosing interval, the smaller the fluctuation in PDC during a dosing interval. For drugs administered at an interval equal to the elimination half-life, PDC will fluctuate twofold between doses. The relationship between drug half-life and dosing interval also influences the number of samples collected for therapeutic drug monitoring. For drugs with a long half-life (compared to the closing interval), a single sample (often trough) may be sufficient (e.g., bromide, often phenobarbital), whereas both peak and trough samples are indicated for drugs with a short half-life (e.g., digoxin) that allows fluctuation during the dosing interval.

Drugs that accumulate protect the patient in that PDC are stable (i.e., do not fluctuate during a dosing interval). However, drugs that accumulate also present problems that

are not encountered with drugs administered at an interval that precludes accumulation. Maximum therapeutic efficacy will not be realized until steady-state concentrations have been reached, which may be an unacceptable time for some patients (i.e., epileptics receiving potassium bromide which has a 21 to 24 day half-life in dogs). In such situations, a loading dose can be administered. This single dose, based on bioavailability and V_d of the drug and target concentrations (usually between C_{max} and C_{min}),

$$\text{Dose} = C^*V_d/F,$$

is intended to achieve therapeutic concentrations with the first dose. A disadvantage to loading dose is that the body cannot gradually adapt to the drug. Additionally, the maintenance dose may not maintain PDC reached by loading. In such cases, PDC may gradually decrease below C_{min} *or* increase above C_{max} and the change may not be evident until a new steady-state has been reached 3 to 5 drug half-lives later. For bromide, monitoring immediately after a loading dose and at one month (1 half-life) allows proactive evaluation of the maintenance dose. If the two concentrations are not similar, the maintenance dose can be appropriately modified. For drugs that accumulate, the addition of a single maintenance dose of the drug to the total amount of drug in the patient's body at steady state can be considerably small, and multiple doses (i.e., a small loading dose) must be given to immediately influence PDC. Alternatively, the maintenance dose will need to be increased and a new steady state reached 3 to 5 drug half-lives later.

Therapeutic Range

The therapeutic range provides a target for the dosing regimen and is designed to generate therapeutic but not toxic concentration at the tissue site. Fixed dosing regimens comprise a dose (e.g., mg/kg) and an interval (e.g., every 8 hours) that should result in PDC in the therapeutic range throughout most of the dosing interval. The therapeutic range generally consists of a minimum effective PDC (trough or C_{min}), below which therapeutic failure is likely to occur; and a maximum effective PDC (peak or C_{max}), above which a type A adverse reaction is more likely (see Figure 134-1). However, a therapeutic range is a population statistic and targets concentrations between which a large proportion (e.g., 95% of the population) will respond. A small percentage of animals will respond above or below the therapeutic range whereas others will exhibit clinical signs of toxicity below the maximum therapeutic range. When possible, therapeutic drug monitoring should establish the therapeutic range for the individual patient. The most appropriate therapeutic range for a drug as a target is complicated the class and intent of the drug. For example, therapeutic ranges for antimicrobials are based on the microorganism (e.g., immune-inhibited) and whether or not the antimicrobial is a time (e.g., beta-lactamase) versus concentration (e.g., aminoglycosides) dependent drug. The therapeutic range for digoxin is greater if improved contractivity is the target as opposed to decreased heart rate.

CHAPTER 135

Antimicrobial Drug Therapy

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The administration of antimicrobials to animals is among the most common treatments in veterinary medicine. The development of new drugs, revised approaches to dosing, and the emergence of resistant bacteria have modified this approach to therapy. The intent of this chapter is to discuss the important factors that guide and affect antimicrobial drug therapy in animals. Although "antimicrobial therapy" encompasses other aspects of therapy, such as antifungal, antiparasitic, and antiviral therapy, this chapter focuses on antibacterial therapy.

STRATEGIES FOR SELECTION OF AN APPROPRIATE ANTIBIOTIC

Empirical Drug Selection

Initial bacterial therapy can be instituted for many infections based on the presumptive activity of drugs against the bacteria and the historical performance (or in some instances anecdotal performance) of available drugs. Prescribing empirically is more reliable when resources provide guidelines on the susceptibility of bacteria, or clinical trials predict efficacy. Several surveys have been published and drug manufacturers have provided susceptibility information on their package inserts that is helpful. Based on this information, some general guidelines are possible:

If the bacteria is suspected to be a streptococci (but not *Enterococcus* spp.), β-streptococci, or *Bacillus, Actinomyces,* or *Pasteurella* spp., successful therapy can be achieved by administration of a penicillin such as ampicillin, or amoxicillin, amoxicillin + clavulanate (e.g., Clavamox), a tetracycline, or trimethoprim-sulfonamide. Other drugs also may be effective, but the more expensive, newer drugs or injectable agents might be considered overkill for such susceptible bacteria.

Staphylococcal infections in small animals are usually caused by *Staphylococcus intermedius*. Susceptibility can be expected to first-generation cephalosporins (e.g., cephalexin, cefadroxil, or cefazolin), amoxicillin-clavulanate (Clavamox), clindamycin, or one of the fluoroquinolones (e.g., enrofloxacin, difloxacin, marbofloxacin, or orbifloxacin). All of these drugs have been effective in clinical trials.

Gram-negative bacteria are more likely to develop resistance. Gram-negative bacilli of the Enterobacteriaceae (e.g., *Escherichia coli, Klebsiella pneumoniae*, and *Enterobacter* spp.) are resistant to many of the commonly used first-line drugs such as amoxicillin, ampicillin, tetracyclines, and first-generation cephalosporins (e.g., cephalexin, cefadroxil). Published studies have shown that the proportion of these bacteria resistant to these drugs can exceed 50%.[1-3]

Other problem bacteria include indole-positive *Proteus* spp., such as *Proteus vulgaris*, and *Pseudomonas aeruginosa*. Of the gram-positive bacteria, the problem bacteria include the enterococci, such as *Enterococcus faecium* or *Enterococcus faecalis*. *Staphylococcus* spp. (especially *S. aureus*) may acquire a resistance gene and become unaffected by β-lactam antibiotics, including cephalosporins. Fortunately, the prevalence of resistant staphylococci is still low in veterinary medicine.

P. aeruginosa is inherently resistant to many drugs because it lacks high-permeability porin proteins by which antibiotics gain access to bacteria. It also may produce beta-lactamase. A wild strain of *P. aeruginosa* has inherent resistance to most common drugs but should be susceptible to amikacin, gentamicin, or tobramycin, extended-spectrum penicillins (ticarcillin, piperacillin), some selected third-generation cephalosporins (e.g., ceftazidime), carbapenems (e.g., meropenem or imipenem), and perhaps a fluoroquinolone. Of the fluoroquinolones, ciprofloxacin, a human-registered drug, is the most active.

In clinical cases in which a resistant strain or bacteria with unpredictable sensitivity is suspected, a susceptibility test is advised to confirm the drug selection. But before results are available, initial therapy to treat infections caused by gram-negative enteric bacteria can be initiated with a fluoroquinolone (e.g., enrofloxacin, ciprofloxacin, difloxacin, marbofloxacin, or orbifloxacin), a cephalosporin, amoxicillin-clavulanate (e.g., Clavamox), or an aminoglycoside (e.g., gentamicin or amikacin).

If the bacteria is anaerobic, the gram-positive species such as *Clostridium* or *Actinomyces* species are susceptible to penicillins (e.g., penicillin G, ampicillin, amoxicillin), metronidazole, or clindamycin. The gram-negative anaerobes are usually susceptible to the same group of drugs except that bacteria of the *Bacteroides fragilis* group may be β-lactamase producers. In these cases, one should consider amoxicillin-clavulanate, metronidazole, clindamycin, or a second-generation cephalosporin (e.g., cefoxitin or cefotetan). Chloramphenicol also is active against anaerobic bacteria, but this drug is not as available as in previous years. The activity of first-generation cephalosporins and trimethoprim-sulfonamide combinations may be unpredictable for anaerobic infections.[4]

BACTERIAL SUSCEPTIBILITY TESTING

Bacterial susceptibility testing is recommended for cases that are not responding to antibiotic treatment, or in cases in which the suspected bacteria is known to possess a pattern of resistance that makes empirical drug selection unreliable. Although not perfect, susceptibility tests help refine the antibiotic selection process. If an organism tests resistant to a particular antimicrobial, the likelihood of successful therapy with that drug is diminished. On the other hand, a test that indicates susceptibility is no guarantee of clinical success.

Agar-Disk Diffusion Test

The most familiar test for measuring bacterial susceptibility to antimicrobials has been the Agar-Disk-Diffusion (ADD) test, also known as the Kirby-Bauer Test. Details for performing this test have been previously described.[5,6] The ADD test measures the inhibition of bacterial growth against the antimicrobial concentration from a paper disk placed on the agar. The zone size is roughly correlated to the minimum inhibitory concentration (MIC). The larger the zone size, the lower the MIC, and vice versa. Since each antibiotic diffuses at different rates throughout the agar, use published standards for interpreting the sensitivity.[6]

Dilution Test for MIC Determination

The dilution test directly measures the MIC. This test is now available in many veterinary microbiology laboratories. It is a more quantitative measurement of susceptibility, and the test better correlates with clinical efficacy. The interpretation of the MIC test relies on knowing the breakpoints for each drug. Some selected MIC breakpoints[6] for bacteria are shown in Table 135-1.

Interpretation of Susceptibility Information

The interpretation uses the "SIR" system, which is sensitive, intermediate, and resistant. If the MIC is below the susceptible breakpoint, the organism is sensitive and a cure can be expected using standard doses. If the MIC is above the resistant breakpoint, the organism is resistant and drug therapy with that drug is not recommended. MIC values between resistant and sensitive categories fall in an "intermediate" zone. (This also has been called "moderately susceptible.") If the MIC is intermediate, the organism should ordinarily be considered resistant. However, successful therapy can be achieved when the drug concentrates at high levels as it does when treating a lower urinary tract infection, or when topical therapy is used. In extreme cases, high doses have been used to achieve drug levels for organisms with susceptibility in the intermediate range, but this should not be considered unless the drug has a high therapeutic index (e.g., with the β-lactam antibiotics). For some fluoroquinolones, the intermediate interpretation was called the "flexible dose" zone, for which high doses can be considered, but the flexible dose category was recently abandoned by the NCCLS.

Limitations of Bacterial Sensitivity Testing

There are important limitations to consider when assessing the clinical relevance of *in vitro* antibacterial susceptibility tests. Sensitivity tests assume equal plasma and tissue concentrations and will overestimate the antimicrobial activity in tissues that may be difficult to penetrate, such as the central nervous system, prostatic fluid, and mammary gland. Sensitivity tests will underestimate activity of topical treatments, local infusions, and antibacterials that concentrate in the urine. Susceptibility tests also may underestimate activity at drug concentrations below the MIC (sub MIC effects). Sensitivity tests do not detect potentially synergistic antibiotic combinations (except for trimethoprim-sulfonamides and amoxicillin-clavulanate). An example of a synergism is the combination of a β-lactam antibiotic and an aminoglycoside. Bacteria may be resistant to either drug alone but sensitive when administered in combination. Finally, sensitivity tests cannot consider the local factors that may affect antimicrobial activity such as pus, necrotic tissue, low oxygen tension, and poor blood perfusion. For example, an aminoglycoside may not be effective *in vivo* if the infection is in necrotic tissue or an abscess, despite an *in vitro* test that indicates susceptibility. Likewise, the activity of fluoroquinolones is decreased in an acid environment, or one in which there are cations present (e.g., Mg^{++}, Ca^{++}), such as urine. In these instances, even when the MIC is in the "susceptible" range, the organism may be resistant *in vivo*.

Table 135-1

Minimum Inhibitory Concentrations (MIC) Breakpoints

ANTIMICROBIAL	SUSCEPTIBLE (μg/mL)*	RESISTANT (μg/mL)
Amikacin	≤16	≥64
Ampicillin	≤8†	≥32
Ampicillin/ clavulanic acid	≤8/4†	≥32/16
Cefazolin	≤8	≥32
Cefotaxime	≤8	≥64
Ceftazidime	≤8	≥32
Cephalothin‡	≤8	≥32
Cefoxitin	≤8	≥32
Chloramphenicol	≤8	≥32
Ciprofloxacin	≤1	≥4
Clindamycin	≤0.5	≥4
Difloxacin	≤0.5	≥4
Enrofloxacin	≤0.5‖	≥4
Erythromycin	≤0.5	≥8
Gentamicin	≤2	≥8
Imipenem (and meropenem)	≤4	≥16
Marbofloxacin	≤1	≥4
Orbifloxacin	≤1‖	≥8
Oxacillin¶	≤2	≥4
Rifampin	≤1	≥4
Tetracycline	≤4	≥16
Ticarcillin	≤64†	≥128
Trimethoprim/sulfa	≤2/38	≥4/76
Vancomycin	≤4	≥32

*Values between the susceptible and resistant range are interpreted as "intermediate."
†There are exceptions for interpreting some pathogens. (See NCCLS, 2002 for details.)
For ampicillin, susceptibility for staphylococci and streptococci is ≤0.25 μg/mL;
For amoxicillin/clavulanate, susceptibility for staphylococci is ≤4/2 μg/mL;
For ticarcillin, susceptibility for *Pseudomonas* spp. is ≤64 μg/mL for *Pseudomonas* spp., and ≤16 μg/mL for enteric gram-negatives;
For erythromycin, susceptibility for streptococci is ≤0.25 μg/mL.
‡Cephalothin is used as a marker to test for susceptibility to cephalexin and cefadroxil.
‖For enrofloxacin and orbifloxacin, the "intermediate" category may require higher doses.
¶If organisms are resistant to oxacillin, they should be considered resistant to other β-lactam antibiotics also.

DESIGNING OPTIMAL DOSING REGIMENS

Pharmacodynamics refers to the action of the drug on the bacteria (i.e., if it is bactericidal, bacteriostatic, time-dependent killing, concentration-dependent killing). *Pharmacokinetics* describes the disposition of drug in the body and forms the profile of the drug concentration versus time in the body. The pharmacokinetic-pharmacodynamic (PK-PD) relationships are used to define optimal dosing guidelines for antibiotics in animals. To accomplish this, the pharmacokinetic profile is defined according to its relationship to the MIC.

PK-PD relationships have been correlated to certain variables such as the peak plasma concentration (C_{MAX}), the area of the plasma concentration versus time curve (AUC), and the length of time that the plasma concentration is above the MIC (T>MIC) during a 24-hour interval. These relationships are shown graphically in Figure 135-1. Antibacterial drugs have been described as either bacteriostatic or bactericidal. Bacteriostatic drugs inhibit bacteria, but growth may resume when the drug concentration falls below the MIC. Bactericidal drugs kill the bacteria if the drug concentration is high enough above the MIC, or if the MIC is exceeded for a long enough time. Bactericidal drugs may be either time-dependent in their killing or concentration-dependent. The optimal dosage regimens for classes of drugs can be devised by consideration of these relationships.

Bacteriostatic Drugs

Drugs considered bacteriostatic include tetracyclines, macrolides (erythromycin), azithromycin, sulfonamides, and clindamycin. Under most conditions, chloramphenicol also is bacteriostatic. For these drugs, optimum therapy is achieved by using dosage regimens that maximize the drug concentration above the MIC throughout the dosing interval. Therefore, all bacteriostatic drugs are considered time-dependent (T > MIC). For drugs in this group, if they do not have long half-lives, they must be administered frequently to achieve this goal. Some of the macrolide antibiotics, such as azithromycin, achieve this goal because the drug concentrations persist in tissues much longer than in the plasma after dosing.

Bactericidal Drugs

For the *time-dependent* bactericidal drugs, clinical efficacy is achieved when the time of drug concentration above MIC is maximized (T > MIC). The time-dependent drugs include the β-lactam antibiotics such as penicillins, potentiated-aminopenicillins (e.g., amoxicillin-clavulanate), and cephalosporins. There is a threshold of four to five times the MIC, above which increased bacterial killing is not observed. Therefore the most effective treatment is expected with these drugs when they are administered at more frequent intervals, rather than by increasing the dose. A constant rate infusion, although impractical in many veterinary settings, would be the most optimal. For intermittent dosing, the optimum duration of time above the MIC has not been determined for all bacteria, but in general, the T > MIC should be at least 50% of the dose interval in the non-neutropenic patient. Since most penicillins and cephalosporins in small animals have elimination half-lives of only 1 to 2 hours, dosage regimens should consider these pharmacokinetic-pharmacodynamic relationships. When a gram-negative infection is treated, especially a serious one, penicillin derivatives and cephalosporins are administered at least three to four times per day for optimum results.

A few exceptions exist to these guidelines: For the specialized group of β-lactams, the carbapenems (e.g., imipenem and meropen), the T > MIC may be less than 50% because these drugs are more bactericidal. For example, meropenem can be administered twice daily for infections in small animals.[7] Secondly, since the MICs of β-lactam antibiotics are lower for some gram-positive bacteria (e.g., *Staphylococcus* spp.), and antibacterial effects occur at concentrations below the MIC, longer dose intervals may be possible compared with regimens used for other bacteria. For example, cephalexin is effective for treating infections caused by *Staphylococcus* spp. when administered only once or twice a day in dogs[8], despite a half-life of only a few hours.

For *concentration-dependent drugs*, either the peak concentration (C_{MAX}) or the area-under-the-curve (AUC) is the best predictor of clinical efficacy. Aminoglycoside antibiotics such as gentamicin or amikacin are more bactericidal when the

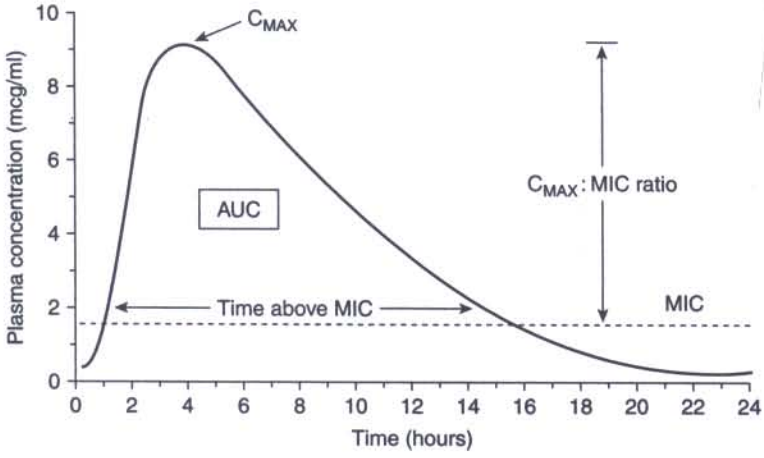


Figure 135-1 The variables of minimum inhibitory concentration (MIC), maximum (peak) plasma concentration (C_{MAX}), area-under-the-curve (AUC) for the plasma concentration versus time profile, are used to derive the time above MIC (T > MIC), C_{MAX}:MIC ratio, and AUC:MIC ratio.

peak plasma concentrations are 8 to 10 times above the MIC. After attaining this peak, plasma concentrations can fall below the MIC for several hours and still achieve a cure. Current dosage regimens for these drugs are designed to produce a C_{MAX}:MIC ratio of 8 to 10 when administered only once daily. Because nephrotoxicosis associated with aminoglycosides is increased by the duration of exposure, not the peak, the once-daily regimens for these drugs are as effective, and less nephrotoxic than lower doses administered more frequently.[9]

The fluoroquinolone antimicrobials (e.g., difloxacin, enrofloxacin, ciprofloxacin, marbofloxacin, and orbifloxacin) also are concentration-dependent. Although, the peak concentration (C_{MAX}:MIC ratio), has been correlated with *in vitro* bactericidal activity, the AUC:MIC ratio for a 24-hour period is probably a better predictor of clinical efficacy. Optimum therapy is achieved when this ratio is above 125, but a ratio of 50 in an immunocompetent animal is also sufficient for a clinical cure for many bacterial pathogens, especially when treating gram-positive bacteria.[10]

The AUC is proportional to the dose administered. Therefore to achieve appropriate AUC:MIC ratios, fluoroquinolones can be administered to treat highly susceptible organisms with the lowest registered dose, once daily. Susceptible bacteria of the Enterobacteriaceae usually have low MIC values in this range. For bacteria that are more resistant (i.e., the MIC values are higher, even though they are still considered susceptible), a higher dose is needed. For example, to achieve the necessary peak concentration for treating infections caused by *Pseudomonas aeruginosa*, which often has an MIC of 0.5 µg/ml or higher, doses at or near the highest registered dose, once daily, may be needed.

TISSUE DISTRIBUTION OF ANTIBIOTICS

If the drug cannot reach the site of action (the tissue), even the most active drugs will be ineffective. With adequate perfusion, there is no barrier to impede diffusion of antibiotics from the vascular compartment to extracellular fluid of most tissues. Antibiotic drug concentrations in the serum or plasma will predict the drug concentration at the site of infection in the extracellular space (interstitial fluid). Pores and fenestrations in the endothelium of capillaries are large enough to allow drug molecules to pass through, unless the drug is highly protein bound in the blood. Therefore most soft tissues and bone do not present a barrier to drug diffusion as long as there is adequate blood perfusion. Only a few drugs are so highly bound that protein binding will impair their tissue penetration. Doxycycline is one of the few examples of a highly protein bound antibiotic used in small animals.

Because protein binding, rather than lipophilicity, is the most important factor for drug tissue penetration, there is no evidence for differences in efficacy among antibiotic drugs that can be attributed to differences in drug's lipid solubility. But drug diffusion can be limited when a lipid membrane (such as tight junctions on capillaries) presents a barrier to drug diffusion. These tissues include sequestered sites such as the central nervous system and eye, the epithelial lining fluid of the lung, and glandular tissues such as the prostate and mammary gland. To treat infections in tissues for which there is a permeability barrier, a drug must be sufficiently lipid soluble to diffuse through the lipid barrier or penetrate via carrier-mediated transport.

An example of a sequestered site is the central nervous system (CNS), which generally restricts poorly-lipid soluble and polar antibiotics. Most cephalosporins (except those classified as third generation), penicillins, and aminoglycosides do not attain adequate antibacterial concentrations in the central nervous system when administered systemically. Antibiotics with better penetrating ability include metronidazole, chloramphenicol, trimethoprim, and the third-generation cephalosporins such as cefotaxime. If more polar, less lipophilic drugs are used for treating CNS infections, high doses must be given to attain effective antibacterial concentrations.

TREATMENT OF SPECIFIC INFECTIONS

Skin and Soft-Tissue Infections

The most important skin pathogen in dogs is *Staphylococcus intermedius*. Other bacteria identified usually are opportunistic. Other staphylococci have been identified (e.g., *Staphylococcus aureus*) that are often more resistant. Wound infections or skin-fold infections may be caused by *Pseudomonas aeruginosa* or bacteria of the Enterobacteriaceae (*Escherichia coli*, *Klebsiella* spp., and *Proteus* spp.). Anaerobic bacteria, including *Actinomyces* spp., have been isolated from deep infections. Bacteria causing skin or other soft-tissue infection in cats induced by a bite wound can be *Pasteurella* spp., streptococci, or other inhabitants of the oral cavity, including anaerobes.

Since most skin and soft-tissue infections are extracellular, the most important feature of drug delivery is to ensure there are sufficient antibiotic drug concentrations in the extracellular fluid. As discussed previously, adequate concentrations in plasma usually ensure effective concentrations in these tissues.

When purulent infections are treated, drug activity can be diminished by wound or tissue components. For example, pus may bind and inactivate certain drugs and a necrotic environment with cellular debris may inhibit activity of aminoglycosides and trimethoprim-sulfonamides. This issue may be important when treating an infection associated with an abscess or when treating otitis.

For treating infections caused by *Staphylococcus* species, the *in vitro* incidence of resistance is lowest for first-generation cephalosporins (e.g., cefadroxil, cephalexin), β-lactamase inhibitor combinations (e.g., amoxicillin-clavulanate), and fluoroquinolones (e.g., enrofloxacin, difloxacin, marbofloxacin, orbifloxacin). Other drugs that have a somewhat higher incidence of resistance but have been used successfully include erythromycin, lincomycin, clindamycin, and trimethoprim-sulfonamide or ormetoprim-sulfonamide combinations. After treatment with these drugs, resistance can be acquired, especially in cases of recurrent pyoderma.

Urinary Tract Infections

The most common bacteria in dogs and cats causing urinary tract infections (UTIs) are gram-negative bacilli such as *E. coli*, *Klebsiella*, and *Enterobacter* species. *Proteus mirabilis* and *P. aeruginosa* also may be isolated. Of the gram-positive bacteria causing infections, *Staphylococcus* spp. and streptococci are the most common. Occasionally enterococci cause infection of the urinary tract in dogs and cats, although this is usually an opportunistic pathogen of low virulence.

Treatment considerations include the antibiotics that are excreted via renal mechanisms and concentrate in the urine. These drugs include any of the penicillins and cephalosporins, tetracyclines (except doxycycline), fluoroquinolones, aminoglycosides, and trimethoprim-sulfonamides. These drugs are concentrated 10- to 100-fold in the urine compared with the plasma. Therefore it is possible to attain high drug concentrations in urine and good treatment success unless the infection is complicated by an underlying problem. Dose rates administered usually can be at the lower end of a dose range because of the concentrating effect of antibiotic in the urine. Empirical selection of antibiotics is acceptable for urinary tract infections because the antimicrobial susceptibility tests can underestimate the true activity of the drugs *in vivo*.

If the animal is an intact male, infection of the prostate gland is possible. Drug penetration into the prostate is limited because of a barrier between prostatic glandular cells and the serum or plasma.[11] Drugs that are poorly lipophilic at the pH of plasma (e.g., penicillins, cephalosporins, and aminoglycosides) do not diffuse well into prostate. Drugs that are lipophilic at the pH of plasma, such as macrolides (e.g., erythromycin), lincosamides (e.g., clindamycin), trimethoprim, or fluoroquinolones diffuse more easily into the prostate and can achieve concentrations in the prostate that exceed plasma concentrations. However, the macrolides and clindamycin usually do not have the gram-negative spectrum needed for a prostate infection. Therefore the most effective drugs for prostatic infections are the fluoroquinolones, and trimethoprim (usually administered as the combination of trimethoprim-sulfonamide). Chloramphenicol and tetracycline concentrations in prostate fluid of dogs are low after systemic administration.

Respiratory Tract Infections

Treatment of infections in the respiratory tract is challenging because these usually occur in small animals that are compromised by another primary problem, such as megaesophagus or immunosuppression. Antibiotics distribute into the parenchyma of lung tissue and achieve therapeutic drug concentrations in most cases because there are no barriers to diffusion as long as there are not consolidated lung lobes. Drugs administered to animals with pneumonia will achieve concentrations in the extracellular fluid of the lungs that are equal to, or exceed, plasma concentrations. However, the bronchial secretions present a barrier owing to the blood-bronchus barrier, and non-fenestrated capillaries of the alveoli. In these cases there may be insufficient drug concentrations in the epithelial lining fluid of the respiratory tract to treat infections associated with bronchitis.[12]

Drugs with poor lipid solubility such as penicillins and aminoglycosides produce low concentrations in bronchial secretions after systemic administration, but this barrier may be diminished when it is inflamed. Drugs that are able to achieve effective concentrations in bronchial secretions are macrolide antibiotics, tetracyclines (but not necessarily doxycycline), chloramphenicol, and fluoroquinolones. (However, the availability of chloramphenicol has diminished recently.)

When the infection is in the chest cavity (e.g., pyothorax) drug diffusion into the pleural cavity is not compromised. However, when fluid is present, or the condition has caused pus and fibrin to accumulate, this may compromise diffusion of antibiotic concentrations in the chest cavity high enough to achieve a cure. In these cases, effective drainage or surgical intervention is necessary to assist drug penetration.

The bacteria causing respiratory infections in small animals can cover the full spectrum of gram-positive, gram-negative, and anaerobes and may include *Bordetella bronchiseptica*, *Streptococcus zooepidemicus*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *Staphylococcus* spp., alpha- and beta-streptococci, and *Pasteurella multocida*. A culture and sensitivity test obtained from a bronchoalveolar lavage (BAL) or transtracheal wash (TTW) is usually used for drug selection. However, the results of a TTW or BAL may not always represent the bacterial pathogen causing disease deeper in the lung, nor are cultures from nasal secretions likely to represent the cause of an infection deeper in the airways.

In the case where a gram-positive cocci is identified, or a gram-positive anaerobe, a penicillin, cephalosporin, or a penicillin-β-lactamase inhibitor combination (e.g., amoxicillin-clavulanate or ampicillin-sulbactam), is a good choice. When the organism is a gram-negative bacilli, a fluoroquinolone, aminoglcoside (e.g., amikacin, tobramycin, or gentamicin), or an extended-spectrum cephalosporin (e.g., cefoxitin, cefotaxime) are needed. Combinations of these drugs are rational in cases of mixed infections.

The role of *Mycoplasma* spp. in respiratory infections has been a source of debate. Although *Mycoplasma* spp. can be isolated from a high percentage of animals with respiratory signs, it is unclear whether or not this organism plays a role in the disease. It also is possible that the *Mycoplasma* spp. are simply inducing inflammation that has allowed other organisms to colonize the respiratory tract. Most *Mycoplasma*-positive dogs have co-infection with other organisms, and selection of drugs active against *Mycoplasma* is usually not an important factor in achieving a cure.

Bordetella bronchiseptica presents a special case. *Bordetella* spp. are a gram-positive aerobic coccobacilli. Among its important virulence factors is the ability to adhere to the bronchial epithelium (ciliated epithelial cells) and produce exotoxins that inhibit neutrophil migration to the infection site. Infections are often mild and self-limiting that require no specific antibiotic treatment. But in cases where antibiotics are indicated, one should select a drug that achieves concentrations in bronchial secretions, such as: tetracyclines, chloramphenicol, or macrolides (e.g., erythromycin, azithromycin). Aminoglycosides, cephalosporins, and penicillins may not achieve drug concentrations at the infection site and quinolones are not consistently active against this organism. Another treatment route that is considered is aerosolization of antibiotics (e.g., tobramycin).

Treatment of Infections in Bones and Joints

Staphylococci, *E. coli*, *Pseudomonas*, *Proteus*, and anaerobes have been causes of joint and bone infections in small animals. Often these may be mixed infections. Staphylococci can be particularly troublesome because they adhere to bone by expression of receptors for components of bone matrix. It also may be internalized by osteoblasts and survive intracellular. Infections in bone, especially those associated with surgical sites that contain metal implants, are difficulty to treat because of the presence of a biofilm that can render bacteria resistant to antibiotics.[13]

Aggressive treatment is necessary because the consequences of treatment failure is often loss of a limb or long-term morbidity. Drug selection should be made on the basis of a reliable susceptibility test taken from a culture deep within the wound. Drug safety also is an important consideration since treatment is required for a long duration, usually a minimum of 6 weeks. Bone and joints do not present a barrier for drug diffusion; therefore one drug group is not preferred over another because of superiority of better penetration. However, the presence of pus, necrotic tissue, devitalized bone, or foreign body may delay antibiotic diffusion. Surgery to remove or reduce this material is recommended.

β-lactam antibiotics active against staphylococci can be administered orally for long periods. These first-line drugs include first-generation cephalosporins (e.g., cefadroxil, cephalexin), and amoxicillin-clavulanate. Other drugs effective for small animals are the fluoroquinolones, and clindamycin. Bacterial infections caused by *Pseudomonas* spp., *E. coli*, or *Enterobacter* spp. may be resistant to the drugs listed above and a susceptibility test is needed to accurately select the most appropriate drug. In some instances, aggressive treatment with injectable drugs may be necessary.

Treatment of Nonspecific Fever

Often the only sign of a potential infection is fever. If there also is evidence that the patient is immunosuppressed, antibiotic therapy is justified. Evidence of immunosuppression may include documented neutropenia, corticosteroid administration, Cushing's disease, or anticancer treatment. In patients treated for cancer, granulocyte counts less than 1000 cells/μL accompanied by fever should immediately warrant antibiotic administration. Blood cultures are recommended but may be unrewarding. Since results of blood culture may not be available for 48 to 72 hours, empirical antibiotic treatment should be instituted.

Select a drug protocol that gives maximum coverage with minimal risk of adverse effect. For patients that can be treated with oral drugs, a combination of a fluoroquinolone (e.g., enrofloxacin, difloxacin, marbofloxacin, or orbifloxacin) plus a potentiated amoxicillin (e.g., Clavamox) or an oral cephalosporin (e.g., cephalexin or cefadroxil) is a rational combination with a high safety index. If the patient is more critically ill, or if the infection becomes more life-threatening, injectable drugs should be considered. In these cases, the combination of an aminoglycoside (gentamicin or amikacin) plus a cephalosporin or potentiated ampicillin (e.g., Unasyn) is a rational combination. Alternatively, injectable enrofloxacin plus a cephalosporin (e.g., cefazolin), or potentiated ampicillin (e.g., ampicillin-sulbactam combination: unasyn) covers the spectrum of bacteria that may be causing the problem. If the organism has been refractory to therapy and resistance is possible due to infection caused by *E. coli*, *Klebsiella* spp., or another gram-negative bacilli. In these situations, the administration of drugs with greatest activity should be considered, such as cefotaxime, amikacin, or possibly a carbapenem (e.g., imipenem-cilastatin, or meropenem).

CHAPTER 136

Glucocorticoid Therapy

Leah A. Cohn

Glucocorticoid agents are among the most commonly used veterinary drugs. They exert myriad effects on nearly every tissue in the body and result in desired and undesired actions. These effects vary with potency and preparation of the glucocorticoid product, dose and route of administration, duration of glucocorticoid exposure, and individual patient factors. Most often, the desired action of therapeutically administered glucocorticoids is suppression of inflammation or of a damaging immunologic response. Other properties of glucocorticoids are exploited for the treatment of hormonal deficiency states, neoplasia, and shock, among other miscellaneous uses.

Unfortunately, even for disease states in which glucocorticoid therapy is proven to be beneficial, there is little scientific evidence of what constitutes an optimum treatment protocol. Instead, veterinarians rely largely on anecdote and experience to design glucocorticoid treatment regimens. Because effects vary with dose and potency, the veterinarian must be familiar with the equivalent dose range of various drug preparations required to produce physiologic, anti-inflammatory, immunosuppressive, or other effects. As a general rule, glucocorticoids should be used "to effect" rather than at an arbitrary dose and therefore minimize exposure and adverse effects.

PHYSIOLOGY OF GLUCOCORTICOIDS

Glucocorticoid drug preparations are derivatives of the endogenously produced adrenal hormone cortisol (hydrocortisone). Most glucocorticoid actions result from altered cellular gene transcription.[1] Glucocorticoids move passively into cells and then bind intracytoplasmic receptors; receptor numbers vary with tissue and cell type. Bound receptors translocate to the nucleus, where they modify gene transcription. Proteins are either up- or down-regulated by the actions of glucocorticoids, which leads to specific cellular actions. Together, these actions

affect the function of nearly every tissue type and result in a tremendous variety of effects (Box 136-1). Metabolic, anti-inflammatory, and immunosuppressive effects of glucocorticoids are particularly relevant to their therapeutic use.[2] Metabolic effects are primarily catabolic and include insulin antagonism, increased glycogen formation, and increased gluconeogenesis. Glucocorticoids inhibit liberation of arachidonic acid to diminish production of eicosanoid proinflammatory mediators, and they increase production of anti-inflammatory proteins.[3]

Many anti-inflammatory effects of glucocorticoids overlap with immunosuppressive effects. The glucocorticoid stress leukogram (mature neutrophilia, lymphopenia and eosinopenia, and variable monocytosis) results from altered membrane expression of cellular adhesion molecules. The most pronounced immunologic effects of glucocorticoids are diminished mononuclear phagocytic function and altered cytokine production.[3] Although glucocorticoids affect cell-mediated immunity directly and profoundly, the effect on humoral immunity is largely indirect and not as pronounced.[3] Although dog and cat lymphocytes are resistant to glucocorticoid-induced lysis, neoplastic and activated lymphocytes are susceptible to glucocorticoid-induced apoptosis.[3]

The release of endogenous glucocorticoids is controlled by an endocrine-feedback axis consisting of the hypothalamus, the pituitary gland, and the adrenal gland (HPA axis).[2] The hypothalamus produces corticotropin-releasing hormone (CRH), which stimulates production of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. In turn, ACTH causes production and release of cortisol from the zona fasciculata and zona reticularis of the adrenal cortex. Cortisol then inhibits release of CRH and ACTH and dampens further glucocorticoid production. Pharmacologic derivatives of cortisol exert a similar negative feedback, but suppression varies with glucocorticoid potency.

PHARMACOLOGY OF GLUCOCORTICOIDS

Numerous modifications of the 17-carbon atom steroid nucleus have been developed to enhance or diminish particular glucocorticoid drug properties (e.g., mineralocorticoid or glucocorticoid potency, receptor binding strength).[4] Other modifications have been made through esterification of the glucocorticoid drug product to change solubility and duration of action.[4] Although affinity of the particular product varies, the majority

Box • 136-1

Selected Physiologic Effects of Glucocorticoids

Metabolic Effects
Increase gluconeogenesis
Increase protein catabolism
Antagonize insulin
Mobilize free fatty acids
Redistribute adipose tissue

Dermal Effects
Thinning or atrophic skin
Atrophic hair follicles

Cardiovascular Effects
Optimize catecholamine receptor numbers
Positive inotropic effects
Vasoconstriction

Gastrointestinal and Hepatic Effects
Induce alkaline phosphatase enzyme (dogs only)
Decrease calcium and iron absorption
Promote hepatic fat and glycogen deposition
Alter mucin structure
Increase secretion of digestive hormones

Renal Effects
Increase glomerular filtration rate
Inhibit renal tubules response to antidiuretic hormone
Promote water, sodium, and chloride retention
Promote potassium and calcium excretion

Neurologic and Muscular Effects
Euphoria or behavioral change
Increase numbers or sensitivity of adrenergic receptors
Muscular atrophy
Muscular weakness

Endocrine Effects
Decreased ACTH production
Suppressed thyroid stimulating hormone and T3/T4 concentrations

Hematopoietic Effects
Increase circulating mature neutrophils
Decrease circulating lymphocytes, lymphocyte sequestration, lymphoid tissue involution
Apoptosis of activated and neoplastic lymphocytes
Decrease circulating eosinophils
Increase circulating monocytes
Increase circulating red blood cells
Increase circulating platelets

Inflammatory and Immunologic Effects
Decreased eicosanoid (prostaglandin and leukotriene) formation
Inhibit mononuclear phagocytosis and chemotaxis
Decrease or increase cytokine production
Depress cell-mediated immunity
Diminish humoral immunity (secondary effect)

Miscellaneous Effects
Stimulate appetite
Inhibit fibroblast proliferation and collagen synthesis
Accelerate bone reabsorption
Stabilize lysosomal membranes
Antioxidant

of glucocorticoid in plasma is bound to proteins. Corticosteroid binding globulin (transcortin), and to a lesser extent other proteins including albumin, hold glucocorticoid unavailable for diffusion into the cell.[4] Only glucocorticoid in excess of this binding capacity enters the cell and exerts a biologic effect.

Modifications of the basic glucocorticoid hormones have resulted in the development of numerous drug products available for either systemic or topical administration. The potency of these products is expressed as it relates to cortisol (Table 136-1). Importantly, the same metabolic effect can be attained by any of these glucocorticoid products when administered in a metabolically active form at equipotent dosages. The biologic half-life of systemically administered glucocorticoids is disparate from the plasma half-life. Because the biologic effects are largely due to alterations in genetic regulation of protein production, biologic effects are delayed and prolonged in comparison with plasma drug concentration. Glucocorticoid drugs are often divided into three groups based on duration of HPA suppression. Short-acting glucocorticoids typically suppress the HPA less than 12 hours; long-acting glucocorticoids more than 48 hours; and intermediate-acting products fall somewhere between.[5]

Many glucocorticoid products are combined with esters that affect water solubility of the compound and therefore affect rate of absorption of injectable preparations.[4] Sodium phosphate, hemisuccinate, and sodium succinate esters are the most water soluble and allow for rapid absorption and action. The duration of action of these esterified compounds is equivalent to that of the base glucocorticoid. Acetate and diacetate esters are poorly water soluble, whereas pivalate, diproprionate, hexacetate, and acetonide are least soluble. Slow absorption from the site of injection prolongs the duration of action of any glucocorticoid base with which these esters are combined.[4,5] For example, although the biologic duration of methylprednisolone is 12 to 36 hours, the duration of the repositol formulation methylprednisolone acetate is 3 to 6 weeks.

Certain synthetic glucocorticoid compounds require conversion to an active metabolite.[6] An example is prednisone, which requires hepatic conversion to prednisolone for activity; prednisone would therefore not be suitable for topical application. The two drugs are used interchangeably via systemic administration, however, because hepatic conversion is rapid and nearly complete.

An anecdotally supported belief by some veterinarians holds that a proportion of normal cats inadequately convert prednisone to prednisolone, so prednisolone is often preferred in this species. Cats have fewer, less sensitive, cellular glucocorticoid receptors than dogs.[7] Therefore cats often require twice the glucocorticoid dosage to achieve equivalent biologic effects, and side effects of glucocorticoid use in cats are less pronounced than those in dogs.

CLINICAL UTILITY OF GLUCOCORTICOIDS

Glucocorticoids are used to treat a variety of disease processes and often suppress the consequences of disease rather than curing disease. Evidence supporting these usages varies from irrefutable (e.g., hypoadrenocorticism) to unsubstantiated (e.g., septic shock). Even when good evidence exists to support the use of glucocorticoids in a particular disease process, there are few "right" or "wrong" treatment regimens.

Equipotent amounts of any metabolically active glucocorticoid exert similar effects, which means that a higher dose of a less potent glucocorticoid can achieve the same effect as a lower dose of a more potent product. Physiologic actions of glucocorticoids occur at a much lower dose of an equipotent glucocorticoid than do anti-inflammatory effects, which in turn occur at a lower dose than do immunosuppressive effects.[8] When choosing an initial treatment protocol, the veterinarian must begin by recognizing a goal of glucocorticoid therapy (physiologic replacement, suppression of inflammation, suppression of immunity, or some other action). Additional variables relate to the patient (e.g., species, concurrent disease), the disease process (e.g., chronic or acute, localized or systemic), and available glucocorticoid products (e.g., solubility, duration of action, route of administration). Ideally, when glucocorticoid therapy is required in only a localized area (e.g., ocular inflammation), treatment can be administered topically, thus minimizing effects of glucocorticoids on other tissues. Systemic therapy using parenteral or oral products is best suited to situations in which several body systems and/or tissues are targeted for therapy (e.g., anaphylaxis, systemic lupus erythematosus). Realistically, glucocorticoids are often administered systemically even when only a single tissue is targeted.

Table • **136-1**

Comparison of Various Glucocorticoids

	RELATIVE ANTI-INFLAMMATORY POTENCY	EQUIVALENT PHARMACOLOGIC DOSE (mg)	RELATIVE MINERALO-CORTICOID POTENCY	PLASMA HALF-LIFE DOGS/PEOPLE (HOURS)	BIOLOGIC HALF-LIFE IN PEOPLE (HOURS)
Short-Acting Glucocorticoids					
Hydrocortisone	1	20	2	1/1.5	8-12
Cortisone	0.8	25	2	?/1.5	8-12
Intermediate-Acting Glucocorticoids					
Prednisone	4	5	1	?/1	12-36
Prednisolone	4	5	1	1-3/2-3	12-36
Methyl-prednisolone	5	4	0	1.5/3	12-36
Triamcinolone	5	4	0	?/4 or more	24-48
Long-Acting Glucocorticoids					
Dexamethasone	30	0.75	0	2/5 or more	35-54
Betamethasone	30	0.6	0	?/5 or more	>48

Physiologic Replacement Therapy

Hypoadrenocorticism is the failure of the adrenal gland to produce enough corticosteroid hormones. Commonly, both mineralocorticoid and glucocorticoid deficiency exists, but isolated glucocorticoid deficiency can occur. Administration of prednisone or methylprednisolone, which are detected along with endogenous cortisol during assay, should be avoided prior to completion of diagnostic ACTH stimulation testing. If a substantial delay in testing is unavoidable, dexamethasone may be administered (0.1 to 0.2 mg/kg) without altering diagnostic test results. Life-long hormonal replacement is the basis of therapy.[9]

Although some corticosteroid drugs possess glucocorticoid and mineralocorticoid activity, separate replacement of each is often required. The glucocorticoid of choice for replacement should be administered systemically at a physiologic dose and should have a biologic duration of approximately 24 hours. Predniso(lo)ne 0.2 to 0.3 mg/kg once daily meets these requirements. During times of stress (e.g., boarding, illness) the amount of glucocorticoid administered should be temporarily increased (typically doubled) to meet increased physiologic demands.[9]

Anti-Inflammatory Therapy

Glucocorticoids are used most often for their excellent anti-inflammatory properties. Prior to initiating glucocorticoid therapy, attempts should be made to identify and eliminate the underlying cause of inflammation. Frequently, an underlying cause either cannot be found or cannot be entirely eliminated. Anti-inflammatory therapy can be of benefit in such cases, and glucocorticoids are often the most effective such therapy.

It is particularly important to rule out infectious causes of inflammation, especially fungal infection, prior to beginning glucocorticoid therapy. Because inflammation is intimately tied to innate defense mechanisms, and because of the additional suppressive effects of glucocorticoids on specific immunity, these drugs are relatively contraindicated in infection. Glucocorticoids often lead to a temporary improvement in animals with inflammation secondary to infection, but failure to control infection can lead to worsening of disease or even death. Because glucocorticoids reduce fever, stimulate appetite, and can induce feelings of euphoria and suppress clinical evidence of inflammation, it can be difficult to detect worsened infection until it is too late. There are exceptions to every rule, and glucocorticoids are actually indicated for the treatment of some infectious diseases.[10] Typically, they are combined with antimicrobial therapy to reduce inflammatory (e.g., *Pseudomonas* otitis)[11] or immunologic (e.g., red cell destruction due to *Mycoplasma hemofelis*) consequences of infection.[12]

Specific treatment decisions regarding anti-inflammatory therapy with glucocorticoids are based on a number of factors, including desired rapidity of action and expected duration of therapy. Rarely, a rapid onset of action is required, such as when respiratory inflammation compromises the animal's ability to breathe; injectable phosphate or succinate preparations are most useful in these situations. In most cases, anti-inflammatory therapy will be required for days, weeks, or months. Intermediate acting steroid preparations allow dosage to be titrated to effect and thereby minimized for chronic administration. The most often used anti-inflammatory glucocorticoid is predniso(lo)ne at an initial dosage of 0.5 to 1.0 mg/kg/day for dogs or 1 to 2 mg/kg/day for cats. Because the biologic half-life is 24 to 36 hours, there is little obvious advantage to division of the daily dosage. Once initial inflammation is suppressed, steroid dose is reduced to the lowest necessary level. Treatment with repositol products (e.g., methylprednisolone acetate) is not advisable in dogs even when long-term therapy is anticipated. Repositol therapy severely suppresses the HPA axis, prevents accurate dose titration or early drug withdrawal, and is associated with more pronounced side effects. Additionally, such therapy can interfere with accurate diagnostic testing (e.g., allergen skin testing, endocrine testing) for long periods of time.[13] There are limited indications for the use of repositol therapy in steroid-resistant cats. Repositol therapy may be used to treat feline eosinophilic granuloma or allergic and inflammatory skin conditions when the owners are unwilling or unable to administer oral medications, but iatrogenic hyperadrenocorticism and its consequences (i.e., insulin resistance) may result.[14]

Regional inhibition of inflammation can often be accomplished via local application of glucocorticoids. Glucocorticoid products are available in a variety of formulations designed specifically for local application, and injectable preparations can be used to achieve a local effect. Because the intended actions are local rather than systemic, the products should include only metabolically active glucocorticoids (e.g., prednisolone rather than prednisone). Although local application minimizes unwanted effects, absorption does occur and can lead to systemic effects and suppression of the HPA axis.[15,16]

The eyes, skin, respiratory and gastrointestinal tracts, and joints are the sites most often treated via local glucocorticoid application. Topical suspensions (e.g., 1.0% prednisolone acetate), solutions (e.g., 0.1% dexamethasone phosphate), or ointments (e.g., 0.05% dexamethasone phosphate) are indicated for inflammatory disease of external ocular structures or the anterior segment, such as non-infectious conjunctivitis or uveitis. Therapy is typically titrated to effect by adjusting frequency of application (every 1 to 8 hours). Contraindications to ocular glucocorticoid use include corneal ulceration or ocular infection. Ulcers can be exacerbated by glucocorticoids, and in the presence of infection stromal melting may occur.[17] Because of its frequent association with infection, feline conjunctivitis is a relative contraindication to ophthalmic glucocorticoid use.[18]

Dermatologic inflammation is often treated via systemic glucocorticoid administration, but topical products can augment or replace systemic glucocorticoids. Glucocorticoids should not be used to treat dermatologic disorders until serious attempts are made to diagnose the cause of dermatopathy. They should only be used after efforts are exerted to eliminate or control precipitating and predisposing factors. Even then, steroids should be used sparingly; topical therapy may spare excessive tissue exposure. Glucocorticoids in the form of 1% hydrocortisone (the metabolically active form of cortisone) are available in shampoos, conditioners, lotions, creams, ointments, and otic medications. These products are particularly useful in reduction of pruritus associated with atopy when used in conjunction with other therapies such as antihistamine medications. Stronger glucocorticoid preparations, including triamcinolone acetonide (e.g., Panalog®), betamethasone valerate (e.g., Gentocin Spray®, Otomax®) and fluocinolone acetonide (e.g., Synotic®), are effective in reducing erythema, swelling, and pruritus. However, systemic absorption makes these products inappropriate for extended daily use, particularly when dermal barriers are no longer intact.

Glucocorticoids are frequently used to treat chronic inflammation of the respiratory and gastrointestinal tracts. Methods of local application have been developed for use in people to minimize the adverse effects associated with long-term systemic administration. Metered dose inhalers (MDI), nasal sprays or drops, glucocorticoid retention enemas, rectal foams, and suppositories can be used in small animals. Although systemic steroid administration remains the mainstay of treatment for cats with reactive airway disease, bronchodilators and glucocorticoids (e.g., fluticasone propionate) can be applied to the airway lumen directly via MDI delivery.

Delivery systems for MDI use in cats can either be obtained commercially or made by simple modification of

readily available, inexpensive equipment.[8] Although unproven, the method has met with good anecdotal success. Some dogs and cats with allergic or idiopathic rhinitis respond well to intranasal glucocorticoids; such therapy should not be attempted until neoplastic and infectious diseases have been ruled out. Nasal sprays are available, but two drops of ophthalmic 1% prednisolone acetate instilled in each nostril two to three times daily can be used successfully. Topical therapy of gastrointestinal disease is limited to the mouth, rectum, and colon. Dogs with refractory colitis have been successfully treated with glucocorticoid suppositories and rectal foams, whereas successful intralesional injection of oral eosinophilic granuloma with glucocorticoids has been described in cats.[8,13]

Orthopedic pain and inflammation may be relieved by local injection of glucocorticoids, although such injections are never considered curative. Although injections can bring about a rapid return to function, they are also associated with potentially devastating complications (e.g., cartilage damage and impaired healing of osteochondral defects, accelerated osteoarthritis, and joint sepsis).[19,20] Intra-articular glucocorticoids injections are used less often in small animals than in either horses or people.[19,21] Perhaps the best use of local glucocorticoid therapy in small animal orthopedic medicine is in the treatment of bicipital tenosynovitis in dogs. Typically, 1 mg/kg of repositol methylprednisolone acetate is injected directly into the tendon and tendon sheath.[22] Injection is followed with several weeks' strict rest prior to slow return to activity.

Immunosuppressive Therapy

Suppression of damaging immunologic responses in dogs and cats is most often achieved by the administration of systemic glucocorticoids at a dosage higher than that required to suppress inflammation. The beneficial role of glucocorticoids in the treatment of autoimmune disease is well documented. Additionally, glucocorticoids are used to suppress harmful immunologic reactions associated with diseases like feline infectious peritonitis or rejection of transplanted organs.[23,24] Oral administration of intermediate-acting preparations is the most common choice for chronic immunosuppression. The initial dose of predniso(lo)ne required for immune suppression is usually 2 to 4 mg/kg/day for dogs or 2 to 8 mg/kg/day for cats. Despite predniso(lo)ne's biologic half-life of 24 to 36 hours, dividing this high dose and administering the drug twice daily may lessen GI irritation.

Some clinicians recommend initiating immunosuppressive therapy with dexamethasone rather than prednisone,[25] but evidence for an advantage of one drug over the other at equipotent dosages is lacking. Dexamethasone injection should be chosen when oral drug administration is difficult (e.g., due to vomiting or inability to swallow). Ideally, once disease is controlled, the use of glucocorticoids can be slowly tapered until it is discontinued altogether.

Immune-mediated disease refractory to glucocorticoids alone may be controlled by the addition of a different immunosuppressive agent (e.g., azathioprine). Such combination therapy may have a steroid sparing effect, which allows control of disease using a lower total glucocorticoid dose. This type of combination therapy is particularly useful in animals with unacceptable adverse effects from glucocorticoid therapy.

Anti-Neoplastic Therapy

Glucocorticoids have proven useful in the treatment of several neoplastic and paraneoplastic conditions. Benefits can be attributed to direct tumorcidal effects, anti-inflammatory and/or immunosuppressive properties, and to metabolic properties of glucocorticoids. Commonly, glucocorticoids are used in conjunction with other chemotherapeutic agents in the treatment of lymphoma.[26] Although glucocorticoids sometimes induce remission of lymphoma when used alone (predniso[lo]ne 2 mg/kg/day), rapid development of multi-drug resistance leads to brief remission and decreases the chance that other, more aggressive chemotherapy protocols will be successful.[26] Because glucocorticoids induce apoptosis of neoplastic lymphocytes, the use of these drugs prior to diagnosis may interfere with the ability to cytologically or histopathologically confirm lymphoma. Other cancer types that may respond directly to glucocorticoids include multiple myeloma, certain leukemias, and mast cell tumors.[26-28]

Some paraneoplastic syndromes and some complications from neoplasia may respond to glucocorticoid therapy even when glucocorticoids are not directly tumorcidal.[8] Glucocorticoids are antagonistic to insulin and are therefore used to increase plasma glucose concentrations in animals with insulinoma (predniso[lo]ne 0.5 mg/kg/day). Hypercalcemia resulting from lymphoma or a variety of other neoplastic conditions may respond to systemic glucocorticoid therapy as well (predniso[lo]one 1 to 2 mg/kg/day). In addition to direct effects on lymphoid neoplasia, they inhibit bone resorption, inhibit intestinal calcium absorption, and promote caluresis. Edema and inflammation associated with many types of neoplasia are frequently treated with systemic glucocorticoid therapy on either a short (e.g., during perioperative period surrounding tumor manipulation) or long-term basis (e.g., as palliative therapy for brain tumor).

High Dose, Short-Term Therapy

In certain disease processes, glucocorticoids are used for short periods (often a single dose) in dosages much higher than those required to initiate immunosuppressive therapy. At such dosages glucocorticoids exert actions in addition to those mediated by gene transcription; these actions are somewhat nebulous but include antioxidant properties, membrane stabilization, and hemodynamic effects. Examples of processes treated in this way include central nervous system trauma and various shock states.[29-31] Because a rapid onset of action is required, injectable succinate and phosphate esters are most appropriate. Animals with recent spinal cord injuries (<8 hours from time of insult) benefit from treatment with methylprednisolone sodium succinate (15 to 40 mg/kg IV), although a similar benefit has not been demonstrated for animals with brain injury.[29,32,33] Repeated boluses of 15 mg/kg may be administered 2 and 6 hours later, followed by either boluses of 7.5 mg/kg every 6 hours for 24 hours or by a 24 hour continuous rate infusion of 2.5 mg/kg/hr.

High-dose glucocorticoid treatment for shock has fallen repeatedly in and out of favor. Anaphylactic shock is the only type for which routine treatment still involves the administration of high-dose glucocorticoids.[34] Decades ago, high-dose glucocorticoids were used to treat hemorrhagic shock because of their ability to increase blood pressure. Steroids have fallen out of favor for this use, and treatment should focus on volume, colloid, and hemoglobin replacement. The role of glucocorticoid therapy in septic shock is more controversial. Experimental literature of the 1970s seemed to support claims that high doses of short-acting glucocorticoids (30 mg/kg methylprednisolone) decreased morbidity from septic shock. However, clinical trials in people failed to support these claims, and high-dose steroid therapy in sepsis was discouraged.[35] Recently, glucocorticoids have regained favor in the treatment of sepsis and septic shock, but at much lower dosages designed to counter occult adrenal insufficiency.[36] Thus far, occult adrenal insufficiency has not been documented in critically ill dogs,[37] which leaves the role of low-dose steroids for septic animals in doubt.

Many veterinarians utilize short-term high dose glucocorticoid therapy for treatment of conditions in which massive cytokine release is anticipated (e.g., gastric-dilatation volvulus,

snake bite envenomation). A beneficial role for glucocorticoids in most such situations has been neither confirmed nor denied. Serious complications from intensive short-term glucocorticoid treatment are rare, but they do occur.[38] Therefore it is difficult to recommend high-dose glucocorticoids therapy in the absence of proven benefit for these types of conditions.

ADVERSE EFFECTS OF GLUCOCORTICOIDS

Adverse reactions associated with glucocorticoids are numerous and range from the merely bothersome to the life threatening (Box 136-2). Conditions exacerbated by glucocorticoid effects (e.g., infection, diabetes mellitus, pancreatitis) are relative contraindications to their use. Generally speaking, the more potent the product, higher the dosage, and more prolonged the administration, the more serious are the adverse effects. The most common side effects of glucocorticoid use are polyuria, polydipsia, and polyphagia. Iatrogenic hyperadrenocorticism, distinguishable from pituitary or adrenal dependent hyperadrenocorticism only through clinical history and suppression of response to exogenous ACTH, can occur during prolonged corticosteroid administration.[39] Rapid withdrawal of exogenous glucocorticoids in an animal with suppression of the HPA axis can leave the adrenal gland unable to produce requisite levels of glucocorticoids, creating a state of adrenocortical insufficiency that can have life-threatening consequences. More commonly, rapid cessation of chronic (>2 weeks) therapy results in a constellation of clinical signs including depression, decreased appetite, and vomiting.

Glucocorticoid administration can impact therapy with other pharmaceutical agents. For example, animals receiving immunosuppressive dosages of glucocorticoids should not be given modified live vaccines due to the risk of vaccine-induced disease.[40] Certain pharmaceuticals alter metabolism or clearance of the glucocorticoids, which results in either increased or decreased biologic glucocorticoid effects at a given steroid dose. Additionally, glucocorticoids can impact the effectiveness or toxicity of co-administered pharmaceuticals.[41]

Box • 136-2

Adverse Effects of Glucocorticoid Administration

- Abortion
- Alopecia
- Calcinosis cutis
- Colonic perforation
- Comedones
- Delayed wound healing
- Diabetes mellitus
- Gastrointestinal ulceration
- Growth suppression
- Hypercoagulable state
- Hyperlipidemia
- Iatrogenic hyperadrenocorticism
- Immunosuppression (secondary infection, worsened infection, recrudescence of latent infection)
- Insomnia, agitation, behavioral changes
- Insulin resistance
- Ligament and tendon rupture
- Muscle atrophy
- Muscle wasting
- Myotonia/myopathy
- Osteoporosis
- Panting
- Polyphagia
- Polyuria/polydipsia
- Proteinuria
- Psychosis/behavioral change
- Seizure threshold lowered
- Skin thinning
- Vacuolar hepatopathy

GLUCOCORTICOID REDUCTION PROTOCOLS

Ideally, glucocorticoids should be used at the lowest dose possible to achieve the desired effect. When administered for more than 2 weeks, the dosage should be reduced slowly. This principle fits nicely with the ideal of adjusting the glucocorticoid dose "to effect," particularly in those cases requiring prolonged therapy (e.g., autoimmune disease).

Once clinical evidence suggests that the condition being addressed is controlled (e.g., red cell count normalized when treating immune mediated hemolytic anemia [IMHA], diarrhea resolved when treating inflammatory bowel disease), the dosage of glucocorticoids should be tapered. There is no single ideal way to conduct this tapering, but certain principles apply. First, the clinical condition should be monitored closely. Worsening soon after a dose reduction suggests that the taper is too rapid. Second, the severity of the condition holds implications as to the rapidity of the taper. Glucocorticoids used to treat life-threatening disease (e.g., IMHA) should be tapered more slowly than glucocorticoids used to treat other conditions. Third, consolidated dosing with prolonged dosing intervals might spare HPA suppression while maintaining much of the desirable biologic drug effect. For example, if administering 5 mg prednisone twice daily, it may be better to first switch to 10 mg once a day rather than simply decreasing the twice daily dose. The daily dose can then be decreased incrementally. Dose interval is then changed to an every-other-day (EOD) basis, usually when the daily dose nears a minimal anti-inflammatory range (0.5 mg/kg for dogs). Often, veterinarians choose to increase to dose given on the treatment day so that the total 2-day dose remains unchanged or only slightly decreased initially. Eventually, the glucocorticoid dose is lowered until it is discontinued altogether. Theoretically, EOD (or even every third day) dosing allows the HPA axis to recover from suppression during the "off steroid" day.[42,43] This type of EOD dosing scheme depends on the biologic duration of the steroid preparation and is thus only serviceable using intermediate acting glucocorticoids.

CHAPTER • 137

Over-the-Counter Human Medications

Etienne Côté

Using human nonprescription (over-the-counter, or OTC) drugs in veterinary medical therapy is an attractive option because these drugs usually are inexpensive and widely available. Veterinarians deal with OTC drugs either when they advocate their use for medical treatment or when they manage OTC drug intoxications.

A dizzying variety of brand names and products exists on the OTC pharmaceuticals market. Products with similar names often have very different components. Therefore the veterinarian needs to specify the active ingredients of the drug in question to avoid confusion. For example, many products containing acetylsalicylic acid (ASA) can safely be used for treating dogs and cats, yet varieties of these same products are available in nearly identical packaging and are labeled "aspirin-free," "pain-relief," "cold," "flu," or "sinus." These versions often contain acetaminophen as the active ingredient instead of ASA and therefore have a completely different, and potentially adverse, pharmacologic profile.

A brand name alone (e.g., Anacin, Benadryl) often is inadequate and could be disastrously misleading. Manufacturers may change the contents of a product without changing the brand name. For example, the active ingredient in Kaopectate was formerly kaolin-pectin; now, the active ingredient is either attapulgite or bismuth subsalicylate, but the name of the product remains the same. When the veterinarian advocates the use of a product, confusion can be minimized by giving the client the names of the desired active ingredients and the name of active ingredients to avoid, in writing, and urging the client to seek pharmacist confirmation at the time of purchase (Box 137-1).

Human drugs approved for OTC sale in the United States must be proved to be safe and efficacious in humans, but not in ill dogs or cats. The absorption characteristics of OTC human preparations, particularly time-release or enteric-coated formulations, are designed for the human gastrointestinal (GI) tract but not for that of dogs or cats. Clinical trials assessing the effectiveness of any human OTC-formulated drug against placebo in the veterinary setting remain rare. Therefore when a prescription veterinary drug is available, it may often be safer and more reliable to prescribe it rather than to advocate a human OTC equivalent.

None of the drugs described in this chapter has Food and Drug Administration approval for non-prescription use in dogs or cats in the United States. Advocating the use of these drugs in an extralabel manner signifies that the veterinarian and client understand the risk inherent in using medications not specifically designed for use in animals.

Box • 137-1

Equivalence of Units Commonly Used in Over-the-Counter Human Medications

1 teaspoon (tsp) = 5 ml
1 tablespoon (tbsp) = 15 ml
1 fluid ounce (oz) = 28 ml
1 cup = 237 ml
1 grain = 65 mg
1 pound (lb) = 0.454 kg

ANALGESICS

Aspirin, plain (e.g., Norwich, St. Joseph, Bayer, Anacin, ASA) or buffered (e.g., Bufferin, Ascriptin, Ecotrin), has traditionally been a common treatment for musculoskeletal pain in dogs and cats. The widespread availability of prescription anti-inflammatory drugs that cause fewer adverse GI effects (e.g., carprofen, etodolac, meloxicam) has made aspirin a second choice for therapy. A recommended therapeutic dose of aspirin in dogs is 5 to 12 mg/lb (10 to 25 mg/kg) by mouth two to three times a day, and dogs may require 10 to 39 mg/lb (23 to 86 mg/kg) twice a day to control signs of osteoarthritis. Substantial overlap between therapeutic and toxic doses exists; in dogs, doses of 12 mg/lb (25 mg/kg) by mouth three times a day for 14 days systematically produced adverse GI effects, and doses of 45 to 50 mg/lb (100 to 110 mg/kg) once a day for 1 to 4 weeks were lethal. Concurrent treatment with misoprostol or omeprazole can reduce GI toxicity, but treatment with the H_2-receptor blocking drug cimetidine does not.

Parenteral administration of the salicylates also produces GI toxicity; therefore administering aspirin in pulverized form and/or with a full meal may reduce topical irritation in the stomach, but not all adverse GI effects can be eliminated this way. One regular aspirin tablet, plain or buffered, typically contains 325 mg ASA; "baby" or "low-dose" tablets, 81 mg; and "extra strength" tablets, 500 mg.

Aspirin is indicated for anticoagulation in dogs and cats at doses much lower (dogs: 0.22 mg/lb [0.5 mg/kg] orally every 12 hours; cats: 81 mg/*cat* orally every 72 hours) than the anti-inflammatory dose. Few adverse GI effects can be expected at these doses, but efficacy in animals in a hypercoagulable state, particularly cats with heart disease that are susceptible to arterial thromboembolism, is questionable.

Acetaminophen (Excedrin, Feverall, Liquiprin, Midol, Panadol, Pamprin, Percogesic, Tempra, Tylenol, Bromo-Selzer, paracetamol, and many others, including most "aspirin-free" formulations) is an analgesic drug sometimes used in dogs (7 to 13 mg/lb [15 to 28 mg/kg] by mouth every 8 hours for up to 4 days). It is strictly contraindicated in cats because it induces methemoglobinemia and hemolytic anemia. Hematologic and hepatic adverse effects occur in dogs ingesting large doses (usually >45 mg/lb [>100 mg/kg], but as little as 9 mg/lb [20 mg/kg] in one case). Acetylcysteine (65 mg/lb [140 mg/kg] by mouth or slowly intravenously once, then 32 mg/lb [70 mg/kg] by mouth or slowly intravenously every 4 hours for three to seven treatments) is an antidote.

Other OTC nonsteroidal anti-inflammatory drugs are not currently recommended for veterinary use. Naproxen (e.g., Aleve, Naprosyn) and ibuprofen (e.g., Advil, Motrin, Nuprin) are associated with severe GI ulcerations and perforations in dogs. Ketoprofen (e.g., Actron, Orudis) is approved for use in horses as an injectable, Ketofen, and may eventually be approved for use in dogs and cats in the United States given its common use in small animal medicine in other countries. The current OTC human formulation, like other enteric-coated preparations, may have variable absorption characteristics in small animals.

ANTIDIARRHEALS

Such adsorbents as attapulgite (e.g., Kaopectate, Donnagel) are considered generally harmless but of questionable clinical efficacy. Bismuth subsalicylate (e.g., Pepto-Bismol, 8.7 mg salicylate/ml; Pepto-Bismol Maximum Strength, 15.7 mg salicylate/ml; Pepto-Bismol Caplets, 102 mg salicylate/caplet) has been shown to have a beneficial effect on the morbidity of acute diarrhea in humans. The liquid is given at a dose of 0.125 ml/lb (0.25 ml/kg, or approximately half of a 5 ml teaspoon for a 25 lb [11 kg] patient) by mouth every 4 to 6 hours in dogs and cats. Doses of up to 0.9 ml/lb (2 ml/kg) every 6 to 8 hours has been advocated for dogs only. Cats reportedly are more sensitive to salicylates than are dogs and probably should not receive frequent or high doses of bismuth subsalicylate because some of the salicylate is absorbed systemically.

Loperamide (e.g., Imodium A-D) is an effective opiate antidiarrheal medication. The recommended dose for dogs, 0.04 mg/lb (0.08 mg/kg) by mouth three to four times a day, may be difficult to achieve in smaller animals receiving the tablet form (2 mg loperamide/tablet). The oral liquid preparation (0.2 mg loperamide/ml) may allow a more accurate dosage in smaller patients (e.g., half of a 5-ml teaspoon for a 14 lb [6 kg] dog). Intoxication, manifesting with central nervous system (CNS) signs and vomiting, has been reported in dogs (especially collies) and cats. Naloxone (0.001 to 0.01 mg/lb [0.002–0.02 mg/kg] intravenously or intramuscularly) is an antidote.

ANTIEMETICS

The efficacy of OTC human antiemetics in small animal medicine remains unproved. Such drugs as dimenhydrinate (e.g., Gravol, Dramamine [50 mg/tablet]; dose: 2 to 4 mg/lb [4 to 8 mg/kg] by mouth up to every 8 hours), meclizine (e.g., Bonine, Dramamine II; dose: 0.6 mg/lb (1.25 mg/kg) by mouth once daily; maximum single dose: 25 mg), and cyclizine (e.g., Marezine) are sometimes given for the short-term prophylaxis of motion sickness in dogs and cats. Adverse effects appear to be uncommon, but CNS depression and lethargy have been reported anecdotally in dogs receiving 4 to 9 mg/lb [10 to 20 mg/kg] dimenhydrinate, and similar, mild signs have occurred with dogs that ingest meclizine 2.2 to 4.5 mg/lb (5 to 10 mg/kg).

CHRONIC RENAL FAILURE DRUGS

Such phosphate binders as aluminum hydroxide (e.g., Amphojel, 64 mg $Al(OH)_3$/ml; AlternaGEL, 120 mg $Al(OH)_3$/ml) are advocated for use in the treatment of hyperphosphatemia at an initial dose of 4.5 to 14 mg/lb (10 to 30 mg/kg) by mouth every 8 to 12 hours. Exact titration of the dose depends on effect (subsequent serum phosphorus levels). Constipation and loss of appetite are possible side effects. Other phosphate binders include calcium carbonate (e.g., Titralac, Tums [500 mg $CaCO_3$/tablet]; dose: 4.5 to 14 mg/lb [10 to 30 mg/kg] by mouth every 8 to 12 hours and adjusted based on degree of control of phosphorus levels), although less effective phosphate binding and hypercalcemia are possible drawbacks. The use of magnesium-containing phosphate binders (e.g., Maalox, Mylanta) is discouraged because of the commonly impaired ability to excrete magnesium in cases of renal failure, potentially leading to hypermagnesemia.

COUGH SYRUPS

Most OTC cough syrups contain one or more of the following five active ingredients: acetaminophen, chlorpheniramine, pseudoephedrine, guaifenesin, and dextromethorphan. Acetaminophen and pseudoephedrine are described elsewhere in this chapter. Guaifenesin is considered to be of minimal therapeutic value in the treatment of coughs; it has been thought to attenuate the cough reflex and to make respiratory secretions thinner, but clinical trials have shown that it does neither. Antihistamines are considered minimally useful in the treatment of nonallergic causes of cough. Of these five active ingredients, dextromethorphan has been used successfully (though empirically) in the treatment of coughing dogs and cats at a dose of 0.22 to 0.9 mg/lb (0.5 to 2 mg/kg) by mouth every 6 to 8 hours. Although seemingly less effective than opioid antitussives, it is an effective cough suppressant and therefore is contraindicated when cough is beneficial, such as in the expectoration of pus in cases of pneumonia. Most cough syrups contain multiple active ingredients, and currently only a few, such as Vicks Formula 44 (not 44D, 44E, or 44M) and Robitussin Maximum Strength Cough contain only dextromethorphan (2 mg/ml and 3 mg/ml, respectively). Unwanted and potentially dangerous active ingredients are present in many preparations. For instance, NyQuil liquid contains dextromethorphan as a cough suppressant, but it also contains pseudoephedrine and more than 150 mg acetaminophen/5 ml teaspoon.

DERMATOLOGIC DRUGS

Several antihistamines are used in veterinary dermatology. Chlorpheniramine (e.g., Chlor-Trimeton; dose: 2 mg/*cat* by mouth every 12 hours; 2 to 8 mg/*dog* by mouth every 12 hours, not to exceed 0.22 mg/lb [0.5 mg/kg] every 12 hours), effectively controls 70% of seasonally pruritic cats and is of some value for the same problem in dogs. Clemastine fumarate (e.g., Tavist Allergy; dose: 0.022 to 0.045 mg/lb [0.05 to 0.1 mg/kg] by mouth every 12 hours) and diphenhydramine (e.g., Benadryl Allergy; dose: 1 to 2 mg/lb [2 to 4 mg/kg] by mouth every 8 hours) also control pruritus of allergic origin in some dogs.

Such topical antibacterials as bacitracin (e.g., Bacitracin Plus) and triple antibiotic combinations (e.g., Neosporin) are probably minimally effective but also minimally harmful. Such antifungals as clotrimazole (e.g., Lotrimin, Cruex) and miconazole (e.g., Micatin) are effective against several types of fungi, including *Malassezia* yeasts, dermatophytes, and saprophytes such as *Aspergillus* spp. The reader is referred to additional sources for exact protocols for the use of these drugs.

Zinc oxide creams (e.g., Desitin) frequently are applied to burned or irritated skin. The usefulness of zinc oxide in treating such conditions, and as a sunscreen, must be weighed against the potential for toxicity, which can manifest as vomiting and lethargy after animals lick the product off the skin.

Benzocaine is present in some dermatologic "soothing" preparations. It can cause hemolytic anemia in cats and dogs that ingest it. In these species, such preparations should be used cautiously if at all.

EMETICS

For those situations in which emesis is to be induced, oral administration of syrup of ipecac is effective and safe (2 to 6 ml by mouth). Only one additional dose is recommended if vomiting has not occurred within 15 minutes. Orally administered 3% hydrogen peroxide (dose: 0.11-0.22 ml/lb [0.25-0.5 ml/kg] by mouth; the dose can be repeated once after 5 to 15 minutes if vomiting has not occurred) also effectively induces emesis in many dogs and cats. Both of these products are widely available as generics. Large doses of table salt, although sometimes emetic, are not recommended because of the potentially serious consequences of hypernatremia if no vomiting occurs.

GASTRIC ACID–REDUCING DRUGS

The phosphate binders described earlier are also antacids. They are rarely used in canine and feline medicine because of the frequent dosing needed to maintain a high gastric pH. The H_2-receptor blocking drugs cimetidine (e.g., Tagamet HB 200; dose: 4.5 mg/lb [10 mg/kg] by mouth every 8 hours), ranitidine (e.g., Zantac; dose: 0.9 mg/lb [2 mg/kg] by mouth every 8 to 12 hours), famotidine (e.g., Pepcid AC; dose: 0.22 mg/lb [0.5 mg/kg] by mouth every 12 to 24 hours), and nizatidine (e.g., Axid AR; dose: 1.1 to 2.2 mg/lb [2.5 to 5 mg/kg] by mouth every 24 hours) all decrease gastric acid secretion. Some (ranitidine, nizatidine) also have GI prokinetic activity. Famotidine and nizatidine do not affect hepatic p450 enzymes. The H_2-blockers have a wide margin of safety; for example, no deaths were recorded in dogs acutely given famotidine 900 mg/lb (2000 mg/kg) by mouth or nizatidine 360 mg/lb (800 mg/kg) by mouth, nor were there overt adverse effects in dogs given cimetidine 65 mg/lb (144 mg/kg) by mouth once daily for 7 years.

LAXATIVES AND ENEMAS

A variety of OTC preparations is available to effectively manage constipation. Such stimulant laxatives as bisacodyl (e.g., Dulcolax, Correctol, Ex-Lax Ultra; dose: 5 mg/*cat* by mouth once daily; 5 to 20 mg/*dog* by mouth once daily) increase myenteric nervous activity and peristalsis. They are advocated for short-term use only. Emollient laxatives (docusate [Colace, Surfak]; dose: 1 mg/lb [2 mg/kg] by mouth once daily in dogs; 25 mg/*cat* by mouth once daily) soften the stool and are said to be more effective in acute rather than chronic constipation. Hard capsule formulations make the dosage of this type of laxative challenging in small patients. Constipation prevention may be achieved using such soluble fiber products as psyllium mucilloid (e.g., Metamucil; dose: 1 tsp/11 to 22 lbs [5 to 10 kg] body weight, added to the food), with the exact dose titrated to result in soft, formed feces. Newer laxatives containing anthraquinone derivatives like senna have yet to be used in a widespread fashion in veterinary medicine and some aspects of their effects remain controversial in human gastroenterology.

Phosphate enemas (e.g., Fleet) are contraindicated in cats, and possibly small dogs, because of the severe hyperphosphatemia they induce. Instead, pediatric emollient enemas (e.g., docusate sodium) have been used successfully and safely.

OPHTHALMIC DRUGS

Irrigating solutions (e.g., Dacriose, Collyrium for Fresh Eyes) are used for cleaning debris and pus from the eyes on a short- to long-term basis. Artificial tears (e.g., Adsorbotear, Tears Naturale) are used for tear replacement; solutions that contain polyvinyl alcohol may be irritating, however. Ophthalmic decongestants (e.g., Visine, OcuClear) are of essentially no therapeutic worth; they obscure the diagnosis and may cause chronic conjunctivitis.

URINARY INCONTINENCE DRUGS

In 2000, phenylpropanolamine was completely withdrawn from the U.S. market due to its association with hemorrhagic stroke in humans. Although no such link has been noted in veterinary medicine, the lack of OTC phenylpropanolamine has increased interest in pseudoephedrine (e.g., Sudafed 30 mg or 120 mg tablets; also in many cold/flu products [see cough syrups, above]) as an alternative drug for controlling urinary incontinence at a starting dose of 0.1 to 0.2 mg/lb (0.2 to 0.4 mg/kg) by mouth every 8 to 12 hours. Clinical evaluation of pseudoephedrine for urinary incontinence in dogs is limited; higher doses of 15 or 30 mg by mouth every 8 hours to dogs weighing less than or more than 55 lbs (25 kg), respectively, have effectively controlled signs of incontinence with no recorded side-effects. However, a narrow margin appears to exist between therapeutic and toxic doses of pseudoephedrine in some dogs, with clinical signs occurring with single-dose ingestions of 2.2 to 2.8 mg/lb (5 to 6 mg/kg) and deaths with ingestions of 4.5 to 5.4 mg/lb (10 to 12 mg/kg). The high concentration of drug in tablets can make exact dosage more difficult in small dogs; choosing other medications, or meticulous preparation of exact doses, may be preferable for these patients. Advocation of the use of pseudoephedrine should be cautious, and with an understanding of the possible, common adverse reactions (e.g., restlessness, excitement, and tachycardia), which could be detrimental, particularly in patients with cardiac or neurologic diseases.

Over-the-counter drugs may be useful in specific therapeutic situations in which convenience, lack of an effective veterinary equivalent, or cost play an important role in drug selection. These advantages need to be weighed against the drawbacks of drug formulations meant for humans, frequent lack of proven efficacy, absence of veterinary labeling for these products, and the potential for selection of the wrong product by the client.

CHAPTER 138

Compounding Drugs

Ron Johnson

For drug therapy to be considered rational, practitioners must ensure that administration of the drug is safe and efficacious for its intended use. Veterinary medicine does not have a plethora of U.S. Food and Drug Administration (FDA)–approved animal drugs and dosage forms. Added to this dilemma is the need to treat several species of different sizes and biologic make-ups. Compounded drugs can alleviate some of the drug-related issues that face veterinary medicine, provided compounding is approached in a rational manner. The Animal Medical Drug Use Clarification Act (AMDUCA) of 1994 legitimizes compounding from approved animal and human drug dosage forms provided certain criteria are met.[1,2] In this context, compounding is defined by the FDA as any manipulation of the product to produce a drug dosage form other than that manipulation provided for in the directions for use on the labeling of the approved drug product.[2] This form of compounding results in extra-label use of the approved drug product. Compounding from unapproved drug products and bulk products (active ingredient in the unfinished form) are also possible. To encompass these situations, a more general definition of compounding is needed. This includes the preparation of therapeutic compounds that utilize active ingredients and vehicles obtained within the law.

PHARMACOLOGY CONSIDERATIONS WHEN COMPOUNDING IN COMPANION ANIMALS

Veterinarians need to understand the pharmacologic issues associated with the use of compounded drugs in their patients. Although the decision to compound can be necessary and acceptable under certain conditions, it should not be driven by convenience or economics. Rather, rational therapy based on scientific justification should prevail. The mixing or combining of drugs or the addition of diluents (e.g., lactated Ringer's solution), vehicles (e.g., propylene glycol, dimethylsulfoxide), or flavoring agents to a drug may produce a chemical or physical interaction that renders the product inactive and yields therapeutic failure or may produce a potentially toxic compound. These forms of drug interactions are pharmaceutical interactions or incompatibilities and are demonstrable *in vitro*, that is, outside the body. Manipulations of the dosage form can also result in contamination of a sterile product meant for injection or affect drug bioavailability through alterations in drug release rates.

Compounding by medical professionals and pharmacists is not equivalent to the formulation of commercially manufactured products by reputable pharmaceutical firms. Drug formulation requires an immense understanding of the physical and chemical characteristics of the active ingredient, along with the other agents (e.g., vehicles, excipients) used to produce the administered drug's effectiveness and safety profile. To this end, a compounded drug must possess adequate potency and purity and demonstrate stability (shelf-life) to maintain acceptable bioavailability (extent of systemic drug absorption) of the active ingredient but not produce toxicity or adverse effects. However, for most drugs compounded by veterinarians or pharmacists, there is a lack of adequate pharmaceutical testing and clinical testing to ensure drug quality. Because safety, efficacy, and drug pharmacokinetics have not been determined for most compounded products, and likely not to be, it is important for the veterinarian to establish objective parameters, which indicate whether the compounded product is efficacious, subtherapeutic, or toxic.[3] Objective parameters can include hematologic or clinical chemistry changes, serum drug levels when drug monitoring is available, clinical signs, and clinical end-points.

COMPOUNDING BY THE VETERINARIAN VERSUS PHARMACIST

Compounded products for use in veterinary medicine must be prepared either by the veterinarian in conjunction with a valid Veterinarian-Client-Patient Relationship (V-C-P-R) or by a licensed pharmacist under the order of the veterinarian. Some of the reasons for employment of compounded drugs in animals include the lack of FDA-approved animal product at an appropriate concentration, drug formulated in a usable dosage form, or available in the required combination.

Requests to pharmacists from veterinarians for compounded prescriptions often surround reformulation of human-labeled drugs for use in companion animals, particularly tablets and capsules.[4] Requests for the mixing of multiple drugs in a single product and formulation of novel systems for drug delivery such as transdermal gels are also increasing. Palatability concerns with various oral preparations have seen the use of flavoring agents to enhance preparation acceptability. Most pharmacists will compound drugs for veterinarians; however, care must be exercised with the selection of a compounding pharmacist. With the need for compounding on the rise, many pharmacists have become members of societies dedicated to reputable compounding, such as the International Academy of Compounding Pharmacists or the Professional Compounding Center of America. Pharmacists with advanced training in compounding can provide valuable expertise and should be sought when the decision to use a compounded drug is made by a veterinarian. Veterinary organizations such as the American Veterinary Medical Association, the American College of Veterinary Clinical Pharmacology, and the American Academy of Pharmacology and Therapeutics along with published literature in reputable journals also represent valuable sources of information on compounding for animals.

The FDA Center for Drug Evaluation and Research has made available a concept paper that evaluates drug products for human use that demonstrate difficulty when compounded because of reasons of safety or effectiveness.[5] The goal of the paper is to identify drugs that are demonstrably difficult

to compound based on several evaluating factors, which are also pertinent to compounding for veterinary use. Among these evaluating factors training, facilities and equipment, testing, and quality assurance provide the clearest argument for separating compounding by the pharmacist versus the veterinarian, when other than minor manipulations to the product are required.[4,5] Product categories found notoriously difficult to compound that should be avoided include sterile products, sustained release products, and most transdermal delivery systems.[5] In contrast, candidates most suited for compounding can include drugs with a wide therapeutic index, and drugs for which therapeutic drug monitoring or quantitative end-point measurement is possible and clinical data regarding their use in the intended species and condition is available.

DOSAGE FORMULATION AND STABILITY OF COMPOUNDED PRODUCTS

Compounded preparations must possess acceptable potency, purity, and quality with appropriate labeling and packaging to ensure effectiveness, proper use and safety.* Compounding should be conducted in accordance with good pharmacy practices and relevant scientific literature. Pharmacy facilities used for compounding should have adequate room and equipment and be maintained in a clean and sanitary condition to be effective and prevent contamination and errors. Areas used for preparation of sterile products such as sterile injectables or ophthalmic solutions should be separate from nonsterile compounding areas (Box 138-1).

The stability of a compounded preparation is critical to the determination of an expiry or beyond-use date, after which the compounded product should not be used. When a manufactured product is used as the active ingredient source for compounding nonsterile preparations, the manufactured product expiration date cannot be used to directly extrapolate a beyond-use date for the compounded product. Whenever possible, drug-specific and general stability data and literature should be consulted prior to compounding. In the absence of stability data applicable to a particular drug and specific compounded preparation, the conservative maximum beyond-use or expiry dates recommendations listed in Box 138-2 may serve as suggested general guidelines for nonsterile compounded drug products, which are packaged in tight, light-resistant containers and usually stored at room temperature.

Transdermal Delivery of Drugs with Organogels

The skin offers an ideal alternative to systemic delivery of drugs in veterinary patients; however, significant interspecies differences in skin structure and function represent potential challenges to this route of drug delivery. Delivery of drugs that use transdermal gels is among the newest drug delivery system being utilized in veterinary medicine. Transdermal gels can be utilized effectively and safely in veterinary medicine and can enhance patient compliance. Absorption of drug via the transdermal route is primarily passive. As such, ideal drug molecules for this route of delivery are low molecular weight (<400 Daltons), lipophilic in nature, and soluble in both water and oil.[7]

The growing list of drugs available in transdermal gel formulation from compounding pharmacists includes antimicrobials,

*Information presented in this section, including recommendations and precautions regarding dosage formulation and expiry dates of compounded drugs listed in Boxes 138-1 and 138-2, respectively, can be found in the United States Pharmacopeia and National Formulary.[6]

Box • 138-1

Aspects of Dosage Formulation Applicable to Drugs Compounded for Companion Animal Use

1. When formulations require the use of water for compounding nonsterile preparations, purified water must be used.
2. Water used for preparation of a sterile product must be either: (a) water for injection, (b) sterile water for injection, or (c) bacteriostatic water for injection.
3. When compounding any formulation starting with a solid material or component, the particles should be reduced to the smallest reasonable size before mixing.
4. When compounding emulsions, solutions, or suspension dosage forms, or semisolid dosage forms such as creams, ointments, topical gels and pastes, an excess amount of the total formulation should be prepared to ensure the prescribed amount can be accurately dispensed.
5. Solutions should contain no visible undissolved materials when dispensed to the client.
6. Emulsions and suspensions should contain instructions to "shake well before using" to ensure uniform dispersion of the active ingredient.
7. Creams, topical gels, ointments, and pastes should not be prepared with ingredients that are irritating or caustic to the skin, and appropriate vehicles or bases should be employed to achieve the desired local or systemic therapeutic effects.
8. The uniformity of dispersion of the compounded gel, cream, ointment, or paste should be assessed by spreading a thin film of finished product on a flat transparent surface, e.g., clear glass.

Box • 138-2

Guidelines for Maximum Expiry Dates for Nonsterile Compounded Drug Products

1. For solid dosage formulations and nonaqueous liquids where the manufactured drug product is the active ingredient source, the beyond-use date should not exceed 25% of the time remaining until the manufactured products expiration (or 6 months, whichever is earlier).
2. For water-containing formulations prepared from active ingredients in solid form such as bulk drug (active ingredient in the unfinished form), capsules or tablets, the beyond-use date should not exceed 14 days from preparation when the compounded product is cold-stored.
3. For other formulations, the beyond-use date should not exceed the duration of therapy (or 30 days, whichever is earlier), unless supportive stability date for the compounded preparation exists.

anticonvulsants, hormones, antineoplastics, prokinetic drugs, analgesics, and anti-inflammatory agents. The vast majority of these compounded products are prepared in a pluronic lecithin organogel (PLO) vehicle. Lecithin is an emulsifying agent that forms a viscous gel when combined with water. Pluronic is a surfactant that enhances the formation of drug-containing micelles in a gel matrix. Together, these carriers can dissolve and deliver either hydrophilic or lipophilic molecules, which makes them convenient for delivery of a variety of chemical agents. The transdermal route of drug delivery provides for several advantages, including owner compliance, patient tolerance, ease of administration, and most importantly, the ability to by-pass first pass metabolism by the liver.[7,8] As such, it is possible to deliver agents with low oral bioavailability. Transdermal gels offer an exciting new mode of drug delivery for the veterinary patient. Although investigations with transdermal delivery of drugs are currently underway, most agents compounded with organogels have had little to no clinical data generated with their use. Therefore the clinician must assess both benefits and risks with this mode of drug delivery.

REGULATION OF COMPOUNDING FOR VETERINARY MEDICINE

The FDA Center for Veterinary Medicine (CVM) provides regulatory surveillance and enforcement of drug compounding for veterinary medicine under the authority of the Food and Drug Cosmetic Act. The circumstances whereby compounding from approved drugs (animal and human) for animal use by veterinarians is legal can be found in the contents of AMDUCA.[1,9] The FDA-CVM does recognize the need, in limited situations, to compound products from unapproved drugs and occasionally from bulk drugs, provided certain conditions are met. Compliance Policy Guideline 7125.40 was written by the agency to outline guidelines for compounding from approved animal and human dosage form drugs, and unapproved drugs and bulk drugs that ordinarily will not merit regulatory action even though they are technically in violation of AMDUCA.[1] The latter is termed *regulatory discretion*.

Recent FDA concerns regarding compounding have focused on pharmacies that generate large amounts of unapproved drugs for animal use that are largely copies of FDA-approved drugs. These practices constitute attempts to by-pass the drug approval process and can be construed as illegal manufacturing disguised as compounding. The purpose of compounding by a veterinarian or pharmacist under the order of a licensed practitioner is to prepare an individualized drug treatment and not manufacture products for resale.[3,4] Summary recommendations for compounding drugs for use in companion animals are found in Box 138-3.

Box • 138-3

Recommendations for Compounding Drugs for Companion Animal Use

1. The use of compounded drugs should be based on rational therapy originating from a veterinarian and not a pharmacist.
2. Compounding drugs to provide appropriate medical therapy may be necessary when (a) a legitimate medical need exists such as suffering or death resulting from a lack of treating the affected animal, (b) an appropriate dosage regimen does not exist for the species, size, age, or medical problem of the intended animal, or (c) there is no marketed approved animal or human drug available to treat the condition or there is reason to believe the approved drugs will not be efficacious or safe in the intended animal.
3. Compounding must be conducted within the limits of a legitimate pharmacy or veterinary practice.
   Legitimate Pharmacist: A person dispensing pharmaceuticals based on a valid prescription while holding a valid license and conforming to state laws.
   Legitimate Veterinarian: A person prescribing or dispensing pharmaceuticals based on a valid Veterinarian-Client-Patient Relationship while holding a valid license and conforming to state laws.
4. The advice or assistance of pharmacists dedicated to reputable compounding should be sought.
5. Compounded drugs dispensed by a veterinarian (or pharmacist) should contain adequate labeling information to ensure safe and acceptable product use and patient records must be kept.
6. Compounded products should be sold to the individual client and not to other veterinarians or pharmacists for resale.

CHAPTER 139

Nutraceuticals

John E. Bauer

Development of complete and balanced formulated pet foods has been the foundation for dietary recommendations in small animal practice. Modern veterinary nutrition and food manufacturing techniques have culminated in consistent and reliable "functional food" products. Their use is not likely to be abandoned and improvements continue to be made. Nonetheless, many individuals who are interested in dietary supplements, functional foods, and beverages (e.g., nutraceuticals) are also pet owners who wish to provide an extra margin of nutritional benefit for their companion animals. Thus it is no surprise that functional ingredients, treats, supplements, and even beverages have begun to appear that are specifically designed for dogs and cats. These owners see maintaining companion animal health and seeking optimal nutrition for dogs, cats, and other companion animals as an important component of responsible pet ownership. With the myriad products and supplements currently available, veterinary health professionals are often asked to comment on the use of these materials and may find themselves recommending some of them for pet health management. Thus it is important to obtain a better understanding of nutraceuticals, supplements, and functional food ingredients.

REGULATORY ASPECTS

Legal definitions for the term *nutraceutical* do not exist, although the word was originally coined to refer to any substance that can be administered orally (as are foods) to promote good health and that is not a drug.[1] The Food and Drug Administration (FDA) defines a food as a substance that provides nutrition, taste, or aroma.[2] By comparison a drug is a substance that is either a food or non-food substance used to treat, cure, mitigate, or prevent disease.[2] Drugs, by law, must undergo an approval process that substantiate their safety and efficacy. Therefore an important distinction between a food and a drug exists. In the midst of these definitions, nutraceuticals have found a place for themselves somewhere between foods and drugs. One of the well-known examples of such a substance is fish oil, available in gel capsules from several manufacturers. These and other such substances are in use today in veterinary practice.

The Dietary Supplement Health and Education Act (DSHEA) was passed by the U.S. Congress in 1994. This act facilitated the availability of various nutritional products and supplements for human beings because it considered dietary supplements as a separate food category. It also opened the possibility of certain types of claims (i.e., structure/function claims) to be made without having any scientific evidence submitted to the FDA prior to marketing. However, DSHEA applies only to human foods. Discussion of animal dietary supplements was left out of the deliberations.

With respect to animal foods, responsibility for enforcing all aspects of the Food, Drug and Cosmetic Act that may apply to foods and drugs for animal use rests with The Center for Veterinary Medicine (CVM) of the FDA. This group is involved in reviewing food and feed additives. For reasons beyond the scope of this chapter, the CVM has essentially assigned "low regulatory significance" to most nutraceuticals. As a result, individual states were left to rule on market access to these substances.[3]

CLINICAL USE

It is helpful to know that, although the DSHEA governs human dietary supplements, this act is generally interpreted by the FDA's CVM office to not apply to animals.[4] However, pet owners often purchase nutraceuticals and other supplements labeled for human use and administer them to their pets. What, then, should be the basis for veterinary recommendation of a specific substance?

GENERAL GUIDELINES

In the absence of a science-based regulatory consensus, the best advice is to proceed cautiously and seek out new information as it becomes available. Scientific data about certain substances is often unknown or incomplete, although they may be promoted as if conclusive evidence exists.

Four important types of information should be borne in mind during consideration of the use of a particular dietary supplement in companion animals. This type of information ideally should be known prior to recommendation of any widespread or long-term nutraceutical usage. The more gaps that are found in a particular substance's information profile, the more cautiously one should proceed regarding dosage, indications, and patient monitoring. These four categories of information can be easily recalled using the acronym *PETS* (Product Quality, Efficacy, Tolerance, and Safety) and can be used to assist discussions with clients about a particular supplement.

Product Quality (P)

The product quality of a substance should be documented and available. Independent of any scientific proof of efficacy or safety (discussed below) if a product is making a structure/function claim, it must first contain an amount within a realistic concentration range of potential efficacy and safety. Some manufacturers reportedly place a small amount of a popular ingredient in a product, which then allows what is termed "label dressing."[5] This practice is not highly regarded among reliable manufacturers. Also, manufacturers should be knowledgeable about their product, its formulation, and ingredient sources.

For the most part, nutritional supplements should be considered chemicals rather than commodities such as grains or protein meals. Each batch the manufacturer receives should have specifications as to its purity. Some preparations may contain less of the "active" material, which is all right as long

as the product is formulated to provide enough of the ingredient and as long as there are no harmful or interfering materials present. To some extent, the cost of a substance may reflect its quality but not always. Individual distributors should be consulted for further information regarding the manufacturer. The manufacturer then may be contacted for answers to any questions regarding product quality. The answers should include information on specifications and what other substances may be present in the product formulation. The manufacturer should readily supply quality control and other supporting information when requested. This latter point may be an important part of any decision to use a particular product. Any reluctance on the part of the manufacturer or distributor to provide information should warrant finding another source of that particular substance.

Efficacy (E)

Efficacy of any therapy is established by scientific testing. Demonstrating efficacy of a nutraceutical substance requires rigorous and often expensive testing, depending on the extent to which claims for a product are being made and the regulatory environment surrounding that substance. Manufacturers should be asked to supply supportive documentation of efficacy. This information may be proprietary, but reprints of articles and other information should be available upon request. If supporting information is not offered, another product should be selected and the process begun again. Any materials sent should be reviewed with the following questions in mind: What is the active ingredient? Are there several active ingredients acting together? Have any efficacy studies been performed in the species of interest (target species) and, if not, in other species? Were the studies controlled and published under peer-review? Was the same dose used in the studies as is now being recommended for the product?

Tolerance (T)

Tolerance for any nutraceutical must exist for it to be effective. It must be acceptable by the animal and to the pet owner. For example, administering fish oil capsules to dogs is a simple task because most dogs will readily accept them as treats. However, some animals may smell "fishy" and owners may object. Administering fish oil capsules to cats is more difficult, especially if a cat happens to bite into a capsule and develop a taste aversion. In some cases, the inert ingredients that often serve as dispersants or diluents may cause an adverse reaction. An example is the flatulence that may occur due to inclusion of a fermentable fiber. The net effect may result in erroneously shifting blame on the pet food rather than the supplement. Alternatively, product intolerance may cause an owner unnecessary expense in searching for some medical reason for the problem. Milk sugars, such as lactose, may cause gastrointestinal upset, diarrhea, or vomiting. Eliminating the supplement or changing to another product to eliminate these inert materials may be all that is required. However, veterinary personnel must remember to think of these possibilities when owners' insist on using supplements. Also, it must be identified what other medications that animal is receiving. An interaction with the nutraceutical may be occurring, which would render traditional therapies useless.

Safety (S)

Safety is paramount and must be known before using a dietary supplement, as expressed in the dictum, "Above all else, do no harm"? Historical data on usage of certain substances may provide practical information regarding safety. Using a particular supplement in the absence of any published safety data in the target species is particularly risky and caution is advised. Also, lack of reports in the literature of any adverse effects should not be interpreted to indicate safety. The cost and expense to conduct safety studies may be more than some supplement marketers may wish to incur. Even for those substances for which such data is provided, caution is warranted: as the actual concentrations and purities of a particular substance can vary from source to source.

Many pet owners will be administering nutraceuticals to their pets regardless of veterinary advice or supervision. Labels of any products used should list the ingredients along with their amounts and purity in decreasing order of concentration based on weight. Directions for use and other requisite guarantees should be included on the label depending on state feed regulations for specific, more traditional components, such as crude protein, crude fat, fiber, ash, and moisture. Herbal type products should be especially evaluated with caution due to potential toxicities and product quality concerns.

With increased interest in human supplement usage, the opportunity for accidental ingestion of nutraceuticals by companion animals also exists. A recent report summarized 47 dogs suspected of caffeine and ephedrine toxicosis that had access to herbal preparations that contained guarana and ma huang.[6] Clinical signs included the full gamut of those associated with the gastrointestinal tract, CNS, and cardiopulmonary system. Amounts of guarana (caffeine) and ma huang (ephedrine) ingested by these dogs ranged from 80 to 3600 mg of guarana and 24 to 1080 of ma huang.[6]

The ready availability of supplements in retail outlets, by mail order, and the Internet along with supporting brochures may be all that many pet owners need to conclude that a particular product is safe. Clients must be made aware of health concerns with use of an unproven substance against the veterinarian's best judgment. Any dietary histories taken must include the use of any nutraceutical type substances.

NUTRACEUTICALS OF CURRENT INTEREST

Although scientific data in target species remains limited for many types of nutraceuticals, some usage categories of pet dietary supplements and ingredients presently are receiving closer attention by the pet industry and veterinarians. Two of these categories include joint soundness and skin health. Antioxidants are also gaining becoming more popular and these are covered in a separate chapter.

Joint Health

Improvements in pet food quality and feeding practices combined with better veterinary care has resulted in increased longevity of companion animals. However, as with human beings, increased life expectancy has increased the risks for the development of chronic, progressive disease such as osteoarthritis, obesity, renal failure and their complications. With increased age, the genetically influenced degenerative diseases such as intervertebral disk disease, hip dysplasia, cognitive disorders, and familial disorders may also become exacerbated. In addition to specialty foods containing substances with purported benefits, a number of supplement products have been developed in response to improving joint and bone health. Some of these substances are glucosamine, chondroitin sulfate, green-lipped mussel, methylsulfonyl methane, and trace minerals such as zinc, copper, and manganese. Many products use combinations of some but not all of these materials. Although it is often difficult to scientifically prove that one particular substance is efficacious when combined with others, there is growing evidence that some of these products have a beneficial effect on joint health. Some mention will be made of combination products that are available. However, to the extent possible, the discussion focuses on effects of single agents such as glucosamine and other compounds.

Glucosamine is an amino sugar that is naturally produced in the body. It is a component of glycosaminoglycans (GAGs) present in joints, tendons, ligaments, skin, and blood vessels. The GAGs are long chain molecules that can hold water and allow the joint capsule to adapt to changes in pressure and therefore absorb shock induced by mechanical stress. Destruction of cartilage is characterized by destruction of the GAGs and loss of this property of the joint capsule. Theoretically it is expected that provision of supplemental glucosamine to joint issues will stimulate new GAG production. Data demonstrates that glucosamine can be absorbed via the gastrointestional tract in dogs after oral ingestion and is taken up by articular cartilage.[7]

A biochemical basis for the use of glucosamine in treatment of chronic inflammatory disease has also been shown in the rat model of lipopolysaccharide-induced inflammation. Here it was found that glucosamine inhibits inducible nitric oxide synthesis. Excess nitric oxide mediates the pathogenesis of osteoarthritis.[8] Recently, in human osteoarthritis patients, the long-term effects of glucosamine sulphate have been evaluated using a randomized, placebo-contolled clinical trial (1500 mg orally).[9] Symptom-modifying and structure-modifying effects were found, which suggests the compound could mitigate osteoarthritis. Regarding the safety of this compound, no significant differences in adverse events compared with placebo were found.[9]

Long-term safety studies of the chondroprotective agents in dogs or cats have not been reported. However, one caveat regarding the widespread use of glucosamine should be noted. Glucosamine infusions in ducks and dogs have been reported to cause hyperglycemia due to the release of glucagon immunoreactivity and possible insulin suppression.[9,10] Similarly in human beings, glucosamine infusions produced acute insulin resistance[11] and glucosamine may also induce or exacerbate insulin resistance.[12]

Thus, in cases of diabetes or possibly even obese animals prone to type II diabetes, the use of glucosamine may be contraindicated. An anecdotal report using a high oral dose of glucosamine (1000 mg/day, duration unspecified) in an 11 year-old Labrador retriever noted urinary incontinence, polyuria, and polydipsia, which abruptly returned to normal when the dosage was reduced to 500 mg/day.[13] However, serum glucose concentration tested using a midday, nonfasted sample was normal and follow-up tests were not conducted in this dog. By contrast, one study in rats was unable to demonstrate adverse effects of glucosamine or chondroitin sulfate on glucose metabolism.[14] Until more usage data is obtained, caution is advised and patients should be carefully monitored, especially if higher dosages are being used or considered.

With respect to other chondoprotective agents, data exist that support an interactive, or synergistic, effect between glucosamine and chondroitin sulfate in helping maintain joint health. Combinations of glucosamine with other products that contain mucopolysaccharides or other substances may help alleviate joint problems or rebuild degenerating cartilage. One proprietary product in particular, which combines glucosamine with chondroitin sulfate and manganese ascorbate, has been subjected to several cell culture and animal studies in dogs and other target species.[15-18] Survey data of practicing veterinarians have provided information that pain relief as well as mobilility was good to excellent with this type of combination product.[16]

Other substances that may benefit joint health include methylsulfonylmethane (MSM) and green-lipped mussel extracts. Purported benefits of MSM relate to it as a bioavailable source of sulfur, which is a component of several structural compounds found in joints.[19] The use of MSM in dogs or cats remains to be evaluated. Studies using green-lipped mussel extract, a mixture of glucosaminoglycans and omega-3 fatty acids and possibly other compounds, have been inconsistent in dogs exhibiting chronic lameness.[20,21] Additional proprietary combinations have also been evaluated.[22,23] In these cases, potential benefits of glucosamine may be further enhanced by the addition of other known collagen-matrix components or even anti-inflammatory agents.

As additional findings of both proprietary mixtures and single substances are reported, further confidence in the safe and efficacious use of chondroprotective materials, in certain clinical cases, will develop. However, at present, caution is advised with these agents in dogs and cats, especially the use of glucosamine compounds in animals at risk for diabetes.

Skin Health

When animals have skin problems, a full dermatologic work-up should be conducted rather than simply using diet or dietary supplements in the hopes of improvement. Shampooing, brushing, and use of moisturizers are significant components of skin care. Ensuring that the animal is fed a well-formulated diet is also important. Supplementation with therapeutic amounts of fatty acids or diet change is generally considered where animals are pruritic due to hypersensitivity reactions, exhibit dry, flaky skin, or have suspected abnormalities of fatty acid metabolism.

Omega-6 fatty acids (e.g., linoleic acid) are used preferentially for select functions. These include incorporation into the lipid ceramide layer of the epidermis, which imparts its water-barrier character or their provision of precursors for physiologically important eicosanoid synthesis to help maintain cell membrane integrity.[24,25] The omega-3 fatty acids, especially long chain types from marine oils (>18 carbon chain length), are noted for their preferential role in neurologic development and potential for reduced inflammatory response.[25,26] The plant-derived 18 carbon omega-3 fatty acid, alpha-linolenic, may also play a supportive role in the inflammatory response. However, their limited conversion to active long-chain derivatives and favored use as substrate for energy requires substantially greater dietary amounts to achieve such an effect compared with supplying the already-formed long chain active fatty acids.[27,28] The 18 carbon omega-3 fatty acids are not as potent a source for the above desired effects as are the 20/22 carbon types. Products that contain both 18 and 20/22 carbons omega-3 acids should have their labels carefully scrutinized as to the source, types, and amounts of the various fatty acids. The dosage needed will be different, depending on the intended use of the product.

Should a therapeutic supplement of dietary omega-3 fatty acids be desired (i.e., as an adjunct to atopy treatment or inflammatory condition), an oil supplement containing 100% fish or other marine oil should be used. Conversely, if redness and inflammation is not present, selection of a proprietary blend that contains both omega-6 and omega-3 fatty acids, or simply 1 teaspoon per 10 lb body weight of a liquid vegetable oil daily should be sufficient in most instances. Although the clinical efficacy of fatty acid supplements is considered only modestly effective[29], a recent study has shown significant short-term improvements in skin and hair coat scores of clinically normal dogs when fed either linoleic (omega-6) or alpha-linoleic (omega-3) acid supplements.[30] Another study found a synergistic effect using linoleic acid, zinc, and biotin noting a reduction in hair coat scaliness scores.[31] Finally the safety of dietary fatty acid supplements in the amounts recommended above and in the literature appear to be well tolerated. However, it should be noted that extra calories are present in fatty acid or vegetable oil supplements (approx. 9 kcal/g) so caution is advised especially in small companion animals prone to obesity.

CHAPTER 140

Nonsteroidal Anti-Inflammatory Analgesics

Karol A. Mathews

Nonsteroidal anti-inflammatory analgesics (NSAIAs) are a group of pharmaceutical agents that possess analgesic and anti-inflammatory properties. The NSAIAs are frequently used in human and veterinary medicine to relieve mild, moderate, and severe pain. The efficacy of many recent NSAIAs can compare to the pure mu agonist opioids (morphine, oxymorphine, hydromorphine) in managing soft tissue and orthopedic post-operative pain[1,2]. When used in combination with opioids, NSAIAs appear to confer synergism and may require reduced dosing of the opioid. The NSAIAs concentrate in inflamed joints and tissues, which likely contribute to duration of effect, which varies between 12 and 24 hours.[3] The duration and efficacy of the NSAIAs makes them ideal for treating acute and chronic pain in veterinary patients; however, due to their potential for harmful adverse effects, animal and NSAIA selection must be considered prior to administration (Table 140-1).

PHARMACOLOGY

A significant part of the NSAIAs' antinociceptive effects is exerted at the spinal cord and supraspinal levels.[4] This action, in addition to pain relief, may account for the observed overall well-being and improved appetite of animals that receive injectable NSAIAs for relief of acute pain. Nonsteroidal anti-inflammatory analgesics are, with varying differences, inhibitors of cyclooxygenase enzyme-1 (COX-1), COX-2 or both, which result in reduced prostaglandin synthesis. Cyclooxygenase-1 is increased approximately two- or three-fold in tissue injury and therefore is involved in pain transmission but to a lesser degree than COX-2. With respect to pain, COX-2 is inducible and synthesized by macrophages and inflammatory cells, potentially increasing by 20-fold over baseline, in the presence of tissue injury and inflammation.[4] Increased cyclooxygenase levels increase prostanoid production, where these compounds mediate inflammation and amplify of nociceptive input and transmission in both the peripheral and central nervous systems.[4] By this mechanism, COX-2 is responsible for most of the pain and hyperalgesia experienced after tissue injury.

Based on these findings emphasis is placed on COX-1 versus COX-2 activity of NSAIAs, with respect to safety and efficacy. However, both have important constitutive functions and the notion of "good versus bad COX" is not an "all-or-none" event. COX-1 is a constitutive enzyme, present in tissues, that ultimately converts arachidonic acid into prostanoids (thromboxanes, prostacycline, and prostaglandins [PG]E_2, PGF_2 and PGD_2).[5] The most common, and clinically apparent, potential adverse effects of a COX-1 preferential NSAIA is the reduction in activity of these prostanoids and consequently affect primary plug formation of platelets, modulation of vascular tone at the level of the kidney, and inhibition of cytoprotective functions on the gastric mucosa.[5] These actions are frequently noted with respect to prostaglandin activity.

However, prostaglandins are ubiquitous throughout the body and regulate many other functions. For example, these functions include thermoregulation and vascular and bronchial smooth muscle tone. Prostaglandins exert a negative feedback effect on cyclic adenosine monophosphate (c-AMP) with potential perturbations in many physiologic functions. As an example, renal water reabsorption depends on the action of antidiuretic hormone (ADH), which is mediated by c-AMP; inhibition of PG (prostaglandin) synthesis may lead to increased levels of c-AMP with a potential for enhanced ADH activity. Urine volume may be decreased through this mechanism but without renal injury.[5,6] Cyclooxygenase-2 has some important constitutive functions; there may be a protective role for COX-2 in maintenance of gastrointestinal integrity, ulcer healing, and experimental colitis in rats. In addition, there is constitutive activity associated with nerve, brain, ovarian and uterine function, and bone metabolism.[6] Most importantly, COX-2 has constitutive functions in the kidney, which differ from those of COX-1. The COX-2 is important in nephron maturation.[7] The canine kidney is not fully mature until 3 weeks after birth; continual administration of a NSAIA during this time, or to the bitch prior to birth, may cause a permanent nephropathy. On the other hand, COX metabolites have been favorably implicated in functional and structural alterations in glomerular and tubulointerstitial inflammatory disease.

Administration of COX-2 selective inhibitors decreased proteinuria and inhibited development of glomerular sclerosis in rats with reduced functioning renal mass.[7] Because COX-2 expression is also increased in glomerulonephritides such as lupus nephritis, it is possible that COX-2 inhibitors may also alter the natural history of glomerular inflammatory lesions.[7] The COX-2 derived metabolite production is regulated and localized to the structures in the kidney that plays an essential role in renal blood flow associated with renin activity and fluid-electrolyte homeostasis.[2] Cyclooxygenase-2 is glucocorticoid sensitive, in that it is reduced after administration of glucocorticoids, which may partially explain the anti-inflammatory and analgesic effects of this class of medications. Of interest, in addition to the COX-2 role in inflammation, aberrantly upregulated COX-2 expression is increasingly implicated in the pathogenesis of Alzheimer's disease and possibly other neurologic conditions and a number of epithelial cell carcinomas, including colon, esophagus, breast, and skin.[8,9] The COX-2 inhibitors are being researched as potential anticarcinogenic agents. Associated with the use of NSAIAs is the risk of purturbation of the constitutive functions of COX-1 and COX-2, resulting in potential organ dysfunction. However, "not all NSAIAs are created equal" in this regard. Some NSAIAs have both COX-1 and COX-2 inhibitory effects (aspirin, ketoprofen, ketorolac), whereas others preferentially inhibit COX-2 or are COX-1 sparing to varying degrees (meloxicam, carprofen, etodolac, tolfenamic acid).

As the COX-2 appears to play a significant role in nociceptive transmission, medications that prevent COX-2 activity and spare COX-1 should be effective, with potentially less adverse effects, in the management of pain. The COX-2 specific inhibitors (rofecoxib, celecoxib), currently available in human medicine, appear to have less gastrointestinal adverse effects than other NSAIAs. However, long-term use in some

Table • **140-1**

Nonsteroidal Analgesic Dosing Regimen Per Body Weight*

DRUG	INDICATION	SPECIES, DOSE, ROUTE	FREQUENCY
Ketoprofen	Surgical pain	Dogs: ≤2.0 mg/kg, IV, SC, IM, PO	Once postoperative
		Cats: ≤2.0 mg/kg, SC	Once postoperative
		Dogs and cats: ≤1.0 mg/kg	Repeat q24h
	Chronic pain	Dogs and cats: ≤2.0 mg/kg, PO	Once
		≤1.0 mg/kg	Repeat q24h
Meloxicam	Surgical pain	Dogs: ≤0.2 mg/kg IV, SC	Once
		≤0.1 mg/kg IV, SC, PO	Repeat q24h
	Chronic pain	Dogs: ≤0.2 mg/kg PO	Once
		≤0.1 mg/kg PO	Repeat q24h
	Surgical pain	Cats: ≤0.2 mg/kg SC, PO	Once
		≤0.1 mg/kg SC, PO lean weight	Daily for 2 to 3 days
	Chronic pain	Cats: ≤0.2 mg/kg SC, PO	Once
		≤0.1 mg/kg PO lean weight	2 to 3 days
		0.025 mg/kg PO lean weight (~0.1 mg/CAT max)	3 to 5 times weekly
Carprofen	Surgical pain	Dogs: ≤4.0 mg/kg, IV, SC	Once upon induction
		≤2.2 mg/kg PO	Repeat q12h-24h PRN
		Cats: ≤2.0 mg/kg SC lean weight	Once upon induction
	Chronic pain	Dogs: ≤2.2 mg/kg PO	q12h-24h
Etodolac	Chronic pain	Dogs: ≤10-15 mg/kg PO	Once daily
Deracoxib	Peri-operative pain	Dogs: 3.0 mg/kg PO	Once daily for 7 days
	Chronic pain	Dogs: 1-2 mg/kg PO	
Tepoxalin	Chronic pain	Dogs: 10 mg/kg PO	Once daily
Tolfenamic acid	Acute and chronic pain	Cats and dogs: ≤4 mg/kg SC, PO	Once daily for 3 days. 4 days off. Repeat the cycle
Flunixin Meglumine	Pyrexia	Dogs and cats: 0.25 mg/kg SC	Once
	Ophthalmologic procedures	Dogs and cats: 0.25-1.0 mg/kg SC	q12h-24h PRN for 1 or 2 treatments
Ketorolac	Surgical pain	Dogs: 0.3-0.5 mg/kg IV, IM	q8h-q12h for 1 to 2 treatments
		Cats: 0.25 mg/kg IM	q12h for 1 to 2 treatments
	Panosteitis	Dogs: 10 mg/DOG ≥30 kg, PO	Once daily for 2 to 3 days
		5 mg/DOG >20 kg <30 kg, PO	
Piroxicam	Inflammation of the lower urinary tract	Dogs: 0.3 mg/kg, PO	q24h for 2 treatments, then q48h
Acetaminophen	Acute or chronic pain	Dogs only: 15 mg/kg PO	q8h
Aspirin	Acute or chronic pain	Dogs: 10 mg/kg PO	q12h

Mathews KA: *J Vet Emerg Crit Care* 12:89, 2002.
*See text for details on the contraindications for use.
PRN, As required.
Modified with permission.

people has resulted in similar gastrointestinal problems as those experienced with commonly used NSAIAs; therefore it cannot be assumed that these NSAIAs will be a safe treatment for all cats and dogs with chronic administration. The COX-2 specific NSAIAs are currently being investigated in veterinary medicine. At the time of publication, deracoxib has recently been approved for control of postoperative pain and inflammation associated with orthopedic surgery in dogs. The incidence of vomiting and diarrhea were similar in dogs receiving deracoxib compared with dogs that received placebo in a perioperative field trial; however, overall the drug was well tolerated and effective. A good review of "the Coxibs" is available.[8]

Recently reported cloning and expression of canine COX-1 and COX-2 reveal these enzymes to be highly homologous to their human counterparts. Assays developed to assess the potency of inhibition of the canine cyclooxygenases by various NSAIAs indicated no difference from their potency on human enzymes, maintaining the same rank order of potency. The researchers concluded that any differences that may occur *in vivo* between canine and human inhibition of COX-1 and COX-2 can be attributed to factors other than inhibition of these enzymes.

Most NSAIAs that inhibit COX have been shown to result in diversion of arachidonate to the 5-lipooxygenase pathway.

This results in an excessive production of leukotrienes, which have been implicated in the creation of NSAIA-induced ulcers.[5] Tepoxalin, a dual COX/lipooxygenase inhibitor, has recently been approved for management of osteoarthritic pain in dogs. *In vitro,* tepoxalin inhibited COX-1 with at least a thirty-fold higher potency than for COX-2. The potencies for tepoxalin as a lipooxygenase and COX inhibitor, seemed to be in the same range; however, *in vivo* studies showed less potency against lipooxygenase than against COX and efficacy comparable with meloxicam or carprofen and safety comparable to placebo.

GENERAL CONSIDERATIONS

The general health of the animal must be considered prior to prescribing NSAIAs. Cats and dogs are more susceptible than people to the adverse effects of NSAIAs. Therefore the reported safety of any drug approved for humans should not be assumed to be safe in dogs or cats. Most NSAIAs require accurate dosing to avoid potential adverse effects, especially when used long term. Anecdotal reports of single, accidental, large overdoses have been reported with no adverse effects; however short-term prophylactic gastric and renal protection may be advised with extremely high overdose.

NSAIAs should be restricted to animals older than 6 weeks of age (may be older depending on the NSAIA) that are well-hydrated and normotensive and have normal renal and hepatic function. Although these are general guidelines, COX-1 sparing NSAIAs may prove safe in animals with non–clinically significant elevations in creatinine and liver enzymes where the benefit outweighs the risk. Some animals may be receiving other medications and NSAIA interaction must be considered.[3]

Plasma levels of NSAIAs are effectively reached within 1 hour after oral administration.[3] When given per os, NSAIAs must be given with food to protect the gastric mucosa from high localized concentrations of the drug increasing the potential for gastric erosion. However, potential for gastric erosion exists with all NSAIAs regardless of route of administration. To reduce this, NSAIAs should be decreased to the lowest possible dose that will confer analgesia. If evidence of gastric erosions/ulcers exists, drug withdrawal and gastroprotective therapy is advised. NSAIA induced renal insufficiency is usually temporary, if identified early, and reversible with drug withdrawal; administration of IV fluids may be required. An increase in serum alanine aminotransferase (ALT) activity can occur with most NSAIAs, is reversible with NSAIA withdrawal, and appears to be of little clinical significance. Rare, acute hepatotoxicity after carprofen administration has been reported in dogs (Labrador retrievers highly represented) in North America[1] but has not been reported in Europe.

INDICATIONS FOR NSAIA ADMINISTRATION

The indications proposed here assume no contraindications (below) to their use.

1. **Postoperative pain:** Orthopedic[1,2] and selected soft tissue surgical procedures[1,2] may warrant NSAIA administration, especially where extensive inflammation or soft tissue trauma is present. Opioid administration is beneficial immediately after most surgical procedures, due to the sedative and synergistic analgesic effects, to ensure a smooth recovery. Injectable NSAIAs can be co-administered with an opioid initially and subsequently used alone as the repeat analgesic after orthopedic and selected soft tissue surgery. The initial dose of NSAIAs depends on the expected severity of pain. Assuming a difficult fracture repair would require the recommended loading dose, then a laparotomy without complications, could be successfully treated with half this dose. The administration of NSAIAs prior to surgical procedures is controversial due to their potential for harm. Various studies investigating pre-operative administration of NSAIAs in animals did not specifically screen for adverse reactions.[1] Studies that specifically assess efficacy and safety of NSAIAs given preoperatively, where intraoperative fluid therapy was administered and patient monitoring conducted, noted rare adverse reactions with some of the NSAIAs[1].

   A recent study conducted at the Ontario Veterinary College demonstrated no ill effects with the administration of meloxicam or carprofen prior to orthopedic or soft tissue surgery in both cats (meloxicam) and dogs (meloxicam and carprofen) (unpublished data). In these studies, in which intraoperative fluids were administered, the NSAIA did provide very good to excellent analgesia, for longer than 24 hours, in approximately 70% of animals that underwent orthopedic procedures. The remaining animals required a much lower dose of opioid than expected to manage moderate to severe postoperative pain. The benefit of preoperative use of NSAIAs is the potential for a pre-emptive effect and the presence of analgesia upon recovery. Analgesia during the recovery period is essential. The recently released deracoxib is also approved for pre- and post-operative use at 2 mg/kg once daily for 7 days. Where NSAIAs are administered postoperatively, opioids should be administered concurrently because 45 minutes are required for therapeutic effect of the NSAIA. Another potential approach could be to administer the NSAIA upon completion of the surgical procedure at least 45 minutes prior to extubation.

   Ketoprofen is an excellent analgesic but is an inhibitor of both COX-1 and COX-2. Therefore unwanted side effects are a potential problem requiring careful patient selection. Ketoprofen should be reserved for postoperative use to reduce the potential for hemorrhage. Flunixin meglumine is used as an antiinflammatory agent in selected ophthalmologic surgical procedures; however, the potential for side effects is of major concern[1] and potentially safer NSAIAs are as effective.
2. **Inflammatory conditions:** NSAIAs appear to be more efficacious than opioids for relief of pain due to meningitis, soft tissue inflammation, polyarthritis, cystitis, otitis, severe inflammatory dermatologic diseases, or injury (i.e., degloving, animal bites). Because many of these animals may be more prone to NSAIA toxicity, careful patient selection and management is advised. Combination opioids and low dose NSAIAs are also effective in these conditions. An exception is necrotizing fasciitis where NSAIAs are reported to increase morbidity and mortality.[1]
3. **Miscellaneous conditions:** Other indications for the use of NSAIAs are panosteitis, hypertrophic osteodystrophy (HOD), cancer pain (especially of bone), radiation-induced stomatitis in cats and dental pain[1]. Non–COX-1–sparing NSAIAs should be used with caution after dental extractions where bleeding is, or may be, of concern. Ketoprofen or ketorolac is suggested for the management of refractory pain associated with hypertrophic osteodystrophy and panosteitis. The HOD of Weimeraners is poorly responsive to NSAIA therapy and is better treated with high dose, short-term corticosteroids, provided infectious disease has been ruled out and clinical signs are consistent with HOD alone.[1]
4. **Osteoarthritis:** Long-term studies of the adverse effects of NSAIAs (carprofen, meloxicam, etodolac) for osteoarthritis, appear to be minimal and are predominantly

associated with the gastrointestinal tract.[10] As many animals with osteoarthritis are geriatric a rapid reduction of the dose, to affect a comfortable state, is advised to reduce potential toxicity. For example, alternating to every third day therapy of meloxicam, with half the label recommended dose, proved efficacious in some dogs during a 12-month period.[1] As the long-term dosing of carprofen in Europe is 2.2 mg/kg once daily, potentially reduced dosing for dogs in North America may also be beneficial. If a particular NSAIA appears ineffective in managing pain, prescription of a different NSAIA may be effective due to individual variation in response to the different analgesics. In situations in which the adverse effects of an NSAIA are a concern, reduction of the dose and addition of an opioid may be equally as effective for chronic severe pain.

However, for many geriatric animals with renal insufficiency and increased serum ALT activity, NSAIAs may be the only effective class of analgesic. For these animals the quality of life is of major importance. In this situation, a COX-1 sparing/COX-2 preferential NSAIA, at the lowest dose possible, may be suggested for both cats and dogs. Anecdotal reports indicate that worsening of renal function may not be a problem in some animals. Client understanding of potential worsening of renal or hepatic function is necessary prior to treatment. Water must be available at all times. Dietary indiscretions and stressful situations must be avoided. During NSAIA therapy all dogs and cats should be monitored for hematochezia or melena, vomiting, increased water consumption, and a nonspecific change in demeanor. If this occurs, the owner should be instructed to stop the medication and consult the veterinarian. Intermittent monitoring of creatinine and ALT is recommended when NSAIAs are prescribed chronically.

PYREXIA

Most veterinary-approved NSAIAs, aspirin and acetaminophen, are effective antipyretics. The antipyretic effect is obtained with a lower than analgesic dose. Dipyrone is an excellent antipyretic and is available as tablets and solution for injection. Dipyrone should be given intravenously to avoid the irritation when given intramuscularly. The analgesia produced is not adequate for moderate to severe postoperative pain. Gastric ulceration or nephrotoxicity is not a concern in the short term even in critically ill patients.

CONTRAINDICATIONS FOR THE USE OF NSAIAS

Nonsteroidal antiinflammatory analgesics should not be administered to animals with acute renal insufficiency, hepatic insufficiency, dehydration, hypotension, conditions associated with low "effective circulating volume" (i.e., congestive heart failure, ascites), coagulopathies (i.e., factor deficiencies, thrombocytopenia, von Willebrand's disease), concurrent use of any other NSAIAs or corticosteroids, evidence of gastric erosion (vomiting with or without the presence of "coffee ground material," melena), or spinal injury (including herniated intervertebral disc) as most of these patients receive corticosteroid with medical or surgical management. NSAIAs should never be administered to animals in shock or those that have been recently traumatized. NSAIAs should not be given if hemorrhage is evident (i.e., epistaxis, hemangiosarcoma, head trauma). Animals with severe or poorly controlled asthma, or other moderate to severe pulmonary disease, may deteriorate with COX-1 inhibiting NSAIAs. The administration of NSAIAs in head trauma, pulmonary diseases, or thrombocytopenia may prove to be safe with further study of the COX-2 preferential/COX-1 sparing NSAIAs. NSAIAs may have adverse effects on the reproductive tract and fetus as they may block prostaglandin activity resulting in cessation of labour, premature closure of the ductus arteriosus in the fetus, and disruption of fetal circulation.[6] As COX-2 induction is necessary for ovulation and subsequent implantation of the embryo,[6] NSAIAs should be avoided in breeding females during this stage of the reproductive cycle.

Topically applied nonsteroidal anti-inflammatory analgesics were significantly more effective than placebo in many human clinical trials involving acute and chronic painful conditions.[1] Topical NSAIAs were not associated with the gastrointestinal adverse effects seen with the same drugs taken orally.[1] At the time of writing this chapter, there are no published studies investigating the use of topical NSAIAs in the veterinary literature.

NSAIAs NOT APPROVED FOR USE IN VETERINARY PATIENTS (OFF LABEL USE)

Ketorolac parenteral formulation and tablets are comparable to oxymorphone in efficacy and to ketoprofen in duration and efficacy in managing post-laparotomy and orthopedic pain in dogs.[1] Only one to two doses should be administered. Ketorolac is included for the benefit of those working in the human research setting, where the availability of ketorolac is more likely than other NSAIAs. Ketorolac has been used successfully for treatment of severe panosteitis in dogs in which all other therapies had failed. Ketorolac given with food for 2 to 3 days in hydrated dogs resolved signs in approximately 99% of those treated. In the other 1%, signs recurred within a few days to months (unpublished observations). Misoprostol should be coadministered.

Aspirin is available in tablet form. It is most commonly used as an analgesic for osteoarthritic pain in dogs. It is formulated in combination with opioids, aspirin and codeine, or aspirin and oxycodone, for a synergistic effect for the treatment of moderate pain. It is also used as an antipyretic and anticoagulant in dogs and cats.

Acetaminophen is available in tablet form. It may be used as an antipyretic or as an analgesic. It is formulated in combination with opioids, acetaminophen and codeine, or acetaminophen and oxycodone.

Over several years, many studies have reported the safety and efficacy of the commonly used NSAIAs in various clinical settings[1]; similar studies that investigate the use of the recently approved COX-2 specific and dual cyclooxygenase/lipooxygenase inhibitors, with well-designed prospective clinical trials and laboratory studies, should determine the safety and efficacy of these NSAIAs in both the acute and chronic pain management settings.

CHAPTER 141

Antioxidants in Health and Disease

John E. Bauer

Free radicals are molecular fragments that have at least one unpaired electron. This characteristic makes them highly reactive in biologic systems. Their activity can be beneficial because they participate in oxidative burst reactions and other mechanisms that characterize neutrophil and other inflammatory cell function that serve to phagocytose and kill bacterial invaders. However, when free radicals are present in excess, oxidative metabolic damage, and destruction of normal cell membranes, or destruction of cell content may occur. To help keep these mechanisms in check, biologically active scavengers of free radicals help interrupt further cell damage. These scavengers, the antioxidants and related mechanisms, thus normalize the effects of an overabundant and destructive cell process.

Evidence supports the concept that humans who include appropriate amounts of fruits and vegetables in their diet, which are high in antioxidants, appear to lower risk of cardiovascular disease and cancer risk.[1] Specific dietary factors responsible for these benefits are not known. Plant and plant products contain numerous phytochemicals that may play some role. There is a need for carefully conducted studies to determine whether extracted plant or other antioxidant material, when ingested as a single nutrient, would help prevent any specific disease. To date, however, no direct connection has been made between antioxidant consumption and prevention of chronic disease. In some cases overconsumption may even prove harmful.

ANTIOXIDANTS AND FREE RADICAL DAMAGE

Free radical reactions are ubiquitous *in vivo*. They are associated with oxidation-reduction reactions, energy metabolism, biosynthesis, cell signaling, body defense, and detoxification mechanisms. Because of potential adverse effects of oxygen and related oxygen products, cell systems utilize numerous defensive mechanisms. These systems include direct interaction with reducing agents (e.g., vitamin C, glutathione); free radical scavenging (vitamin E, vitamin C, carotenoids, superoxide dismutase); reduction of hydroperoxides (e.g., glutathione peroxidase, catalase); removal of transition metals by protein binding (e.g., ferritin, ceruloplasmin, and other chelators); preventing reactive oxygen from reaching specific sites; and even repair of oxidative damage.[2]

There is considerable interest in the function and metabolism of antioxidants and their ability to scavenge free radicals. The generation of free radicals and its related oxidative damage appears to be a consequence of stress, various diseases, aging, trauma, environmental factors such as cigarette smoke or air pollution, infectious organisms, and other factors. As a by-product of oxidative metabolism, the generation of free radicals can probably not be halted entirely but only moderated. Consequently there is a need for biologically active antioxidants and associated scavenger mechanisms. Because free radicals arising from metabolism or environmental sources interact continuously in biologic systems, the oxidants and antioxidants are in a continual "utilization and replenishment" cycle that must be balanced to minimize cellular and tissue damage.

One of the most well-studied systems of biologic oxidative processes has been the effect of free radicals on lipid peroxidation in both cell free and biologic systems. The mechanism of lipid peroxidation consists of three stages: initiation, progression, and termination (Figure 141-1).[3,4] Initiation of lipid peroxidation occurs by abstracting a hydrogen atom from a methylene group, such as exists on an unsaturated fatty acid, by a free radical species. The resulting molecule is now a free radical, which can react rapidly with molecular oxygen to form a peroxy radical. The peroxy radical then abstracts another hydrogen atom from another unsaturated fatty acid to form another free radical species. Because a new free radical is formed, a chain reaction is created resulting in many free radicals being formed from one event. This chain reaction can be terminated when the chain-propagating species reacts with an antioxidant molecule to form non–free radical products. In the meantime, left to propagate, many highly reactive free radical species are formed. Evidence of this process exists in the numerous molecular markers of tissue destruction that form, such as lipofuscin pigments, iosprostanes, carbonyl and nitrotyrosine protein derivatives, and DNA fragments. Antioxidants thus have the potential to terminate these chain reactions prior to their generating a large degree of cellular damage and hence provide cells the opportunity to complete their individual life cycles.

There are a number of biologic and dietary types of antioxidants. These include various tocopherols (vitamin E), vitamin C, beta-carotene, and the enzyme superoxide disumutase. Among these free radical scavengers, vitamin E is often promoted as a diet supplement or food ingredient. Vitamin E is a fat-soluble vitamin and is absorbed from the intestine into the lymph system on lipoproteins. It is then transported to the liver for utilization or storage. Compared with other fat-soluble vitamins (A, D, and K), vitamin E is not efficiently stored.

Vitamin E

Vitamin E is the major lipid-soluble antioxidant present in plasma, erythrocytes, and tissues. The term *vitamin E* actually refers to a group of fat-soluble compounds known as the tocopherols. α-tocopherol is generally regarded as having the greatest antioxidant activity. Its function as a scavenger of free radicals serves to prevent free radical or oxidative damage to

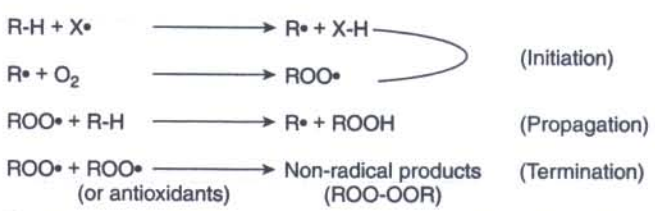


Figure 141-1 Model of fatty acid oxidation by a free-radical mechanism. R-H represents a fatty acid; XX, a free radical capable of abstracting a hydrogen from R-H; RX, a free radical of the fatty acid; ROOX, the peroxy radical; ROOH, a lipid hydroperoxide.

polyunsaturated fatty acids in membranes, thiol-rich proteins of membranes, and nucleic acids. Support for an antioxidant role of vitamin E *in vivo* also comes from observations that synthetic antioxidants can either prevent or alleviate certain clinical signs of vitamin E deficiency. Numerous studies have established vitamin E as an essential nutrient.[5,6] Vitamin E has beneficial effects on the canine immune system and a prolonged dietary deficiency of vitamin E will cause oxidative damage and degeneration of the retina of the eye, and lead to reduced visual acuity.[7-13]

Antioxidant Combination

Vitamin E and other supplementary antioxidants are readily available as commercially manufactured over-the-counter products. Their use as individual dietary supplements is not widespread in veterinary practice. Instead, antioxidant combinations are often incorporated into pet food or supplements are formulated to contain one of more of these substances. One such combination included vitamin E, vitamin C, α-lipoic acid, L-carnitine, and fruit and vegetable-based ingredients that contain flavonoids and carotenoids in a pet food. A study utilizing this food noted that some age-dependent cognitive deficits of dogs were improved.[14] Another report of using combinations of vitamin E, C and beta-carotene resulted in increased serum vitamin E concentrations and suppressed serum biomarkers of lipid peroxidation (i.e., total serum alkenyls) in dogs and cats. Diet supplementation of sled dogs with beta-carotene, lutein, and vitamin E "normalized" adverse effects of exercise on immune status.[16]

One bioflavonoid blend was fed to cats before administration of acetaminophen and was found to provide some protection against Heinz body formation. Methemoglobinemia formation was not prevented[17]. When cats were pretreated with vitamin E, vitamin C, or N-acetylcysteine, no beneficial effect on Heinz body formation induced with onion powder was seen. However, admininstration of N-acetylcysteine was associated with higher relative amounts of reduced glutathione concentrations in whole blood[18]. When propylene glycol was used to induce Heinz body formation, again only N-acetylcysteine showed a significant effect.

Antioxidants and High-Fat Diets

Is there need for additional dietary antioxidants when higher amounts of polyunsaturated fatty acids are present in the diet? The prevailing opinion is that more vitamin E, particularly α-tocopherol, should be consumed. In humans, when the dietary polyunsaturated fatty acid is linoleic acid, a ratio of 0.4 mg α-tocopherol to 1.0 g polyunsaturated fatty acid is considered appropriate.[19] However, studies to support the need for increased intakes of vitamin E when diets are enriched with longer chain omega-3 fatty acids are equivocal.[20] However, in dogs, when diet intake of vitamin E is high, plasma content on a volume basis was lower in a fish oil supplemented group but it was equivalent when expressed on a plasma lipid basis.[21] In humans plasma tocopherol concentrations either increased (volume basis) or did not change.[20] Thus the results appear to depend upon how the data are expressed, the measures of peroxidation used or the tissues studied. Based on this single study using dogs, it would appear that dietary vitamin E content should be increased when diets high in polyunsaturated fat are employed.

Other Antioxidants

Trace Minerals (a Supporting Role)

Trace minerals may be incorporated into antioxidant enzyme proteins. Their adequate provision should help ensure synthesis and activity of these enzyme-based antioxidant systems. These include selenium in glutathione peroxidase, iron in catalase and copper, zinc, or manganese dependent superoxide dismutases. Other antioxidants, such as ceruloplasmin and ferritin, are nonenzymatic antioxidants containing copper and iron, respectively. Assuming that ample dietary quantities of these minerals are present, direct supplementation of these compounds is not required.

Vitamin C

Vitamin C can be synthesized by both dogs and cats, and hence is not considered a dietary essential. Nonetheless in response to stress, dietary supplementation may be beneficial.[22,23] Vitamin C may also help prevent oxidative damage induced by onion powder or propylene glycol ingestion in cats.[24] Studies in other species have shown beneficial effects to immune function.

Carotenoids

Beta-carotene and other plant-derived substances (lycopene) may provide antioxidant activities in dogs and cats. In dogs, beta-carotene is a precursor of vitamin A, but this pathway is nonfunctional in cats. These materials may also have antioxidant properties, although beta-carotene has been shown to act as a pro-oxidant if large quantities are consumed. Several clinical trials in humans have been terminated because of negative side effects associated with supplementation. These results call for their cautious use in dogs and cats until their safety and efficacy has been established.

S-adenosyl-methionine (SAMe)

This compound is synthesized in animals derived from methione in conjunction with adenosine tripohosphate. It is involved in various biochemical and cellular reactions and is a precursor to glutathione via the so-called *transsulfuration pathway*. This pathway is important not only for detoxification reactions but also helps protect against cellular oxidation. In the absence of SAMe, oxidative damage and toxin retention occurs, which presumably contributes to cell injury and disease progression. It has been studied to some extent in dogs and cats and has shown promise in support of liver function in dogs with vacuolar hepatopathy.[24] It has also been evaluated in normal adult cats and appears to be safe at the dosages employed.[24] Its use in clinical cases of liver insult or injury in cats and dogs appears to be increasing although further controlled case studies are warranted.

α-Lipoic Acid

This compound is also involved in modifcation of the relative distribution of reduced versus oxidized glutathione and, as such, provides a protective effect against oxidative injury. α-lipoic acid is similar in structure to octanoic acid (an 8-carbon medium chain fatty acid) and can participate in oxidation-reduction reactions, which are fundamental to numerous antioxidant mechanisms. Administration of α-lipoic acid to dogs over a 6-month period was found to increase the reduced versus oxidized glutathione ratios.[25] A dose-dependent response was not observed because the lowest supplement group resulted in the most significant increase. This finding suggests that a narrow dosage range may exist to achieve the desired effect. Also cats reportedly have a decreased capacity to metabolize α-lipoic acid compared with dogs[26] for which some caution is advised regarding its use in this species.

CHAPTER 142

Herbal Medicine

Rebecca L. Remillard
Susan G. Wynn

Until the twentieth century, most remedies were botanicals found by trial and error at a great human cost. Some remedies were harmful and some even deadly. With advancements in pharmacologic methods of isolation and purification, active ingredients were identified, characterized, quantified, and sold as prescription or over-the-counter drugs. More recently, the use of botanical medications has become increasingly popular (approximately $5 billion per year industry in the United States). The use of herbal medicine by veterinarians has been increasing for the last 30 to 40 years.

The growing use of herbal remedies in the United States has far exceeded the available information on their benefits, adverse effects, and drug interactions. A coherent, easily accessible database (human or animal) on such remedies is still nonexistent. FDA's Center for Veterinary Medicine is concerned about these products because they lack scientific data showing safety, efficacy, or even standard good manufacturing practices.[1-3]

These animal herbal products are believed by many to be sold under the Dietary Supplement Health and Education Act (DSHEA) passed by Congress in 1994 because they contain human dietary ingredients. Under DSHEA, FDA regulation is not required and hence most of these products do not have pre-market approval. However, the FDA contends that DSHEA does not apply to animals, and this position has been upheld in at least one court case. Therefore most of the herbal products currently on the market would be considered *unapproved* animal drugs or food additives for animals. Although these products are technically in violation of the law, they are of low enforcement priority except when there are public or animal health concerns.[4]

There are published case reports of people suffering from lead poisoning, renal failure, CNS disorders, and digitalis toxicity linked directly to their herbal medications. Some people have exclusively embraced alternative therapies while refusing known effective conventional therapies.[1,5] Analogous cases are most likely occurring within the field of the veterinary medicine when owners choose to diagnose and treat their pet's medical condition concurrent with or without a veterinarian. Clearly it has been a "buyer beware" market under DSHEA. Late in 2002, the FDA announced a new initiative encouraging companies to make accurate product health claims and to prevent companies from making bogus claims. Dietary supplement companies will have to show "the weight of scientific evidence" supports their product health claims; however, this initiative did not address the issue of product safety.

"It is time for the scientific community to stop giving alternative medicine a free ride. There cannot be two kinds of medicine: a medicine that works and one that may or may not work." This statement appeared in the *New England Journal of Medicine* in 1998.[5] It would appear that, although herbal medicine has been in use for centuries, the time has come for such remedies to be tested by scientific method. The scientific method is the process by which scientists, collectively, over time, construct an accurate, reliable, consistent, and nonarbitrary representation of the world (Box 142-1). Recognizing that personal and cultural beliefs influence perceptions and interpretations of natural phenomena, through the use of standardized procedures and criteria to minimize those influences, theories are developed. There are pseudo-scientific theories that wrap themselves in a mantle of apparent "experimental" evidence but, when examined closely, they are found to be statements of faith, hearsay, testimonial, or worse, fraud.[6]

The scientific method distinguishes science from other forms of explanation because it requires systematic experimentation. Where there is active study and open communication, the biases of individuals or groups will cancel out because different groups, with different biases and sources of systematic error, repeat similar experiments. A consensus and theory will develop based upon those experimental results that have stood the test of time. Why has the herbal industry not yet chosen to demonstrate product safety and efficacy using the scientific method?

HERBAL POLYPHARMACY

The term *drug* comes from the ancient word for "root." Until the 1930s plant drugs were the primary source of medicines.[7] Plants may contain thousands of chemical constituents. Phytochemicals are nonnutritive plant constituents that contain protective, disease-preventing compounds, and more than 900 have been identified as components of food. Some constituents are pharmacologically unique and have been isolated by the drug industry, but other constituents have important activity as well.

Investigating the efficacy of herbal therapies is complicated by these mixtures of compounds, some of which exist in varied forms. Constituents isolated from herbs and tested may have important pharmacologic activity, but data from an isolate may under- or overstate actions of the parent herb. The other

Box • 142-1

***The Scientific Method—a Simple Version*[6]**

1. Observe some aspect of the universe.
2. Invent a tentative description—hypothesize.
3. Use the hypothesis to make predictions.
4. Test those predictions by experiments or further observations and modify the hypothesis in the light of your results.

Repeat steps 3 and 4 until there are no discrepancies between hypothesis and the experiment results and/or observation. When consistency is obtained, the hypothesis becomes a theory and provides a coherent set of propositions that explain a class of phenomena. A theory is then a framework within which observations are explained and predictions are made.

"minor" constituents may modify the activity of the primary active constituent, either synergistically or antagonistically. For instance, foxglove is less toxic than its active ingredient digoxin because other plant constituents, some of which antagonize, modulate the actions of digoxin.

Quality control problems in the production of herbal medicine exist on several levels. First, plant constituents vary naturally according to climate, culture conditions, and time of year. William Withering, in his famous Account of Foxglove, noted that some patients got minimal results with what he considered to be an overdose and discovered that the only time to gather foxglove leaves for consistent clinical results was while the plant was in early flower.[8]

Manufacturing practices lend a second level of variability to the product. This is due to (1) the use of different (sub-) species and proper identification of the plant; (2) the use of different parts of the plant (herb, roots, leaves, or combination); (3) different methods of extraction (pressed juice, alcoholic extraction); and (4) the variable presence or absence of other plant constituents. An herbal product may contain highly variable amounts of a variety of bioactive ingredients depending on these factors. Herbalists use products usually from one or two manufacturers and continue to do so after becoming comfortable with the potency of those particular products. Some practitioners have found standardized extracts helpful. For a particular medicinal plant, one active constituent is chosen for standardization and that constituent is concentrated to a predetermined level. A "standardized extract" product ensures that the product has one active constituent at a certain known concentration. However, standardized extracts rely on an admittedly incomplete knowledge of the remaining constituents extracted from that plant.

It has been said that herbal remedies cannot be patented and manufacturers do not expect to recoup the estimated $350 million to confirm FDA safety and efficacy studies.[9] Without patent protection, pharmaceutical companies have not provided financial support for herbal medicine research. The National Institutes of Health since 1992 have only been able to offer limited funding. The lack of regulation on quality control and product standardization for active ingredients that may vary 200-fold between different manufacturers, and batches make it difficult to establish safe or reasonable starting dosages in clinical research protocols.

It would appear that the greatest advantage of herbal medicine, polypharmacy, is at this time its greatest downfall to progress. Polypharmacy, use of multiple drugs with similar, synergistic, or complementary actions, in some respects is discouraged in veterinary medicine. The "shotgun" approach may alleviate clinical signs in the short term but does not increase general medical knowledge, and inadvertently, there may be adverse effects long term. In reality, many practitioners find the use of multiple drugs necessary most commonly in geriatric patients or those with complicated medical problems. At other times, animals are treated with use of multiple drug combinations as in antibiotics, antiparasitic control, vaccines, and anesthesia. Similarly, an herbal formula may contain an astringent (blackberry leaf), soluble fiber (slippery elm), and an antimicrobial (barberry) for treating diarrhea, and the adverse effects of each may be mitigated while addressing several therapeutic principles. Herbal polypharmacy offers the same advantages of efficacy while using lower dosages of the individual active ingredients.

In herbal medicine, polypharmacy is befitting. There are two basic functions performed with herbal medicines: (1) elimination and detoxification and (2) health building and management. The individualized polypharmaceutical approach of herbal medicine is intuitively sensible when encountering a complex, chronic, and often recalcitrant inflammatory process, in which it is advantageous to attack several aspects of the disease process simultaneously. Herbal practitioners create many different formulas for different types of applications. The formulation is contingent on the circumstances, condition being treated, type or part of the plant used, and the characteristics of the patient. For example, in treating lupus erythematosus, one patient may be prescribed a formula designed to relieve joint inflammation and glomerulonephritis, whereas herbs against pleuritis and polyarthropathy are prescribed for another. Herbalists attempt to anticipate and manage associated problems and possible side effects of treatments proactively. The treatment concept is not simply to suppress a symptom but optimize function in a variety of systems while symptoms are resolved.

EVIDENCE-BASED APPROACH TO HERBAL MEDICINE

There are appropriately designed clinical studies that assess herbal medicinals in reputable human medical journals, which serve well as examples for veterinary researchers.[10-12] There are substantive veterinary studies in the current scientific literature to help elucidate the effects of herbal constituents mostly in dogs, rarely cats:

- A triple antibiotic ointment and an aloe vera extract gel were evaluated as to their effects on open wound healing of pad wounds in dogs. The primary difference between the two medications was noticed at 7 days when the aloe vera extract gel–treated wounds had a smaller unhealed wound area than did control wounds and wounds treated with triple antibiotic ointment (author abstract).[13]
- The effects of garlic (*Allium sativum* L., Liliaceae) dialysate were studied on arrhythmias induced in anesthetized dogs. Garlic dialysate suppressed premature ventricular contractions and ventricular tachycardia in ouabain-intoxicated dogs (abbrev author abstract).[14]
- Effect of [3] ginger (*Zingiber officinale* Roscoe, Zingiberaceae) extracts (acetone, 50% ethanolic and aqueous) was investigated for antiemetic activity induced by 3 mg/kg cisplatin in healthy mongrel dogs. The acetone and 50% ethanolic extract at the doses of 25, 50, 100, and 200 mg/kg per os exhibited significant protection, whereas aqueous extract at these doses was ineffective against cisplatin-induced emesis (abbrev author abstract).[15]
- To determine the effect of a fraction of licorice extract, FM100, on the endogenous release of secretin and exocrine pancreatic secretion, five dogs were prepared with chronic pancreatic fistulas and gastric cannulas. Intraduodenal administration of licorice extract in three different doses (0.5, 1.0, and 2.0 g) resulted in significant increases of both plasma secretin concentrations and pancreatic bicarbonate secretion in a dose-related manner (abbrev author abstract).[16]
- A single oral dose of the lyophilized deathcap fungus *Amanita phalloides* (85 mg/kg BW) caused gastrointestinal signs of diarrhea, retching, vomiting, and death in beagles. Silibinin (milk thistle) administration (50 mg/kg) 5 and 24 hours after intoxication suppressed the serum biochemical changes and markedly reduced the hemorrhagic hepatic necrosis. All silibinin-treated dogs survived (abbrev author abstract).[17]
- Groups of greyhounds and domestic cats infested with *Ctenocephalides felis* were sprayed once with azadirachtin (neem seed extract) with or without diethyltoluamide (Deet) and/or citronella. The results show that methanolic extracts with 200, 1000, or 2400 ppm azadirachtin reduced fleas in a dose-dependent manner in flea-contaminated environments (abbrev author abstract).[18]
- Treatment with an extract of Saw Palmetto (*Serenoa repens*) for 91 days did not significantly affect the prostate gland

of asymptomatic dogs, and no adverse effects were evident. Although products containing extracts of S repens are widely advertised for men with prostatic hyperplasia, beneficial or harmful effects of this plant extract were not found in dogs with prostatic hyperplasia (author conclusion).[19]

- In an open multi-center study, the efficacy and safety of a standardized 10% tea tree oil cream (Bogaskin) applied thinly and twice daily for 4 weeks was tested in 53 dogs with chronic dermatitis, particularly nonspecific eczema, allergic dermatitis, interdigital pyoderma, acral lick dermatitis, and skinfold pyoderma. Efficacy assessed by investigating veterinarians showed a positive response ($p = 0.05$) to treatment in 82% of the dogs (abbrev author abstract).[20]

HERB TOXICITY

There are reports of medicinal herb toxicity in dogs and cats, although traditional herbal medicine is usually presented with the assumption that humans are the target species (Box142-2). It is well to remember that herbal drugs should be given the same considerations as when using conventional human pharmaceuticals in dogs and cats. Tea tree oil should only be used topically and never as an oral medication. Comfrey, garlic, and ma huang (ephedra) have documented toxicities and should be used orally only with care and diligent monitoring.[21,22]

Cats present a particularly difficult problem with use of compounds that have not been well studied in felines. Cats have anomalous receptor responses to a number of drugs (e.g., narcotics), are particularly susceptible to phenols, have decreased UDP-glucuronyl transferase activity and increased transaminase and deaminase activities, which makes dosing even more tenuous than in dogs, and hemoglobin that is particularly susceptible to oxidation. Cats have known sensitivities to coumarins, salicylates, and essential oils (aromatherapy included). Herbs of concern in cats may include white willow, birch, garlic, chamomile, and essential oils such as tea tree, pennyroyal, thyme, and eucalyptus.

Dogs are generally more tolerant of xenobiotics but there are documented toxicities to d-limonene, hops, and pennyroyal.[23,24] These should not be used unless under the guidance of an experienced veterinary herbalist, if at all. Onions and garlic (*Allium* sp.) can cause intravascular hemolysis with Heinz bodies, hemoglobinemia, hemoglobinuria, anisocytosis, poikilocytosis, reticulocytosis, and anemia.[25-27] The most common cause of Heinz body hemolysis in dogs is related to ingestion of onions (raw, cooked, or dehydrated). The hemolytic episode may be difficult to correlate with onion ingestion because it occurs several days later.[28]

Box • 142-2

***Known Herb Toxicities in Dogs and Cats*[24]**

Ma Huang	Dogs: CNS and CV sympathetic signs
Guarana	Dogs: caffeine signs
5-HTP (Griffonia)	Dogs: GI and CNS—serotonin syndrome
Echinacea	Dogs: GI, lethargy
Valerian	Dogs and cats: lethargy
Chamomile	Cats: GI, lethargy, epistaxis
St. John's wort	Dogs: GI, depression
Garlic	Dogs and cats: Heinz body anemia, GI
Essential oils	Dogs and cats: CNS, contact dermatitis, liver
Hops	Dogs: malignant hyperthermia

HERB-DRUG INTERACTIONS

In clinical practice, polypharmacy is not uncommon, particularly if the owner uses the services from several veterinary practices. Many medicinal herbs and conventional drugs are therapeutic at one dose and toxic at another. Interactions between herbs and drugs may increase or decrease the pharmacologic or toxicologic effects of other.[29] Underreporting of drug interactions in conventional medicine is a major problem that may be more so for herb-drug or herb-herb interactions as herbs are considered "natural and therefore harmless" by the general public. However, in several large hospital studies completed in Taiwan, Philippines, Hong Kong, United Kingdom, and by the World Health Organization Collaborating Center for International Drug Monitoring, herb-drug interactions were documented in 0.2% to 25% of cases, depending on survey design.[30]

Anesthesiologists have reported significant changes in heart rate or blood pressure in human patients taking herbal medications such as St. John's wort, gingko biloba, and ginseng. Research is ongoing to determine how certain herbals interact with certain anesthetics and in general, the findings thus far indicate that certain herbal medicines do prolong the effects of anesthesia and increase the risks of bleeding or raise blood pressure.[7] Herbal medicines significantly affect the cardiovascular system and many herbal preparations have multiple cardiovascular effects, which can be additive. In general, the dilution of active components in herbal medicines results in fewer adverse and toxic effects as compared with the active components in pharmaceuticals; however, these interactions should not be overlooked for the overall well-being of the patient.[31]

One of the best overall reviews completed to date discusses herbal-drug interactions from both the herbal and conventional medicinal perspectives using *in vivo*, *in vitro*, case reports, and clinical (animal and human) studies citing dosages and statistically significance when available.[32,33] Herb and drug interactions should also be researched.[34,35] The German Ministry of Health established the Commission E, a committee of doctors, pharmacists, scientists, and herbalists to evaluate the safety, quality, and efficacy of herbs. The monographs contain recommendations on dose, indications, contraindications, interactions, and mechanisms of action.[36] The chemical composition, pharmacologic action, toxicity, and therapeutic value of more than 400 herbs with correlations between Western pharmacology and the teachings of traditional Chinese medicine for pharmacologists, physicians, and toxicologists can be found in Huang.[37]

In summary, the individualized polypharmaceutical approach of herbal medicine would appear appropriate and not particularly out of the ordinary for veterinary medicine. Although, this approach does make scientific analysis more challenging, the time has come for such analysis; it will be necessary for herbs to gain greater acceptance and widespread use. A systematic analysis and clinical testing of herbal remedies is feasible. Food may serve as a worthy example. Like herbal remedies, foods are not made up of just one nutrient, and their chemical composition is highly variable for the same reasons as herbs. Foods and nutritional supplements also cannot be patented as single ingredients, but specific unique combinations thereof can be reliably produced, researched, and marketed (e.g., Cosequin).*† Veterinary herbalists would do well to proactively develop a standard for some therapeutic herbs, consistently produce and document reliable efficacy, and then participate in the scientific method by publishing their case results.

*NutraMax Laboratories, Inc., Edgewood, MD.

†The Veterinary Botanical Medicine Association (http://www.vbma.org) has begun this work.

CHAPTER 143

Adverse Drug Reactions

Jill E. Maddison
Stephen W. Page

Any harmful and undesirable phenomenon that occurs during treatment of a patient is termed an *adverse event* (AE). When drug treatment is associated with an adverse event, it is termed an *adverse drug reaction* (ADR). Although no universally accepted definition exists, most medical and veterinary authorities concur that an ADR is a reaction that is harmful and unintended and occurs at doses normally used for prophylaxis, diagnosis, or treatment of disease or the modification of physiologic function.

All drugs have the potential to result in an ADR. However, because it is frequently difficult to substantiate the cause of an adverse event, it is common to refer to an ADR as a *suspected ADR* (sADR) until a clearer picture of etiology emerges. ADRs present a continuum of clinical significance, but of greatest concern are serious ADRs described as adverse drug reactions that are fatal, life threatening, disabling, or incapacitating or which result in permanent or prolonged adverse clinical signs. Figure 143-1 provides an overview of the rational approach to investigating AEs and ADRs.

If not prevented, ADRs can result in additional treatment costs, ongoing disability, mortality, and the client's loss of trust in and diminished satisfaction with the veterinarian. To maintain the highest standards of care and to ensure that ADRs are not needlessly replicated, it is critical that sADRs be fully investigated. Reports of sADRs to manufacturers, regulatory authorities, and the profession are valuable. They help build a risk profile of the implicated drug and its class, improve the knowledge and therapeutic skills of clinicians, provide pivotal information for pharmacoepidemiologic studies, and assist in clarification of the cause.

CLASSIFICATION OF ADVERSE DRUG REACTIONS

An alphabetic approach to ADRs has been recommended.[1]

Type A (augmented) ADRs are expected but exaggerated pharmacologic or toxic responses to a drug. They may be an exaggeration of the intended response to the drug, a secondary response affecting an organ other than the target organ but predictable based on the pharmacology of the drug, or at the extreme, a toxic response.

Most ADRs of this type are attributable to differences in drug disposition that result in higher plasma and tissue drug concentrations, which arise from dysfunction of organs of metabolism and excretion, or inappropriate dosage (e.g., the administration of a non-lipid soluble drug to an obese dog with no dose adjustment). Type A ADRs are usually dose-dependent and avoidable if sufficient drug and animal information is available and considered.

Type B (bizarre) reactions are unexpected or aberrant responses that are unrelated to the drug's pharmacologic effect, are not dose dependent, and are unpredictable (idiosyncratic). Type B ADRs include allergic and pseudoallergic (non-immunologic) reactions, direct toxic effects on organs that are associated with actions unrelated to any desired therapeutic effect (the mechanisms for which may be complex and obscure), and aberrant responses in different species.

Type C (chronic) ADRs occur during prolonged treatment programs. For example, iatrogenic Cushing's syndrome with chronic use of prednisolone.

Type D (delayed) ADRs are experienced remote from the time of treatment and therefore may be difficult to diagnose in the absence of an astute clinician and an excellent history. Second cancers developing in patients treated with alkylating agents are classical examples, as is human phocomelia after thalidomide administration.

Type E (end of treatment) ADRs occur in specific situations when drug treatment is terminated suddenly; for example, withdrawal seizures manifested on termination anticonvulsant therapy, or adrenocortical insufficiency subsequent to interruption of chronic glucorticoid treatment.

Type F (failure) ADRs occur when the expected response to treatment is not achieved. Although there are myriad examples of clinical failure, critical analysis reveals primary drug failure to be an infrequent principal cause.

Type G (gaffes) ADRs result from human error, either delayed or inaccurate diagnosis, withholding treatment, prescription of an inappropriate drug, administration of an incorrect dosage regimen, or failure to monitor the response to treatment.

INCIDENCE OF ADVERSE DRUG REACTIONS

The incidence of ADRs in veterinary medicine is not well known. Studies of human ADRs provide a variety of estimates from 1.5% to 35% of patients developing an ADR while hospitalized.[2] It has been estimated that 1% of the veterinary hospital population treated with drugs experience ADRs but there are divergent opinions between clinicians about the frequency and importance of ADRs.[3] It is certain that ADR reporting rates are low within the medial community and likely substantially lower in veterinary practice.

Furthermore, the occurrence of ADRs is not homogenous throughout any population. Animals with genetic, physiologic, or pathologic predispositions have a higher likelihood of an ADR than those without. Although complacency in reporting is widespread, an examination of those factors associated with an increased rate of reporting reveals that the likelihood of reporting is related to the novelty of the reaction, severity of the reaction, limited time of suspected drug on the market, media coverage, and the litigiousness of the owner.

DIFFICULTIES IN DIAGNOSIS OF ADVERSE DRUG REACTIONS

One problem in determination of the incidence of ADRs is difficulty in diagnosis. Appropriate ADR diagnosis is heavily dependent on the expertise of the clinician and the quality of the information available. Even experienced clinicians have

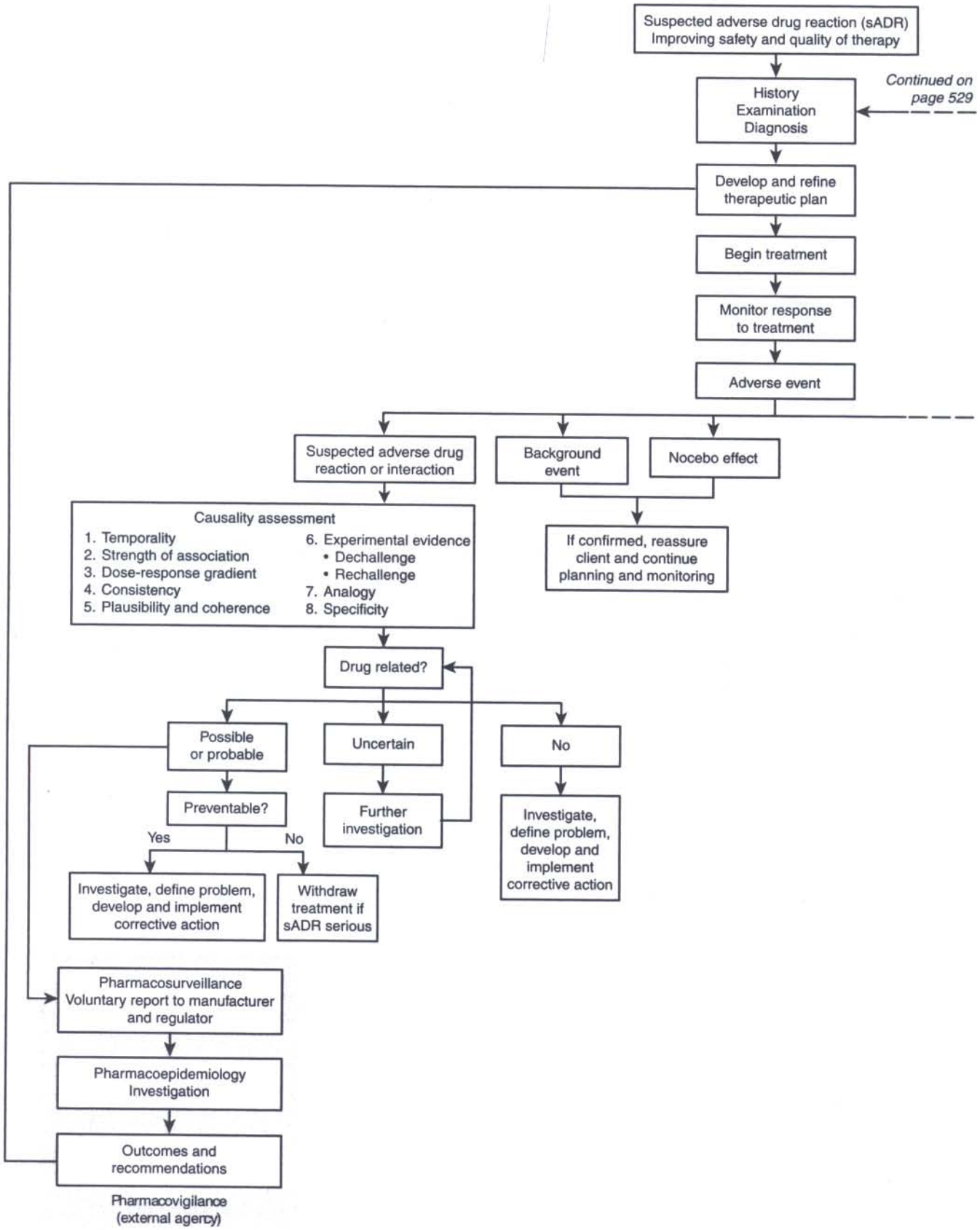
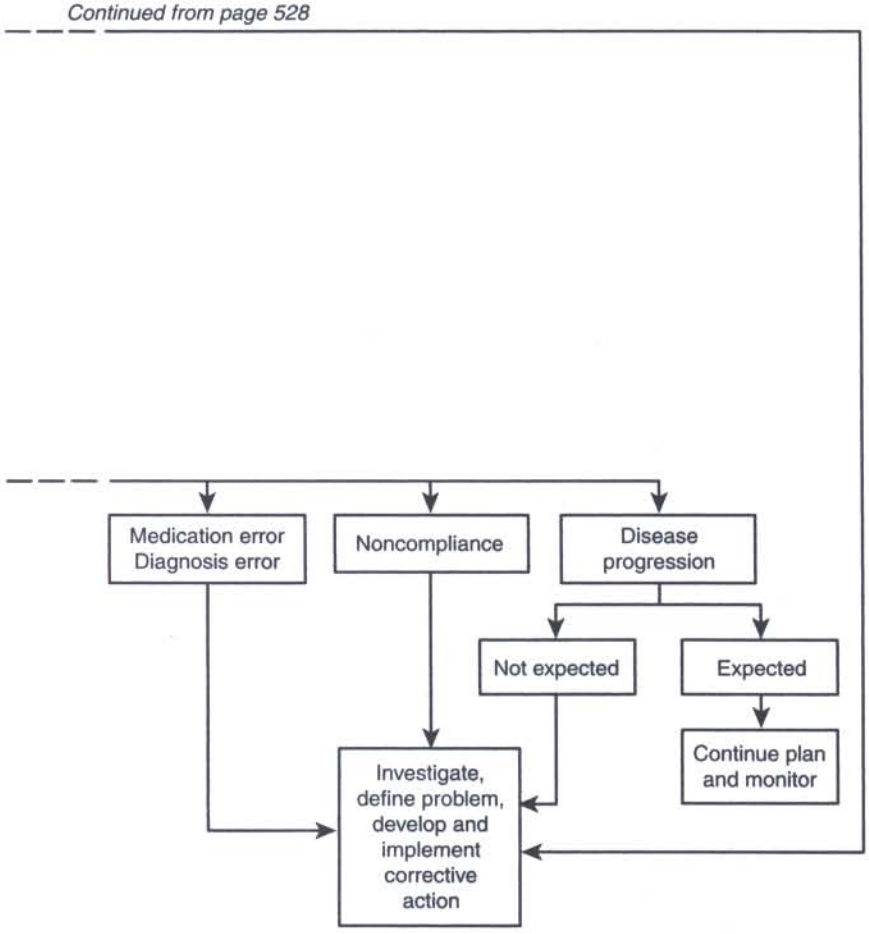


Figure 143-1 Algorithm for adverse drug reactions.

Continued from page 528



difficulty in determining causality, and experts disagree more than 50% of the time when assigning causality to an ADR.

The clinical signs of an ADR are almost always nonspecific and rarely pathognomonic. In humans, the most common symptoms of ADRs (e.g., nausea/vomiting, diarrhea, abdominal pain, rash, pruritis, drowsiness, headache) are also reported in 80% of healthy patients who receive no medication.[2] Placebo administration increases the percentage of patients with symptoms and the number of symptoms per patient.[2] Adverse reactions occurring in response to administration of a placebo are termed *nocebo effects* (from the Latin root that gives rise to noxious and nociception, and which translates as "I will harm").[4] During the clinical field study to substantiate the benefits of carprofen[5] and etodolac,[6] a variety of adverse reactions were reported in dogs that received the placebo formulation, including inappetence (1.6% of dogs), vomiting (2.4%), regurgitation (2.6%), lethargy (2.6%), and diarrhea/soft stools (2.4%). Of the full complement of ADRs that occurred in response to active treatment, a fraction were due to the nocebo phenomenon, and another fraction reflected the background frequency of adverse signs in the untreated population. As veterinarians are reliant on the observations of owners who are potentially subject to various conscious and subconscious influences associated with expectation, suggestion, and prior conditioning, nocebo effects are likely to contribute to reports of ADRs. Complicating ADR identification further is the possible impact of the nocebo phenomenon that influences client compliance.

Other factors that hinder the diagnosis of a true ADR include multiple medications, underlying pathology, and the assumption that the active principle of a medication is responsible for the ADR. Reactions may be due to excipients or may arise in response to degradation products formed during product storage.

IDENTIFICATION OF ADVERSE DRUG REACTIONS

The likelihood, frequency, and severity of ADRs are dependent on the interaction of drug, animal, disease, and client factors. Table 143-1 provides information that should allow the risk of ADRs to be reduced in animals with compromised renal or hepatic function. Table 143-2 identifies drugs not recommended for use in cats. Justification for selection of any drug includes the favorable ratio of anticipated benefits versus potential risks. In life-threatening situations, use of a drug with a narrow therapeutic ratio may be warranted, whereas the use of a drug with a narrow therapeutic ratio to treat trivial problems has little merit.

Accurate identification of an ADR may go undetected if the clinical signs are indistinguishable from those shared with common disease syndromes, including the disease being treated. Clinicians must always be alert to the possibility that abnormalities developed during the course of an illness may be due to the treatment rather than to the disease process itself.

Assessment of causality of an ADR can also pose a significant challenge. Figure 143-1 summarizes eight major steps in the process of attribution of cause. These steps are explained in greater detail by Maddison and Page[7] and in clinical epidemiology texts.[8,9] By application of a systematic approach, a critical, objective, and transparent conclusion can be reached, which avoids undue influence of intuition, preconception, and suggestion.

In many situations, it is not possible to judge an individual case and further information and cases must be sought.

Table • 143-1

Examples of Drugs That Should Be Avoided or Used with Caution in Animals with Hepatic or Renal Disease

DRUG CLASS	SPECIAL CONSIDERATION IN PATIENTS WITH LIVER DISEASE	SPECIAL CONSIDERATION IN PATIENTS WITH RENAL DISEASE
Antimicrobial drugs	Chloramphenicol	Aminoglycosides*‡
	Chlortetracycline*	Amphotericin*‡
	Erythromycin estolate*	Fluoroquinolones
	Flucytosine	Lincomycin
	Griseofulvin	Naficillin
	Ketoconazole	Nalidixic acid
	Lincosamides	Nitrofurantoin
	Macrolides	Polymyxins‡
	Metronidazole	Sulphonamide-trimethroprim
	Sulphonamide-trimethoprim*†	Sulphonamides
	Sulphonamides	Tetracyclines (except doxycycline)
	Tetracyclines	
Anesthetics/ sedatives/ anticonvulsants	Anticonvulsants	Acepromazine
	Barbiturates*†	Chlorpromazine
	Chlorpromazine	Ketamine
	Diazepam†	Methoxyflurane*‡
	Halogenated anesthetics	Procainamide
	Ketamine	
	Lignocaine	
	Propofol	
Cardiac drugs	Beta blockers	Angiotensin-converting enzyme inhibitors
	Lignocaine	
	Quinidine	Cardiac glycosides
		Procainamide
Diuretics		Spironolactone
		Thiazides
Anti-inflammatories and analgesics	Butorphanol	Nonsteroidal anti-inflammatory drugs*‡
	Corticosteroids	
	Meclofenamic acid	Meperidine (pethidine)
	Phenylbutazone	
	Polysulfated glycosamino-glycan	Polysulfated glycosamino-glycan
Cytotoxic drugs	Doxorubicin	Cisplatin*‡
		Doxorubicin*‡
		Fluorouracil
		Methotrexate*‡
Miscellaneous	Doxapram	Allopurinol
	Heparin	Doxapram
	Suxamethonium	Gallamine
		Piperazine

*Avoid.
†Hepatoxic or hepatotoxic.
‡Nephrotoxic.

Table • 143-2

Drugs Not Recommended for Use in Cats

DRUG	EFFECT
Acetominophen (paracetamol)	Methemoglobinemia and Heinz body anemia
Apomorphine	Significant CNS depression
Azathioprine	Bone marrow suppression
Benzocaine	Methemoglobinemia Laryngeal edema
Cisplatin	Fatal, acute pulmonary edema
Hexachlorophene (found in surgical scrubs, enemas)	Vomiting Depression Ataxia Paralysis
Permethrin	Seizures Hyperesthesia Tremor and muscle fasciculation
Primidone	Efficacy as anticonvulsant due to poor conversion to phenobarbitone questionable and high incidence of toxicity
Propylthiouracil	Lethargy Weakness Anorexia Bleeding diathesis
Phenytoin	Sedation Ataxia Anorexia Dermal atrophy
Scopolamine	Tendency to cause behavioral changes
Sodium phosphate enemas	Depression Ataxia Vomiting Bloody diarrhea
Thiacetarsamide	Drug fever Respiratory distress Fulminant pulmonary edema

The potential value of post-marketing pharmacovigilance programs conducted by many national regulatory agencies can be realized only if clinicians submit details of sADR. Important benefits include identification of preventable ADRs, discovery of trends and clusters of significant ADRs, assessment of the safety of drug regimens, measurement of ADR incidence (only if information on drug use is available), and identification of patient risk factors. Clinician-driven ADR reports potentially signal need for further investigations.

Greatest clinical benefit arises from focus on those signals meeting the SNIP criteria[10]: Strength of the signal (number of reports and their plausibility); New and unexpected ADRs; Importance of the ADR clinically as judged by severity and seriousness; and Preventative potential of various interventions. At the time a new drug is first introduced, only an incomplete description of its adverse reaction profile is available due to the limited numbers of animals included in clinical studies, the short duration of most studies, and the relatively narrow population base studied. Only when used in large numbers in a heterogenous population can infrequent adverse reactions be identified and risk factors characterized, highlighting the clinical importance of continued pharmacovigilance.

FACTORS THAT INFLUENCE TYPE A ADVERSE DRUG REACTIONS

It is important to understand the factors that modify the effects of drugs and their dosage to anticipate when a patient may be at increased risk of a Type A ADR. The potential for a Type A ADR is higher in animals with organ dysfunction (see Table 143-1), particularly renal, hepatic, or cardiac dysfunction; in very young or very old animals; in animals to whom a number of drugs are administered concurrently (potentially including all non-prescribed medications); in species for which safe use of the drug or class of drugs has not been established (see Tables 143-2 and 143-3 in relation to cats) and in obese or cachectic patients. In general, type A ADRs should be avoidable if the above factors are considered and dosage regimens are altered appropriately. The reader is referred to other sources for a more complete discussion of these factors.[3,7,11]

TYPE B ADVERSE DRUG REACTIONS (HYPERSENSITIVITY)

Type B ADRs are unrelated to dose, hard to predict, and difficult to avoid. The major example of these idiosyncratic ADRs are allergic or hypersensitivity reactions. Drug hypersensitivity reactions are more common in patients with a prior history of allergic reactions to the drug or atopic patients. However, they can occur in any individual.

Allergic drug reactions may occur as a result of a number of different immunologic mechanisms, including immediate hypersensitivity (Type I), cytotoxic hypersensitivity (Type II), immune complex formation (Type III), and delayed hypersensitivity (Type IV). However, the pathophysiology of many drug reactions eludes precise characterization and some immune reactions are a result of a combination of mechanisms.

Relatively few drugs are responsible for inducing allergic drug reactions as most drugs are not capable of covalently bonding with proteins, a requisite step to render a molecule immunogenic. The drug/drug metabolite-protein complex must have multiple antigenic combining sites to stimulate a drug-specific immune response and to elicit an allergic reaction. For those drugs that are capable of inducing an immunologic response, it is generally the metabolites of the drug that are chemically reactive and easily form covalent bonds with macromolecules.

Drug hypersensitivity may manifest in different ways. Acute anaphylaxis is associated with IgE and mast cell degranulation. It is characterized by one or all of the following clinical signs: hypotension, bronchospasm, angioedema, urticaria, erythema, pruritis, pharyngeal and/or laryngeal edema, vomiting, and colic. The main shock or target organ for anaphylactic reactions varies between species (e.g., hepatic veins are the main target in dogs and the bronchi, bronchioles, and pulmonary vein in cats).

A systemic allergic reaction may also occur associated with drug use related to deposition of immune complexes in tissues and activation of complement. Drug hypersensitivity should be considered in the differential diagnosis of any apparent immune-mediated disease, for example polyarthropathy, hemolytic anemia, and vesicular/ulcerative dermatitis.

Table • 143-3

Therapeutically Useful Drugs in Cats with Different Dose Recommendations or Side Effect Profiles Compared with Dogs

DRUG	EFFECT IN CATS COMPARED WITH DOGS
Aminoglycosides	Cats more sensitive to nephrotoxic and ototoxic effects
Amphotericin	Cats more sensitive to adverse effects including anaphylaxis
Bethanecol	Administer orally only; parenteral administration associated with life-threatening adverse reactions
Carprofen	Chronic use not safe due to long half-life
	Single use only
Chloramphenicol	Much lower dose than dogs; 50 mg/cat bid versus 50 mg/kg bid in dogs
Digoxin	Cats more sensitive to toxicity; reduce dose and frequency 30 µg every other day for cats that weigh less than 3 kg, 30 µg every day for cats that weigh more than 6 kg
Doxorubicin	Renal failure may occur; use lower dose (25 mg/m^2)
Enrofloxacin	Acute blindness reported with (usually but not always) high dose use
Furosemide	More susceptible to dehydration and hypokalemia; use lower end of dose range
Griseofulvin	Bone marrow dyscrasia risk increased in FIV-positive cats
Ketoconazole	Anorexia and GI side effects more common
Lignocaine	Cats more commonly develop seizures with lignocaine and must be used cautiously
Megestrol acetate	Mammary hypertrophy and neoplasia
	Cystic endometritis and pyometra
	Diabetes mellitus
Naloxone	Reversal of opioids is unpredictable
Opioids	Inconsistent sedation
Morphine	Increased risk of excitation
	Use one tenth of dose in dogs
	Meperidine (pethidine), butorphanol, and buprenorphine are more predictable
Potassium bromide	Shorter half-life than in dogs (mean of 1.56 versus 5.3 weeks)
	Adverse effects more common in cats than dogs
	Coughing is common side effect
Salicylates	Aspirin has a longer half-life; dose every 72 hours
	Use sulphasalazine (reduce dosing frequency) and bismuth salicylate (avoid repeated use) with caution
Tetracyclines	Drug fever

Prior exposure to the drug is not essential, because hypersensitivity may develop within the course of repeated drug administration. For example, in humans, drug hypersensitivity can develop within as little as 5 to 7 days in a patient previously unexposed to the drug.

Allergic drug reactions should be managed by withdrawal from the drug and treatment with corticosteroids if needed. Adrenaline and fluid therapy may be needed to successfully manage acute anaphylactic reactions.

CHAPTER • 144

Therapeutic Use of Acupuncture for Pain Control

James S. Gaynor

INTRODUCTION TO ACUPUNCTURE

Acupuncture is the stimulating of specific anatomic points in the body to produce therapeutic or analgesic effects. Clinicians most frequently perform acupuncture by using a fine-gauge needle to puncture the skin, although heat and pressure may also be used. In the last several decades, acupuncture has received increasing attention in the United States and Western Europe, resulting in training programs for physicians and veterinarians. In addition, increased research funding has allowed investigators to formulate and test hypotheses of physiologic explanations of acupuncture's actions.

The results have been promising enough for the National Institutes of Health (NIH) to develop a specific office to organize funding, national research, and workshops centering on acupuncture and other complementary therapies. A recent report from NIH listed several indications for acupuncture, of which pain management was one.[1,2]

WHAT IS ACUPUNCTURE?

Acupuncture is an ancient form of diagnosing, treating, and preventing disease that recognizes and encourages the body's own healing potential. It involves the insertion of needles, or other forms of stimulation, into acupuncture points that are precisely defined loci just beneath the surface of the body. An acupuncture point can be stimulated in many ways, including dry needling, injection of fluid into the point, low-intensity or "cold" laser stimulation, and manual pressure on the point (acupressure). The effects of stimulating these points may be intensified, or the duration lengthened, by heating or electrically stimulating the needles. The effects of acupuncture may be prolonged by injection of fluid (e.g., physiologic saline or vitamin B_{12}) or implantation of gold beads into the point. Several hundred acupuncture points are recognized; most are located along acupuncture meridians, or channels, each of which have specific locations and functions. In practice, however, an acupuncturist's repertoire of points may only include a fraction of these. Characteristics of acupuncture points and of the tissues between them allow for body-wide transmission and integration of bioelectric, humoral, and nervous information.

TRADITIONAL CHINESE MEDICAL BASIS OF ACUPUNCTURE

The commonly accepted explanation for the methods of acupuncture can be traced back over 3000 years, when acupuncture became an important part of traditional Chinese medicine (TCM). With limited knowledge of anatomy or physiology, early explanations were metaphysical in nature and based upon numerology and the philosophy of Taoism. Acupuncture served to increase or decrease the flow of energy (Qi) in hypothesized lines or channels called *meridians*. Although meridians have never been demonstrated to exist, meridian theory is widely enunciated as an explanation for many of the practices of TCM.

From a TCM perspective, pain can be a result of an excess condition leading to the obstruction of the circulation of Qi and blood. Pain can also be caused by deficiency conditions, such as deficiency of Qi and blood and consumption of body fluids from *yin* deficiency. These conditions cause malnourishment of the channels and hence pain. Stagnation of Qi causes distension, with distending pain and no fixed location.[3]

The principles behind acupuncture therapy are to restore a balance in the body. Acupuncture needles placed in appropriate locations can help resolve the underlying causes. This ultimately restores Qi and blood circulation to normal. With no obstruction, no pain is felt.[3] Although some medical professionals may find the concepts of TCM untenable, the physiologic and clinical evidence for acupuncture's usefulness makes it a viable treatment option and prevents it from being cast aside as witchcraft or voodoo.

PHYSIOLOGIC BASIS FOR THE USE OF ACUPUNCTURE

The effects of acupuncture on the central nervous system (CNS) and peripheral nervous system (PNS) include an activation of the body's endogenous multilevel pain modulatory systems, causing a release of serotonin, opioid substances, and other neurotransmitters, thereby serving to alter nociceptive processing and perception.[4,5] Although in the West, acupuncture is most widely recognized for its analgesic and musculoskeletal effects, signals generated from stimulation of acupuncture points can also affect the viscera, the immune system, and more. How these signals enter the nervous system as a result of acupuncture is well researched, with several proposed mechanisms. It is likely that a combination of all of them is responsible for what is observed clinically.

In 1976, shortly after opiate receptors were discovered in the periaqueductal gray matter, the limbic system, and the periventricular gray matter of the CNS, it was demonstrated that acupuncture analgesia could be reversed by naloxone, a pure antagonist at all known opioid receptors.[4] This led to the first awareness that acupuncture analgesia was likely mediated through a system of endogenous opioids.

Nociceptive information is transmitted in the CNS by neurotransmitters. Changes in cerebrospinal fluid (CSF) concentrations of neurotransmitters such as serotonin and biogenic amines have been shown with acupuncture.[6] Although several neurotransmitters are involved in the transmission, inhibition, and perception of nociceptive information, the opioid peptides (met-enkephalin, leu-enkephalin, beta-endorphin, and dynorphin) have been the most thoroughly studied with respect to the observed systemic and analgesic effects of acupuncture.

These opioid peptides are involved in activation of descending tracts that inhibit transmission of nociceptive information in the spinal cord.[6] In addition, no inhibition of ascending tracts that transmit nociceptive information occurs. When large unmyelinated A delta fibers, which transmit touch and pressure sensation, are stimulated by the insertion of an acupuncture needle, impulses from small unmyelinated C fibers, which transmit ascending nociceptive information, are blocked by a "gate" of inhibitory interneurons in the substantia gelatinosa of the spinal cord, which release neurotransmitters such as gamma-aminobutyric acid (GABA) and enkephalins.[6] This results in inhibition of transmission of pain impulses to the brain for conscious perception. In addition, a regional effect is seen when the A delta fibers transmit both cranially and caudally in the dorsolateral funiculus before entering the substantia gelatinosa to stimulate inhibitory interneurons.[6]

Several different lines of basic research show that some of the effects of acupuncture are at least partially mediated by substances with opiate-like activity. Substances known to block opioid biosynthesis (e.g., cyclohexamide) or action (e.g., naloxone) reduce acupuncture analgesia, whereas peptidase inhibitors such as D-amino acids (e.g., D-phenylalanine) can potentiate and prolong acupuncture analgesia, presumably by inhibiting degradation of the analgesic opioid peptides.[7] Mice deficient in opioid receptors and rats deficient in opioids show poor acupuncture analgesia.[8] Opioid levels rise in the blood and CSF and fall in specific brain regions during acupuncture analgesia.[9] In sum, part of the analgesia obtained from acupuncture involves the activation of a neurohumoral system resulting in the release of endogenous substances with opioid analgesic activity.[10] Naloxone administration does not lower baseline thresholds for pain, indicating that the analgesic effects observed are from acupuncture alone. A differential release of beta-endorphin, met-enkephalin, and dynorphin occurs in response to low- and high-frequency electroacupuncture.[11] Electroacupuncture involves the application of electricity to the needles during stimulation of a point. Different opioid receptors mediate the analgesia produced by low- and high-frequency acupuncture. The clinical significance of this differential release is that low-frequency

electroacupuncture (2 to 15 Hz), which causes the release of beta-endorphin and met-enkephalin in the brain and dynorphin in the spinal cord, seems to alleviate deep and chronic pain more effectively than does higher-frequency stimulation (100 Hz), which causes release of dynorphin. In addition, the effects of acupuncture in the periaqueductal gray matter may be predominantly mediated by the enkephalins and beta-endorphin, whereas spinal cord effects are predominantly dependant upon enkephalins and dynorphin.[12] Overall it is likely that the three types of opioids act synergistically because they preferentially bind their receptors; beta-endorphin and met-enkephalin bind both mu and delta receptors, whereas dynorphin is a relatively specific kappa agonist. Because acupuncture analgesia can be largely blocked by antagonists of any of these receptors, or with the removal or blockage of any of these opioids, it is likely that they have a synergistic relationship with respect to conferring analgesia when they are simultaneously stimulated by acupuncture. The lack of decrease in observed analgesia with vascular occlusion is further evidence indicating that a nonhumoral mechanism (i.e., opioid neurotransmitter activity) is responsible for the analgesic effects of acupuncture. The mechanism may involve a change in the body's bioelectric environment leading to modulation of the endogenous pain inhibitory system via the CNS. It is now accepted that acupuncture analgesia is not just the result of the actions of endogenous opioids, even though much of the research has focused on this aspect.

USES FOR ACUPUNCTURE

Acupuncture has traditionally been used for virtually all of the same medical conditions for which conventional medicine has been used. These areas include (but are not limited to) pain, as well as musculoskeletal, neurologic, dermatologic, cardiovascular, respiratory, gastrointestinal (GI), urogenital, and reproductive disorders. Many of the claims of efficacy are related to anecdotal evidence and are not based on good clinical or laboratory research. There is strong evidence to support the positive effects of acupuncture on a number of problems (e.g., its ability to alleviate pain in humans and animals).

SPECIFIC TECHNIQUE FOR PROVIDING ACUPUNCTURE ANALGESIA

Multiple principles exist for choosing points to provide analgesia. One principle indicates choosing points in the affected area. Relative to limb pain, other principles describe using an opposite or contralateral limb. This may be especially useful for limbs that have been traumatized and are not accessible due to bandaging or casting. This is also important for patients with cancer-related pain. Acupuncture may be contraindicated at the sight of a tumor because needle placement may increase blood flow to the area. Another concept is to use empiric points that have been demonstrated to provide analgesia in one or more areas. An evolving principle is to use points proximal and distal to the painful area. All of these treatment principles have been combined for the protocols in Table 144-1. Low-frequency (2 to 5 Hz) electrical stimulation (EAP) is recommended when paired points are listed. For most protocols, points are paired on the same meridian, although exceptions exist. For good analgesia, electrical stimulation should last a minimum of 18 to 20 minutes. It is common for an anesthetized patient's heart rate to drop during this time, a probable indication of central endorphin release.

The acupuncture protocols in Table 144-1 are useful for multiple types of pain. Initially, patients with chronic pain will benefit from frequent treatments. For example, a patient with chronic hip dysplasia will typically be treated three times the first week, two times the second week, once the third week, and then intermittently over weeks to months to maintain comfort. Longer duration chronic pain often requires more frequent treatments early on; it is important for the client to understand that multiple treatments may be required before a significant effect is produced. It is usually recommended that clients commit to six to eight acupuncture treatments before making an assessment of its efficacy for chronic pain.

Table • 144-1

Commonly Used Points for Orthopedic Pain

AREA OF PAIN	POINTS TO BE USED
Hip pain	BL 54-BL 40: EAP
	GB 29-GB 30: EAP
	GB 34
	BL 11 bilaterally
Femoral pain	BL 54-BL 40: EAP
	GB 30-GB 34: EAP
	BL 11 bilaterally
Stifle pain	GB 33-GB 34: EAP
	LIV 8-SP 9: EAP
	Xiyan: EAP
Tibia/fibula pain	BL 40-BL 60: EAP
	ST 35-ST 41: EAP
	GB 34-GB 39: EAP
	SP 6-SP 9: EAP
	BL 11 bilaterally
Tarsal pain	BL 40-BL 62: EAP
	SP 3-SP 6: EAP
	ST 41-ST 44: EAP
	BL 60
	KI 3 (may be needled with BL 60)
	BL 11 bilaterally
Shoulder pain	TH 14-LI 15: EAP
	SI 9-SI 11: EAP
	GB 20
	GB 34
Humeral pain	TH 14-TH 5: EAP
	SI 9-SI 3: EAP
	BL 11 bilaterally
Elbow pain	TH 14-TH 3: EAP
	SI 3-SI 8: EAP
	LI 4-LI 15: EAP
	HT 3
	PC 3
	LU 5
	BL 11 bilaterally
Radius/ulna pain	SI 3-SI 9: EAP
	LI 4-LI 15: EAP
	PC 6-PC 3: EAP
	BL 11 bilaterally
Carpal pain	TH 14-TH 3: EAP
	SI 3-SI 8: EAP
	PC 8-PC 6: EAP
	LI 4-LU 7: EAP
	BL 11 bilaterally

EAP, Electrical stimulation: 2–5 Hz, alternating current, continuous stimulation for 20 minutes.

Acupuncture can be used anytime in the perioperative period for cases involving surgical procedures. Protocols may be useful as preemptive analgesia prior to surgery to help decrease the amount of anesthetics necessary and to aid in keeping the patient more comfortable upon awakening. When used postoperatively, it is ideal to provide the acupuncture while the patient is still asleep. This makes needle placement and electrical stimulation very easy without the constraints of a patient who may wake up immediately painful or in anesthetic emergence delirium. Although electrical stimulation is not necessary, it helps enhance and ensure adequate analgesia that may last hours to days, depending upon the individual and the procedure.

CHAPTER 145

Meeting the Needs of Patient and Client Through Compassionate Care

Gregory K. Ogilvie

Cancer, diabetes, inflammatory bowel disease, osteoarthritis, cognitive dysfunction disorder; these words can be frightening to many pet owners. To our clients and to some crucial members of our veterinary health care teams, these and other terms are as dark and empty as the diseases they represent. Each day we enter our practices to diagnose, treat, and support our patients, but we often forget the emotion and feelings that surround each patient and client. These diagnoses often bring with them feelings of overwhelming fear, a spiraling sense of loss of control, and most devastating of all, the loss of hope. This loss of hope can be paralyzing for clients, for veterinary staff, and for veterinarians. This evaporation of hope and control occurs regardless of whether the patient is a human family member or a precious pet. When clients face many diseases in a beloved pet, it is sometimes even more difficult than if they themselves had these diseases. Clinicians and their clients often feel responsible for making important and life-changing decisions for animals that rely on them for their well-being. These animals not only share our homes, our lives, and our experiences but also our hearts. These "family members" extend unconditional love and attention, and they deserve proper decisions to enhance their quality and dignity of life. Our goal becomes to share as many moments as possible within this wonderful relationship that some term *the human-animal bond*, *the family-pet-veterinary bond*, or just *the bond*.

The purpose of this chapter is to reignite within the reader the very reason why most of us came to this profession: to care for our animal patients not only using our knowledge and skills but also our hearts. The information is not necessarily new, but it is often lost after days and years of busy practice life. These principals reside within every member of the veterinary health care team and are the very reason why the veterinary profession has been revered as one of compassion and caring.

DISPELLING THE MYTH (STEP 1)

It is important for veterinarians to dispel the myths[1,2] and misperceptions that surround many diseases and their treatments with honest, realistic, balanced information that translates into knowledge. Knowledge of a disease, options for care, and the likely course of the malady displaces fear, restores control, and allows for a more objective decision-making process. Indeed, in most situations, clients should be comforted that after they have considered all the information and options, there may still be no ideal decision for their pets; however, the best decision will be one that works at the particular time with the client's finances, philosophy, and goals for quality of life. The reader should note that dispelling the myths does not suggest "sugar coating" information, but it does suggest providing honest, accurate, realistic, measured, honest hope.

The most obvious example of a disease that is shrouded in myths and misperceptions is the diagnosis of cancer. Most people have an irrational fear of cancer. However, cancer is the most curable of all chronic diseases. Unjustified, ingrained fears about unrealistic cost, toxicity, and the lack of efficacy associated with care blocks many of us from even considering options for the diagnosis and treatment of cancer. Dispelling the myths associated with cancer can empower the medical team and the client to make clear rational decisions considering all the options.

Examples of Action Steps for Dispelling Myths

To dispel myths, clinicians can do the following:

- Lend the client a recording of an actual discussion of disease and treatment.
- Write out "bullet points" of the discussion.
- Provide preprinted information on the most common disorders and treatments.
- Give the client phone numbers of past clients who are willing to discuss the realities of care and disease.
- Provide web site information on diseases.
- Tour the hospital and introduce the staff.
- Include the client in as much patient care as law and ethics will allow.
- Ask the client to summarize information.
- Follow up treatment with a phone call.

BUILDING THE TEAM (STEP 2)

The second step in providing excellent veterinary care is to build a team[1-3] of dedicated, caring, and knowledgeable individuals who are compatible in their vision, energy, compassion,

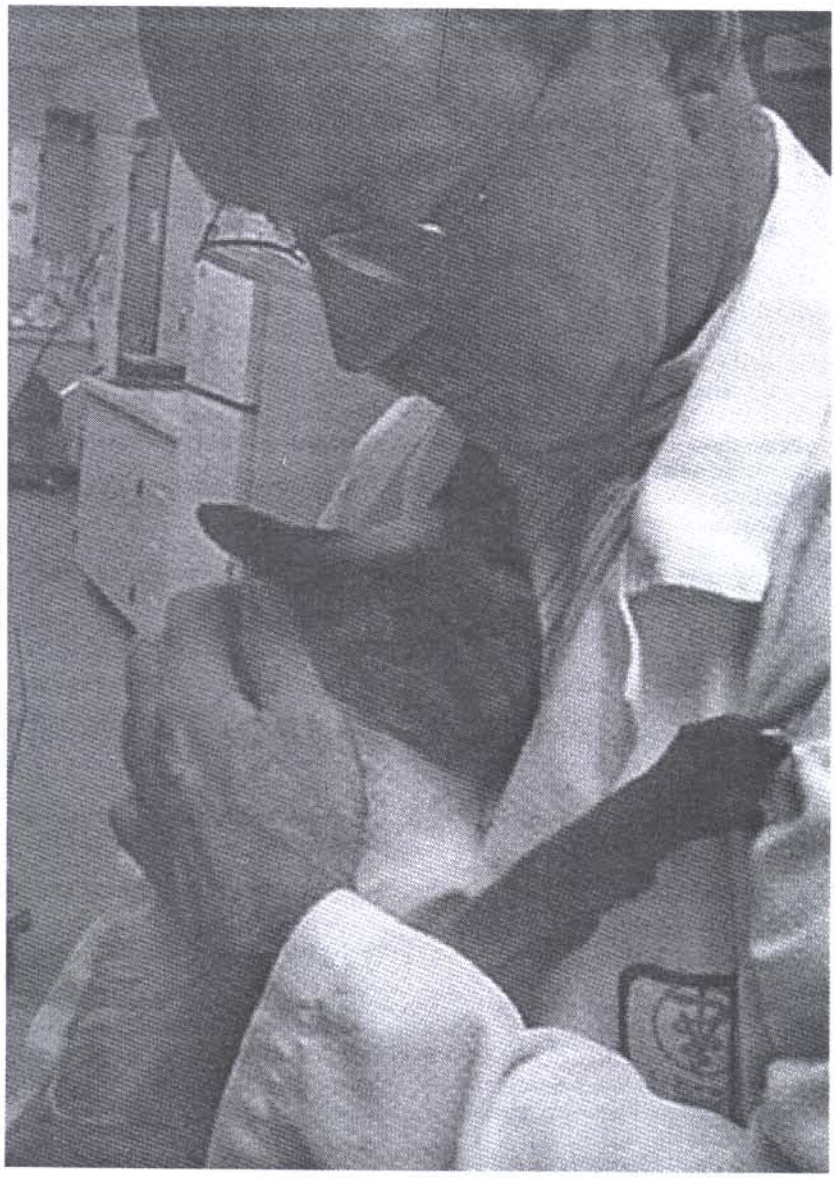


Figure 145-1 Each member of the veterinary health care team, especially veterinary nurses, should be incorporated in the care of patients and clients. When the entire team delivers care, it is more efficient, rewarding, and complete.

and philosophy. Every member of the staff, from the practice manager, office personnel, technicians, nurses, and other staff, should understand that they each play a role in meeting the medical needs of the animal and the nonmedical needs of the client (Figure 145-1). This "team" extends beyond the clinic or hospital to incorporate pathologists, specialists, pharmacists, social workers, and others who should be included whenever possible to maximize quality care. The veterinary health care team should strive to include the client through education and the ability to provide ongoing day-to-day care and assessment. Without input from the client, care of the pet, regardless of the underlying disease, will not be optimal.

Forming a team is not easy. It requires careful selection of people who have similar goals and ideals and using their unique abilities and knowledge. Selecting, rewarding, and allowing people to support each other (as well as the pet and client) are important. Building a team also requires constant education and restructuring to meet the dynamic needs and growth of the team. Finally, it requires willingness to listen, to grow, and to allow the team to improve, evolve, and excel in serving the needs of the client and the patient.

Examples of Action Steps for Building the Team

To build the team, clinicians can do the following:

- Hire, pay, and promote only the best, most compassionate members.
- Frequently review and revise the mission statement and goals written by the team.
- Ensure the team interviews and participates in decisions involving the hiring of new members.

- Share and celebrate when clients or others recognize the work of the team.
- Meet at least weekly to listen to team members; value their input, feelings, and thoughts.
- Introduce nurses and receptionists to the client at the first visit. "Team" the case, and ensure each member of the team is aware of changes in the case.

DELIVER THE CARE (STEP 3)

Once the myths and misperceptions have been dissolved and a caring team is forged, the delivery of *compassionate care* can begin.[1-3] Compassionate care focuses not only on the pet in health and disease but also on the client (caregiver or "owner") who has sought out veterinary care for the pet. Compassionate care is the outward manifestation of caring with both science and sincerity. This type of care should be operational in health and wellness, as well as in sickness and disease. Compassionate caring begins from the first moment of contact, through the process of making a diagnosis, to understanding the pathogenesis of the disease in the pet, to treatment of the condition, and finally to supporting the pet and client. After a diagnosis is made, then the real and perceived concerns should be addressed.

Delivering care can be done in several steps that can be divided into two main phases. The first phase involves providing caring support of the animal by anticipating or responding to the pet's medical needs and the client's nonmedical concerns. During this phase, the clinician should remember several things:

- Pain control is an extremely important medical priority. The use of analgesics, especially to prevent pain, will reassure the caregiver that quality of life is important. This can be in the form of oral medications (morphine, codeine, feldene, carprofen, or others), transdermal delivery systems for fentanyl, and intravenous delivery systems.
- Preventing or treating nausea, vomiting, and diarrhea is important for the pet and client. With the availability of new drugs and knowledge of the ways therapies can be administered with few adverse effects, nausea and vomiting as a result of chemotherapy can be minimized. Other chapters in this book provide details on specific medications for these problems.
- The veterinarian, client, and other members of the team often accurately perceive appetite and adequate nutritional intake as integral with quality and quantity of life. Nutrients and specific dietary profiles have been shown to be helpful for cardiac disease, diabetes, gastrointestinal (GI) disorders, renal disease, and even cancer. Basic nursing care is valuable (warming food, providing aromatic foods and comfortable environments). These animals may benefit from medicinal appetite stimulants and, when needed, assisted-feeding techniques such as esophagostomy, gastrostomy, or jejunostomy tube placement.

The second phase of delivering care involves providing direct therapy for the underlying disease. Each phase of the process of compassionate care is interdependent on the others. In addition, each client has his or her own goals for quality and length of life, as well as personal limits regarding adverse effects and cost of care.

Examples of Action Steps for Delivering the Care

To deliver care, clinicians can do the following:

- Avoid prejudging client desires and capabilities (review all options, regardless of cost or outcome).
- Discuss team philosophy for patient care with the client.
- Outline the steps to prevent toxicity or illness.
- Outline the procedure to follow if problems occur, including plans for weekends, nights, and holidays.
- Provide the client with information about the particular disease and its treatment (the goal should be to have clients know as much as possible).
- Anticipate and listen to client's needs, goals, and concerns.

SETTING THE GOALS FOR CURE, CONTROL, OR SUPPORT

As mentioned previously, all options should be given for each pet, regardless of the disease, from the very highest level of curative treatment, to palliative therapy, to supportive and hospice care, and finally to euthanasia. Each client should be allowed to make the choice and set goals for cure, control, or support[1-3] that are appropriate for them; clients should be made to feel that their decisions will be honored and supported by the entire team. The following are a few of the options that may be considered for each dog or cat:

- Definitive, curative intent: Cure is the goal of every client and veterinary health care team, it is often mistaken as the only goal. The success rate of curative intent is improved by determining what disease exists and by planning to achieve these curative goals while maintaining quality of life.
- Palliative care: Palliative care is treatment of a dog or cat to improve quality of life but not necessarily the length of life. For example, course fraction radiation to a site of bony metastasis is primarily designed to alleviate pain but will not cure the animal of its cancer. This is commonly done in many non-neoplastic, chronic diseases such as osteoarthritis and chronic renal failure.
- Supportive care: Little difference exists between palliative and supportive care. Both are defined as treatment to improve quality of life without necessarily lengthening life. Supportive care often implies minimizing clinical signs rather than direct treatment of a disease. Supportive care is often used in combination with all forms of care, including palliative care. The clinician provides supportive care by administering such drugs as analgesics, antiemetics, appetite stimulants, as well as treatments for anemia and leukopenia.
- Hospice care: Hospice care is a type of supportive care; however it is usually defined as comfort or supportive care at the end of life. Hospice care, or care to maintain quality of life, especially comfort in the terminal phases of a disease, is a defined specialty in human medical care. This type of care is developing in veterinary medicine. Dignity and comfort until death, whether due to euthanasia or a natural death, may be important to many clients and veterinarians. As with palliative and supportive care, hospice care requires careful client communication. The client and the veterinary health care team need to define goals and realistic expectations. Boundaries and limits have to be set by both sides, with the intent of providing compassionate care for the patient.

  When philosophic differences exist between the veterinary health care team and the client, referral to another center may be necessary. If support groups or counselors with specific training in pet loss and bereavement exist, their expertise should be used when appropriate (usually before a moment of crisis). In addition, creating a plan for a natural death or euthanasia is important, preferably at a time when objectivity is possible.
- Euthanasia and bereavement: It is essential that the entire team handle this portion of life through adequate client preparation. An ongoing dialogue between the entire veterinary health care team and the caregivers should exist prior to (and at the time of) death and euthanasia.

Examples of Action Steps for Establishing Goals

To establish goals, clinicians can do the following:

- Review all the possibilities for cure, palliation, support, terminal care, and euthanasia (include cost, time requirements, potential toxicity, and probability of success of care).
- Educate the client that care is often a cascade from palliation and support to hospice care and finally to euthanasia.
- Set milestones of time to review goals using medical information in combination with emotional support.

COST OF CARING: COMPASSION FATIGUE

Providing compassionate care requires the ability to express empathy. When we fail to express empathy, then we separate compassion from caring. It is in the action of this empathetic response that can lead to "compassion fatigue."[4] Simply put, compassion fatigue is the depletion of resources from within as we care for others. This development is not a reflection of the character, professionalism, or even professional skill, but rather the strength and willingness to be emotionally engaged with another being that is hurting. This condition is often "diagnosed" by well-meaning individuals as another entity known as *burn out;* however, compassion fatigue is a distinct entity with unique symptoms, outcome, and treatment.

Symptoms of compassion fatigue are often nonspecific but include psychological, emotional, behavioral, work-related, and interpersonal symptoms. Mild symptoms can include lowered frustration tolerance, loss of confidence, dread of working with certain clients, subtle manipulation of clients to avoid painful or traumatic situations, and loss of enjoyment of one's career. The more severe symptoms can result in reduced functioning in and out one's job situation.

Prevention and therapy are actually quite straightforward. The first step is to acknowledge that as caring professionals we are at risk for this condition. Compassion fatigue has struck and will strike us all. By recognizing the condition openly within each clinic and team, and by providing support and encouragement for each other, the symptoms can be more mild and recovery quicker. When we fail to recognize the condition and to support each other, compassion fatigue builds up until individuals become emotionally overwhelmed. One must take proactive steps to develop a balance between personal and professional life, as well as to establish and maintain boundaries.

Examples of Action Steps to Reduce or Treat Compassion Fatigue

To reduce or treat compassion fatigue, the clinician can do the following:

- Educate the entire veterinary health care team about compassion fatigue.
- Establish weekly debriefing sessions for the entire staff to discuss needs, concerns, and cases that weigh upon them.
- Form teams of professionals that look out for each other in the workplace and that identify high-risk moments for compassion fatigue.
- Identify professionals within the community who understand compassion fatigue, and notify team members regarding how to obtain access to these people.
- Establish a library for team members, with books and resources on compassion fatigue.
- Identify a sanctuary or "comfort room" where team members can be alone, meditate, relax, and debrief.
- Ensure team members are fully informed about each case and are allowed to have adequate closure at the end of any patient's life.
- Whenever possible, work out sabbatical or continuing education opportunities for reward and growth. The break from caring can be very rewarding in the long run.
- Teach all staff members the correct limits and boundaries.
- Use humor whenever appropriate.

CONCLUSION

Compassionate care is nothing new, but rather one name of a brand of caring that defines veterinary medicine. This type of care springs from our hearts and minds and is innate. Compassionate care often begins most effectively by dispelling the myths associated with each condition, disease, and treatment. Replacing myths and misperceptions with facts and reality frees the team and client to ensure the care is unfettered. Clinicians can build a "team" by hiring those who have a similar vision and goals. This includes the receptionist, the nurses, the veterinarian, and all other members of the clinic or hospital. Compassionate care is delivered by the team but is not without risk if it is truly done from the heart. Indeed, compassion fatigue is the enemy of compassionate care.

CHAPTER • 146

Gene Therapy

Marilyn E. Dunn

Gene therapy is defined as the introduction of new genetic and synthetic material into a living cell or organism for therapeutic purposes. In contrast to traditional therapeutics, in which a medication is administered to a patient to achieve a therapeutic response, gene therapy allows patients to "manufacture" their own treatment. Traditionally, gene therapy has been thought of as a method to treat monogenic (single gene) diseases, such as hemophilia; however, its scope has expanded to include the treatment of polygenic disorders of infectious, vascular, and neoplastic origin. New deoxyribonucleic acid (DNA) technology has been used to study the role of different genes and their products in disease. This technology has facilitated the diagnosis and treatment of these diseases by producing genetically engineered therapeutic proteins.

The production of such proteins has been the basis of a number of clinical trials in both human and veterinary medicine. Although the majority of clinical trials performed to date have focused on human diseases, a growing number of trials are now being performed in veterinary medicine. Domestic animals increasingly are being recognized as ideal models for a number of human diseases.

HISTORICAL BACKROUND

The term *genetic engineering* was first used in 1932 at the Sixth International Congress of Genetics and was taken to mean the application of genetic principles to plant and animal breeding. The term *gene therapy* was coined to distinguish this modality from genetic engineering. During the 1960s, the basics of molecular genetics and gene transfer in bacteria were established. In the late 1970s, recombinant DNA technology, the discovery of viral genomes, and the basics of gene transfer were established. In the early 1980s, the discovery of retroviruses led to more efficient gene transfer.[1]

In 1990 the first two approved *ex vivo* gene therapy trials in humans were performed in the United States. The first trial involved the use of gene therapy to correct for the enzymatic deficiency responsible for severe combined immunodeficiency syndrome (SCID), and the second trial involved the use of tumor necrosis factor (TNF)-transduced lymphocytes from tumors as immunotherapy for melanoma.[2] Both of these trials were unsuccessful, but they opened the door to a decade of intense research and clinical trials in the area of gene therapy.

In 1999, gene therapy suffered a major setback with the death of a young patient enrolled in a trial for a hepatic enzyme deficiency. This first death of a human patient enrolled in a gene therapy trial raised a number of ethical issues, which are still being actively debated. In 2000 the first two successful gene therapy clinical trials were reported. The first involved the successful treatment of two children suffering from SCID, also known as bubble-boy syndrome, using a retroviral vector for gene delivery.[3] The other reported the successful treatment of three hemophilia B patients using an adeno-associated viral vector for gene delivery.[4]

Over the past decade, research in human gene therapy has increased from two clinical trials in 1990 to 636 approved trials in 2002 involving over 4000 patients. The majority of these trials (64%) have focused on cancer research, 12% have focused on monogenic diseases, 8% on vascular diseases, and 6% on infectious diseases (primarily acquired immunodeficiency syndrome). Only 1% of the trials have thus far reached phase III.[5]

In veterinary medicine, three successful gene therapy trials have been reported: the correction of hemophilia B using an adeno-associated virus for gene delivery in five dogs; restoration of vision in three dogs afflicted with briard hereditary retinal dystrophy using an adeno-associated virus for gene delivery; and disease regression and prolonged survival in 12 dogs with malignant melanoma using cationic liposomes for gene delivery.[6]

SUCCESS FACTORS FOR GENE THERAPY

For gene therapy to be effective, the therapeutic gene must be transferred to the target cell and expressed at an appropriate level for a sufficient length of time to achieve the desired effect. The transfer and expression of the introduced gene must be safe for the cell and the animal being treated.

METHODS OF GENE TRANSFER

A gene may be transferred either by introducing it directly into a patient's cells *in vivo* (injection into a tumor) or by removing cells from the patient (e.g., bone marrow stromal cells), introducing the gene, and returning the cells to the patient (Figure 146-1). For gene transfer to occur, a vector or vehicle is required.[7]

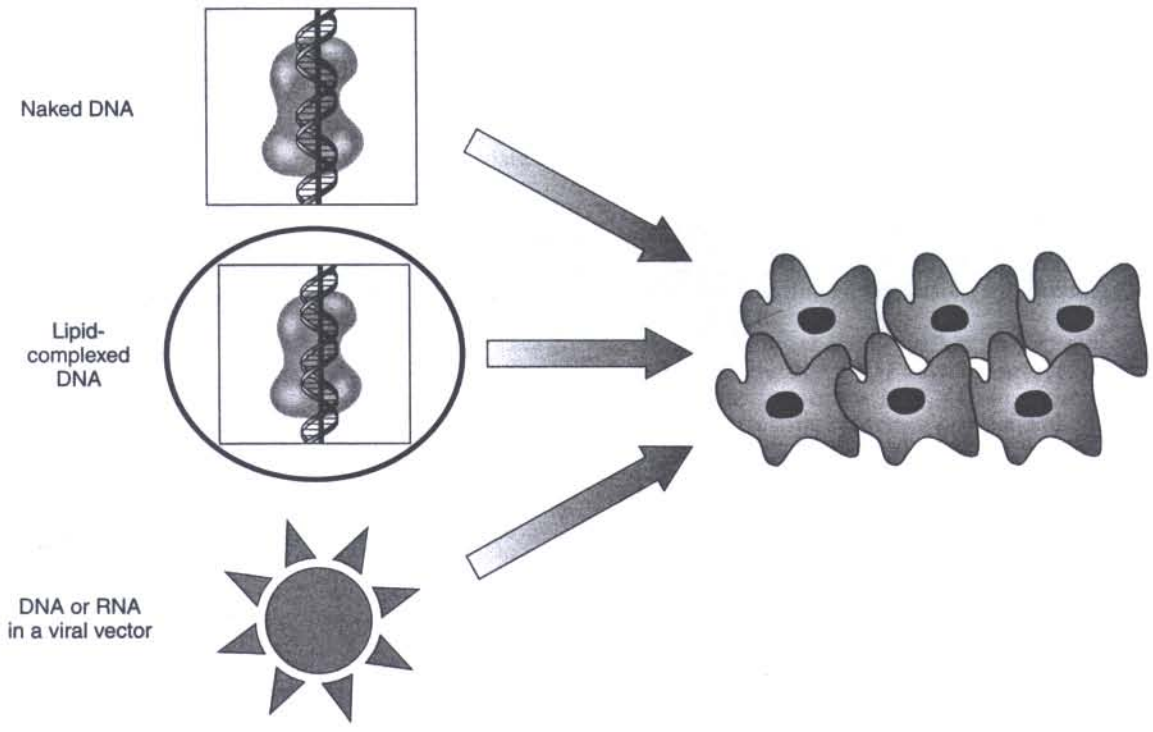


Figure 146-1 Methods of introducing genes into cells.

Viral Systems

To date, the majority of gene therapy clinical trials have used viral vectors for gene transfer. Viruses have acquired biologic mechanisms over millions of years that make them ideal vectors. Viruses effectively recognize and enter cells, travel through the cytosol to the nucleus, translocate into the nucleus, and express their genes in the host cell.[8] Despite these many advantages, viruses also have a drawback: the ability to replicate within the host cell, resulting in the liberation of infectious viral particles. Because this is undesirable, viral vectors must be rendered *replication deficient* before they can be used for gene transfer. This is accomplished using molecular techniques that replace the viral gene's coding for replication with the therapeutic gene or genes of interest.[7]

Retroviral Vectors

Retroviruses are ribonucleic acid (RNA) viruses containing two copies of a single-strand RNA genome capable of integrating DNA within a host cell. Using a specific receptor, the retrovirus attaches itself to and enters a host cell. Viral RNA is then transcribed to DNA by viral reverse transcriptases and transported to the nucleus, where it integrates into the host genome. The *provirus*, or integrated viral DNA, is transcribed and translated to produce viral proteins. Some of the proteins are packaged, via a packaging signal, into viral capsids that bud from the host cell, releasing mature viruses (Figure 146-2). Retroviral vectors have been modified by substituting the gene of interest in place of certain viral protein coding regions (e.g., *gag, pol, env* regions). This substitution renders the vector replication deficient.[9]

Retroviral vectors are the most common vectors used in human gene therapy clinical trials. Their advantages include the ability to stably integrate themselves into a host, the lack of expression of viral proteins, and the ability to carry large amounts of DNA (8 kb). Their disadvantages include low titers, resulting in low levels of gene transfer; an inability to infect nondividing cells; and the risk of insertional mutagenesis.[8,10] The use of new envelopes or pseudotypes has conferred greater physical stability on retroviral vectors, allowing ultracentrifugation and the production of higher titers. Although the inability to infect nondividing cells can be perceived as a disadvantage, in cancer gene therapy, it can be quite useful. Retroviral vectors can be used to target dividing cancer cells specifically without affecting nondividing surrounding tissue. An example is the use of a retroviral vector in the treatment of brain cancer. The vector can integrate itself into the cancer cells without affecting surrounding nondividing nerve tissue.[11]

Adenoviral Vectors

Adenoviruses are double-strand DNA viruses with a tropism for epithelial cells. Unlike retroviruses, which insert themselves into the host's genome, adenoviruses remain episomal or extrachromosomal. Adenoviral vectors are made replication deficient by the removal of genes in the E region. Genes of interest can then be inserted into the adenoviral vector.[9]

The advantages of adenoviral vectors are that they can infect both dividing and nondividing cells; they can be produced in high titers; and they can carry large amounts of DNA (10 kb). However, given their episomal expression, adenoviral vectors do not lead to stable integration of the host genome, which results in transient gene expression. This short-lived effect often requires multiple treatments with an adenoviral vector to maintain therapeutic gene expression. Adenoviral vectors are highly immunogenic and lead to a marked immune response, which may interfere with repeated applications. Given their tropism for epithelial cells, adenoviral vectors have been used extensively in gene therapy research for cystic fibrosis.[12] Although their short-lived effect and ability to provoke an intense immune response may be perceived as disadvantages, these characteristics may be useful in cancer gene therapy in which short-term protein expression accompanied by a marked inflammatory response is desirable.[9,10]

Adeno-Associated Viral Vectors

Adeno-associated viruses (AAVs) are small, single-strand DNA viruses that replicate only in the presence of a helper virus, such as an adenovirus or a herpes simplex virus. In the absence of a helper virus, an AAV cannot replicate but can integrate itself into the host genome. Therefore, compared with adenoviral vectors, an AAV results in more stable, prolonged gene expression. Although the process is technically difficult, AAVs can be produced in high titers; however, a major limitation to their use is their small size, which restricts their DNA carrying capacity to 4 kb.[10,13] Unlike adenoviruses, AAVs do not contain viral coding sequences and thus do not lead to immune or inflammatory responses. To produce an AAV, a helper virus is required. Contamination of the AAV preparation by a pathogenic helper virus (adenovirus or herpes simplex virus) is a concern.[13]

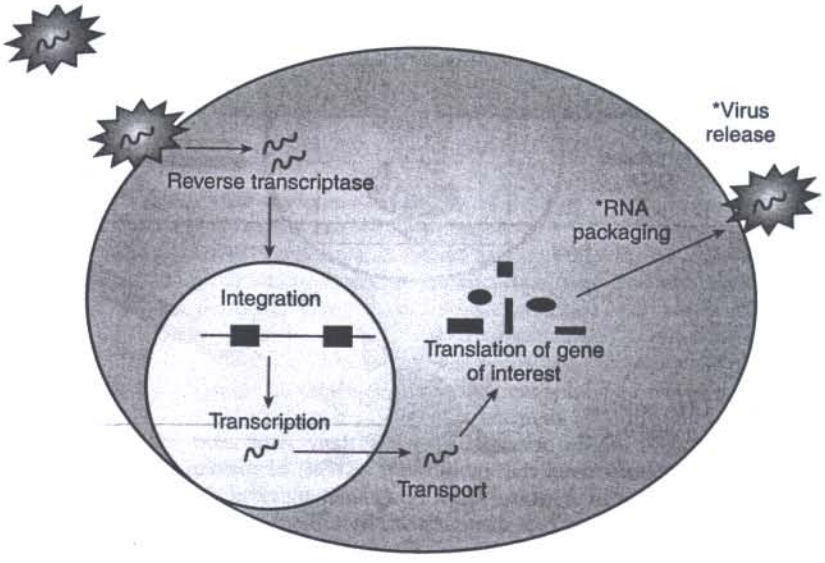


Figure 146-2 Retrovirus replication cycle. The asterisk (*) indicates elements that are absent in a retroviral vector.

Nonviral Systems

Nonviral methods of gene transfer are generally less efficient, resulting in low gene transfer rates. These vectors do not integrate into the host genome, and consequently the majority of DNA molecules entering the cell are rapidly degraded, resulting in only transient gene expression. These methods are best used when long-term gene expression is unnecessary, such as in cancer gene therapy in which transient immune modulation is beneficial or in vaccination with naked DNA.[7]

Nonviral vectors are desirable, because they can be produced under controlled conditions, eliminating the risk of viral contamination.

Naked DNA

Nucleic acid injected directly into a cell is taken up and expressed by the cell and thus can serve as a method of gene delivery. Short-term gene expression makes this method potentially useful for the development of nucleic acid–based vaccines in both human and veterinary medicine.[9]

DNA in Cationic Liposomes

Positively charged cationic liposomes attach to DNA, forming a lipid-DNA complex. The complex binds to the cell membrane and increases the efficiency of gene transfer. These complexes have been used to deliver genes to the lungs by aerosol[14] and by intratumoral injection.[15] Currently, receptors are being incorporated into the lipid-DNA complex to target specific tissues.

Particle-Mediated Gene Transfer

Nucleic acid is adsorbed onto gold beads, which are then shot under pressure by a "gene gun." The DNA-coated gold beads are propelled into cells, resulting in transient gene expression. This method of gene transfer has been used *in vivo* to transfect epithelial cells, giving it a potential role in veterinary DNA vaccination.[7]

Cell-Based Delivery of Therapeutic Genes

Therapeutic genes can be delivered by *ex vivo* manipulation of cells, which are then reintroduced into a patient. Hematopoietic stem cells, mesenchymal stem cells, neuronal stem cells, and embryonic stem cells are preferred for this type of delivery because of their pluripotential capacity or ability to give rise to various cell lineages. Currently, much stem cell research is under way to select vectors that will provide efficient stem cell gene transduction, control of gene expression during lineage progression, and control of stem cell growth and differentiation *in vivo*.[8]

Stem cell research has caused considerable controversy and raised a number of ethical issues that currently are being debated.

CLINICAL APPLICATIONS OF GENE THERAPY IN VETERINARY MEDICINE

Gene therapy has been an area of intense research in human and veterinary medicine over the past 15 years. Gene therapy can be used to treat diseases as varied as monogenic diseases, cardiovascular disease, and cancer. Advancements in gene therapy have been made in a number of areas, although no U.S. Food and Drug Administration (FDA)–approved gene therapy products are commercially available.

Monogenic Diseases

As mentioned previously, gene therapy initially was thought of as a way to correct single-gene defects, such as are present in monogenic diseases. The first human gene therapy clinical trial was performed on a patient suffering from SCID, which is the result of an adenosine deaminase deficiency that causes the loss of T lymphocytes. In human medicine, hemophilia, cystic fibrosis, thalassemia, and hereditary retinal dystrophy (Leber amaurosis) have been investigated as targets for gene therapy. In veterinary medicine, gene therapy has been successful in the correction of briard retinopathy and hemophilia B in the dog.

Briard retinopathy and its human counterpart, Leber congenital amaurosis, both result in retinal dystrophy secondary to a single-gene mutation in the retinal pigment epithelium. This mutation causes the accumulation of toxic metabolites in the retina, leading to progressive degeneration and complete blindness. In the study, an AAV carrying the gene of interest was injected subretinally in three dogs suffering from briard retinopathy. All three dogs in this study, which were blind initially, had complete restauration of vision. Unfortunately, it was not stated in the study whether the improvement was sustained.[16]

Two canine studies have successfully shown long-term phenotypic correction of hemophilia B. The first study demonstrated partial phenotypic correction of hemophilia B in five dogs using an AAV administered by percutaneous intramuscular injection into the tibialis anterior and vastus lateralis muscles. All dogs had a marked rise in factor IX, which prevented spontaneous bleeding episodes; however, coagulation profiles were prolonged, and the dogs still bled with moderate trauma. Thirteen months after AAV administration, factor IX plasma levels were maintained.[17]

The second study demonstrated almost complete phenotypic correction of hemophilia B in three dogs after a liver-directed AAV was administered through a mesenteric vein. All dogs had resolution of bleeding episodes and correction of coagulation profiles. Seventeen months after AAV administration, factor IX plasma levels were maintained.[18]

The question is, despite these apparent successes, why are only 12% of the clinical trials being performed in human medicine focusing on monogenic diseases? One reason is the fact that monogenic disorders are less common than other diseases, such as cardiovascular disease and cancer, therefore the benefits would be felt by a smaller clinical population. Also, current vectors are more suited to cancer therapy, given the difficulty of achieving long-term gene expression.

Monogenic disease is managed differently in veterinary medicine than in human medicine in that breeding programs designed to eliminate the disease can often be accomplished. However, animals suffering from these diseases can serve as models for their human counterparts.

Cancer

The most popular disease target in gene therapy is cancer. Despite great advances in human and veterinary oncology, cancer remains a disease with high morbidity and mortality. This reality has fueled the search for alternative treatments, such as gene therapy.

Cancer gene therapy has six major approaches, which involve introduction of (1) a suicide gene, (2) a cytokine gene, (3) a tumor suppressor gene, (4) an antisense oncogene, or (5) a multiple drug resistance gene, and also (6) inhibition of angiogenesis (Figure 146-3).

Suicide Gene

A suicide gene is one that codes for a specific enzyme that is capable of metabolizing a substance into a toxic metabolite. In one study, a retrovirus containing a thymidine kinase gene was injected intratumorally into human patients with brain tumors. Gancyclovir, which is metabolized to a toxic metabolite by thymidine kinase, was then administered systemically. Small tumors showed partial regression, but larger tumors did not respond. Because retroviruses can infect only dividing cells, surrounding nervous tissue was unaffected.[19] It is

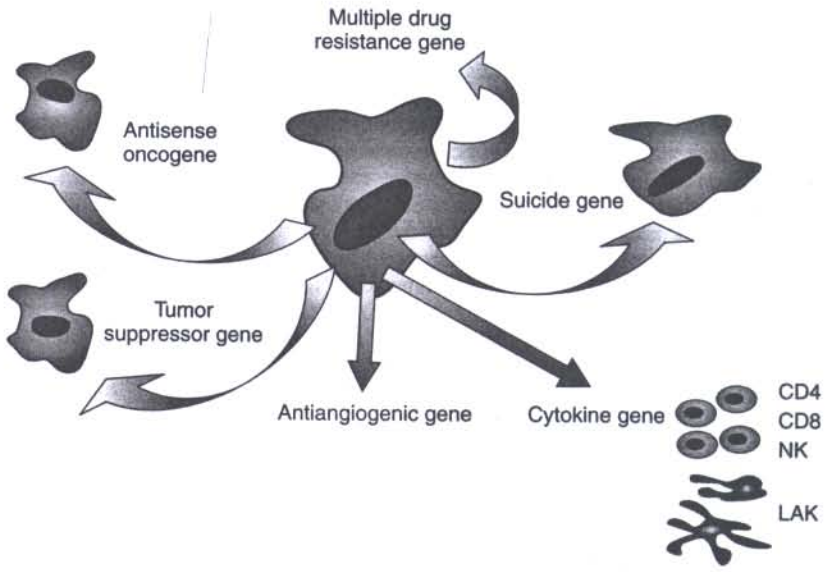


Figure 146-3 Potential targets of cancer gene therapy. *NK*, Natural killer cells; *LAK*, lymphokine-activated killer cells.

believed that a *bystander effect* is partly responsible for some of the successes achieved with suicide gene therapy. The bystander effect is thought to be mediated by the transfer of toxic metabolites from one transduced cell to surrounding cells. The immune reaction secondary to cell death also plays a role in the bystander effect. Currently, suicide gene therapy is being investigated for the treatment of malignant melanoma in the dog.[7] One of the hurdles that must be overcome in suicide gene therapy is low tumor transduction, which often results in poor or partial responses to therapy.

Cytokine Gene

Cytokine genes can be inserted directly into tumor cells, allowing recognition of the tumor cell and distant metastases by the immune system (Figure 146-4). This process has been referred to as *tumor vaccine*. The term *autologous tumor vaccine* refers to *ex vivo* transduction of autologous tumor cells, which are then reintroduced into the patient.[20] In one study, histoincompatible cells expressing interleukin-2 (IL-2) were introduced into animals with spontaneous canine malignant melanoma and feline fibrosarcoma. The outcome of this study was favorable in that treated animals showed improved survival compared with controls.[21] Another study evaluated the effect of intratumoral injection of lipid-complexed DNA encoding for a bacterial superantigen and either IL-2 or granulocyte-macrophage colony stimulating factor (GM-CSF) in 26 dogs with malignant melanoma. This therapy was capable of inducing both local and systemic tumor regression, with an overall response rate of 46%.[22] Another study evaluated the usefulness of an autologous tumor vaccine transfected with GM-CSF in 16 tumor-bearing dogs. Evidence of an antitumor response was seen in three dogs.[23] Despite these encouraging results, a number of other clinical trials have showed marked variability in tumor response to cytokine therapy.

Tumor Suppressor Gene

Cancer can result from mutations or deletions in the tumor suppressor gene, resulting in uncontrolled cell growth. The introduction of a tumor suppressor gene (e.g., p53 gene) into

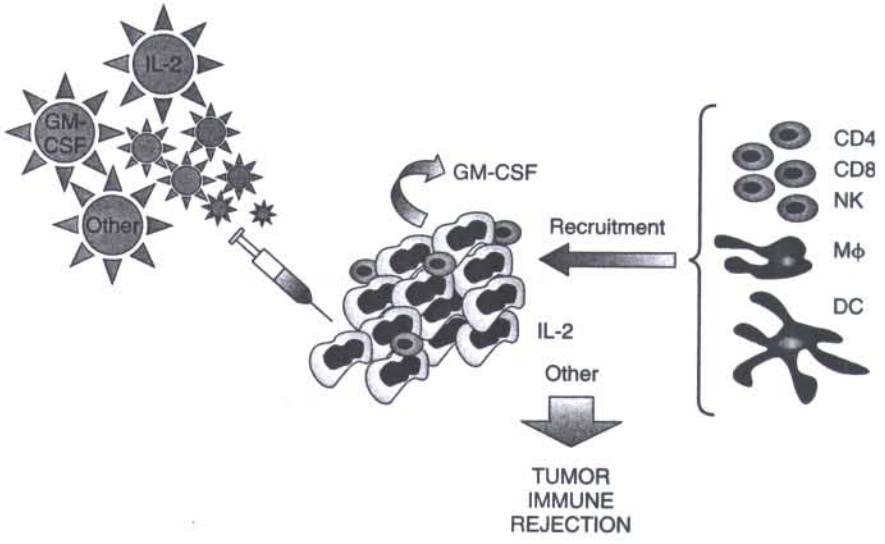


Figure 146-4 Retroviral vectors coding for interleukin-2 (IL-2), granulocyte-macrophage colony stimulating hormone (GM-CSF) or other cytokines can be introduced directly into tumor cells. These tumor cells produce cytokines, resulting in recruitment of inflammatory cells that leads to immune tumor rejection. *M*, Macrophage; *DC*, dendritic cell.

a tumor cell can prevent the cell from entering into the cell cycle, thereby leading to *apoptosis* (programmed cell death). In a human clinical trial, 28 patients with lung cancer were treated by intratumoral injection of an adenovirus containing the p53 gene. Eight percent of the patients showed a partial response, but the treatment had no effect on distant metastases.[24] The lack of vectors capable of efficient systemic gene delivery thus far has limited the usefulness of this approach.

Antisense Oncogene

Oncogenes are genes that, when mutated or overexpressed, result in uncontrolled cell growth. Antisense oligodeoxynucleotides are short sequences of RNA that are complementary to the messenger RNA (mRNA) of an oncogene. The antisense oncogene blocks tumor RNA transcription, blocking tumor protein synthesis and thereby leading to tumor cell apoptosis. Human clinical trials, using antisense oncogenes, have demonstrated partial responses in a small number of patients. A major limitation to this approach is the inability to deliver antisense oncogenes efficiently to tumor cells.[9]

Multiple Drug Resistance Gene

Expression of the multiple drug resistance (MDR) gene decreases toxicity from certain chemotherapeutic drugs such as doxorubicin, vincristine, and actinomycine D by encoding for a transmembrane pump. Expression of the MDR gene by tumor cells is associated with resistance to chemotherapy. Human clinical trials have used this approach primarily in the treatment of leukemic patients. Healthy bone marrow hematopoietic cells are withdrawn from the patient, transduced with the MDR gene, and reinfused. The goal of this approach is to decrease hematopoietic toxicity from chemotherapy by rendering the healthy hematopoietic cells chemoresistant. Some of the difficulties encountered with this approach are poor hematopoietic cell transduction and the occurrence of nonhematopoietic toxicities with the use of high-dose chemotherapy protocols.[8]

Inhibition of Angiogenesis

In 1970, Folkman discovered that tumors produce substances that stimulate the growth of their vasculature.[25] These substances have since been identified as proangiogenic cytokines. Angiogenesis can be inhibited by blocking the production of proangiogenic cytokines. For example, the VHL gene has been shown to downregulate vascular endothelial growth factor in human renal cancer cells.[9] Angiostatin, endostatin, and interleukin-12 are known to be endogenous inhibitors of angiogenesis. Transduction of tumor cells resulting in expression of these inhibitors, has been shown to decrease tumor angiogenesis in murine models.[26]

In the future, combined approaches to cancer gene therapy may prove to be most beneficial. For example, introduction of both a suicide and a cytokine gene into tumor cells may result in a local tumor effect and a systemic immune response directed at distant metastases.

Other Potential Veterinary Applications

Inflammatory, infectious, and cardiovascular diseases are areas in which much gene therapy research currently is under way. Inflammatory conditions such as osteoarthritis and rheumatoid arthritis, which are influenced by the aberrant expression of certain inflammatory cytokines, have been targets of such research.[27] Gene therapy approaches have also been applied to certain infectious diseases, in particular that caused by the human immunodeficiency virus (HIV). One such approach is the transfer of antiviral genes to hematopoietic stem cells to ensure a renewable source of HIV-protected cells to the patient.[28] If successful, these approaches could be used in the treatment of cats infected with feline immunodeficiency virus (FIV).

The usefulness of gene therapy in the treatment of cardiovascular disease in humans has recently been investigated. Attempts are being made to develop vectors that can efficiently deliver genes into the myocardium to treat myocardial infarction and into the vasculature to treat atherosclerosis. These therapies could be used in veterinary medicine to treat patients with myocardial disease.[8]

CONCLUSION

Gene therapy is a relatively new area of research that has yielded a multitude of research protocols but thus far has resulted in few clinically applicable treatments. Gene therapy success has been limited by difficulties in delivering genes safely and efficiently to target cells. In the future, advances in vector design may help overcome some of the hurdles currently encountered. Other issues, such as the risk of insertional mutagenesis and the production of replication-competent viruses, as well as ethical concerns, also need to be addressed.

CHAPTER 147

Constant Rate Infusions

Nishi Dhupa

A constant rate infusion (CRI) is a precisely calculated amount of drug added to a specific volume and type of diluent fluid, delivered as a continual IV infusion for the duration of the treatment period. The intent of drug therapy is to produce the desired pharmacologic response while avoiding adverse drug reactions. Drugs with very short half-lives, such as dobutamine or epinephrine (less than 2 minutes) and nitroprusside (0.4 minutes), must be administered by CRI to maintain steady-state serum concentrations and achieve desired pharmacologic effects. Other drugs such as furosemide may be delivered by CRI to increase efficacy and to reduce total daily dose.

PHARMACOKINETICS

The drug half-life is defined as the time it takes for the blood concentration of the drug to diminish by 50% and is a function of both clearance and volume of distribution. The half-life predicts how long it takes for a drug-dosing regimen to achieve steady-state serum concentrations. With initiation of therapy, if a loading dose is not administered to provide "instantly" a desired serum drug concentration, four to five half-lives will elapse before the patient reaches steady-state drug concentrations. For drugs with very short half-lives (less than 2 minutes), loading doses may not be required. Many cardiac and vasoactive drugs fall into this category. When delivered by CRI, immediate hemodynamic improvement can be achieved and the dose can be titrated to achieve desired effects.

PHARMACEUTICAL DRUG INTERACTIONS

The safe use of parenteral drugs depends on the drug's pharmaceutical integrity, including stability and compatibility. Pharmaceutical drug interactions occur before a drug is administered to the patient *(in vitro)*. These interactions occur primarily because of a drug's physical incompatibility with another drug or fluid solution (acid-base interactions or affinity to charged particles in another solution) or the drug's container (including intravenous tubing). Drug solutions are formulated to ensure their chemical stability; mixing drugs with different preservatives, vehicles, and buffers compromises this stability. These concerns apply most to the veterinary critical care environment, where multiple drug administration is common. Drug incompatibilities can change the chemical or physical nature of the drug and can influence efficacy and toxicity. Although many unstable solutions do not show obvious changes, any change in solution color (or the development of cloudy precipitates) should halt administration and elicit inquiry. Some color changes, such as a pink discoloration of dobutamine solutions, may not affect potency if used within 24 hours; conversely a violet or pink dopamine solution indicates inactivation.

The stability of a drug in fluids is related to an optimal pH and therefore diluent solutions must be chosen carefully. Saline solutions have a pH of 5 to 6, and 5% dextrose solutions have a pH of 5. These may be used as diluents for drugs that are weak bases (formulated as salts of hydrochloric acid) and must be kept in acidic state to maintain their stability in aqueous solution. Examples of these drugs include dopamine, dobutamine, epinephrine, and isoproterenol; they are incompatible in alkaline solutions. Questions regarding the stability of drugs and interactions between drugs in solution can be answered by reading the package insert of each drug and various excellent publications.[1]

The adsorption of drugs to plastic or glass surfaces may result in variable dose delivery. Highly lipid-soluble drugs such as diazepam will lose a significant amount of potency when administered through plastic infusion tubing at slow flow rates. Regular insulin (used as a CRI for treatment of diabetic ketoacidosis) binds to glassware and many plastics. This binding process can be saturated, and the flushing of intravenous lines with a sufficient volume (50 mL) of the drug in solution prior to administration will result in more accurate dosing. Drugs such as nitroprusside, which manufacturers package in brown containers, may be sensitive to light. Care should be taken to provide protection from ultraviolet (UV) light during infusion.

Specific Drugs

A list of drugs administered as CRI in small animal veterinary medicine is presented in Table 147-1. The most common CRI drugs are positive inotropes (dobutamine, dopamine), pressor agents (epinephrine, norepinephrine), vasodilators (nitroprusside), and antiarrhythmics (lidocaine, procainamide).

Dose Calculation and Constant Rate Infusion Preparation

CRI doses must be calculated carefully. In general, doses for most CRI drugs are expressed as *micrograms per kilogram of body weight per minute*, but the drugs themselves are available in concentrations of *milligrams per milliliter*. Therefore dose calculations must convert from micrograms (μg) to milligrams (mg) to ascertain the volume of drug required. The objective is to determine how much drug to add to a specific volume of diluent fluid to achieve the required dose: $\mu g \times kg \times min = \mu g$ *of drug to be added to a known volume of diluent fluid*. In this formula, the microgram (μg) dose and the body weight (kg) of the patient is known; the number of minutes that each bag of intravenous fluid will last is calculated by dividing the volume in the fluid bag by the fluid administration rate per hour; then multiplying this by 60 to determine the number of minutes. The formula can then be solved to provide the total number of micrograms required for addition to the fluid bag; this can be divided by 1000 to convert the dose to milligrams. With a known concentration of drug (mg/mL), the required volume can be added to the diluent intravenous fluid bag. For precise dosing, the equivalent volume of diluent fluid should be discarded prior to addition of drug to the diluent solution.

Note: For infusions lasting exactly 1000 minutes (e.g., 250 mL fluid bag infused at 15 mL/hour or 500 mL infused at

30 mL/hour), a simpler formula may be used: *µg × kg = mg of drug required.*

Example 1: The clinician must calculate a dobutamine CRI in 0.9% saline at 10 µg/kg/minute for a 20 kg dog in septic shock. Using the previous formula (µg × kg = mg of drug required) the clinician would add 200 mg of dobutamine to 250 mL of saline, to infuse at 15 mL/hour. The concentration of dobutamine is 12.5 mg/mL; therefore 16 mL of dobutamine will be added to 234 mL of saline (16 mL removed prior to addition of the drug).

Example 2: The clinician must calculate a lidocaine CRI at 60 µg/kg/minute for a 40 kg dog with ventricular tachycardia. The lidocaine will be added to the maintenance fluids, Normosol R in 500 mL bags, running at a rate of 100 mL/hour. To solve this, the clinician would use this formula: µg × kg × minute = µg of drug to be added to a known volume of diluent fluid.

Text continued on p. 550.

Table • 147-1

*Drugs Administered Via Constant Rate Infusions**

DRUG NAME AND FORMULATION	ACTIONS AND INDICATIONS	CONSTANT RATE INFUSION (CRI) DOSE	RECOMMENDED DILUENT (D) AND INCOMPATIBILITIES (I)	COMMENTS
Atracurium besylate 10 mg/mL	Competitive neuromuscular blockade; induction of respiratory muscle paralysis during mechanical ventilation	LD: 0.2-0.5 mg/kg IV (dog and cat) CRI: 3-9 µg/kg/min (dog) 0.37 µg/kg/min (cat)	D: 5% Dextrose, 0.9% NaCl I: Should not be mixed with other drugs	Infusion started 5 min. after loading dose; respiratory and cardiovascular monitoring should be provided
Butorphanol 10 mg/mL	Synthetic opiate; analgesia +/– sedation	LD: 0.2 mg/kg CRI: 0.1 mg/kg/hr	D: Any IV fluid I: Diazepam, pentobarbital	Partial agonist
Calcium gluconate 100 mg/mL	Treatment of hypocalcemia, hyperkalemic dysrhythmias, hypermagnesemia	CRI: 10 mg/kg/hr	D: Any IV fluid I: Dobutamine, sodium bicarbonate, potassium phosphate	ECG should be monitored; CRI should be discontinued if bradycardia develops
Cimetidine 300 mg/2 mL	H_2 receptor antagonist; used in treatment of gastric ulceration, metabolic alkalosis	LD: 2.5 mg/kg CRI: 0.5 mg/kg/hr	D: Any IV fluid I: Pentobarbital, atropine	Too rapid an infusion or use of a central vein may cause hypotension and arrhythmias
Cisplatin 1 mg/mL	Cell cycle nonspecific antineoplastic agent; used for various neoplasms	CRI: 60-70 mg/m² over 2-6 hours	D: 0.9% NaCl I: Metoclopramide	Should not be used in cats; saline diuresis should be provided to avoid nephrotoxicity
Diazepam 5 mg/mL	Enhances effects of GABA in the brain; anticonvulsant, sedative, and skeletal muscle relaxant effects (tetanus)	LD: 5-10 mg CRI: 0.1-0.5 mg/kg/hr; increase to effect	D: 5% Dextrose, 0.9% NaCl I: Many drugs†; cloudiness in admixture indicates precipitation and reduced potency	Adsorbs to plastic IV tubing resulting in unreliable dosing; does not adsorb to plastic syringes; should be protected from light; new infusion should be started every 4 hours
Diltiazem 5 mg/mL	Calcium channel blocker, negative inotropic and chronotropic effect; used in hypertrophic cardiomyopathy and supraventricular tachycardias	LD: 0.2-0.4 mg/kg CRI: 0.2-0.5 mg/kg/hr or 5-20 µg/kg/min to effect	D: Any IV fluid I: None listed (drug insert should be consulted)	Loading dose is not always used

Continued

Table • 147-1

Drugs Administered Via Constant Rate Infusions—cont'd*

DRUG NAME AND FORMULATION	ACTIONS AND INDICATIONS	CONSTANT RATE INFUSION (CRI) DOSE	RECOMMENDED DILUENT (D) AND INCOMPATIBILITIES (I)	COMMENTS
Dobutamine 12.5 mg/mL (250 mg/20 mL vial)	Synthetic catecholamines; positive inotrope via beta effect; useful in cardiogenic or septic shock to treat decreased cardiac contractility	2-20 µg/kg/min (dog) 1-15 µg/kg/min (cat)	D: 5% Dextrose or 0.9% NaCl I: Alkaline solutions, sodium bicarbonate; mixing with other drugs should be avoided†	Pink discoloration occurs with slight oxidation, but no loss of potency if used within 24 hours; may cause focal facial seizures in cats
Dopamine 40 mg/mL (200 mg/5 mL)	Low dose: Dopaminergic at low dose; improves renal blood flow; may play a role in treatment of oliguric renal failure	2-5 µg/kg/min	5% Dextrose or 0.9% NaCl I: Sodium bicarbonate or alkalinizing solutions	Do not use if solution has a pink or violet color; stable in fluids for 24-48 hours; extravasation may cause necrosis; should be treated locally with 5-10 mg phentolamine in 10-15 mL saline
	Moderate dose: Beta agonist and positive inotrope at moderate dose	5-10 µg/kg/min		
	High dose: Pressor agent at high dose; increases blood pressure	7-20 µg/kg/min		
Epinephrine 1:1000 (1 mg/mL)	Alpha and beta agonist, positive inotrope and chronotrope; used in cardiac arrest, hypotension, severe asthma, and anaphylaxis	0.1-1.5 µg/kg/min to effect	D: 5% Dextrose or 0.9% NaCl I: Alkaline solutions; calcium-containing solutions	Solution should be protected from light
Esmolol 10 mg/mL	Short-acting beta-1 (cardioselective) blocker; used in tachycardia or hypertension	LD: 500 µg/kg (over 1 min) CRI: 25-200 µg/kg/min	D: 5% Dextrose, 0.9% NaCl I: Sodium bicarbonate	Concurrent use of calcium channel blockers should be avoided
Ethanol 100% (1000 mg/mL)	Treatment of ethylene glycol toxicity	LD: 0.6 g/kg CRI: 100 mg/kg/hr	D: 0.9% NaCl to a 7% solution I: None listed	7% solution is prepared by adding 7 mL 100% ethanol to 93 mL NaCl
Fentanyl citrate 0.05 mg/mL (50 µg/mL)	Narcotic analgesic; synthetic opioid; used for analgesia and sedation; may be used to facilitate mechanical ventilation	LD: 10-20 µg/kg IV (dog) CRI: 0.3-0.7 µg/kg/min (dog) LD: 2 µg/kg (cat) CRI: 0.1-0.3 µg/kg/min (cat)	D: 5% Dextrose I: Mixing with other drugs should be avoided	Alternative dose: 1-5 µg/kg/hr
Furosemide 50 mg/mL	Loop diuretic; promotes diuresis in oliguric renal failure, treats pulmonary edema in CHF, promotes calciuria in hypercalcemia	3-8 µg/kg/min or 0.1-1 mg/kg/hr to effect	D: Any IV fluid I: Acidic solutions; precipitates when combined with many drugs†	Should be protected from light

Continued

Table • **147-1**

Drugs Administered Via Constant Rate Infusions—cont'd*

DRUG NAME AND FORMULATION	ACTIONS AND INDICATIONS	CONSTANT RATE INFUSION (CRI) DOSE	RECOMMENDED DILUENT (D) AND INCOMPATIBILITIES (I)	COMMENTS
Heparin 1000 U/mL	Activates antithrombin III, prevents thrombin and fibrin formation; used in DIC and thromboembolic disease	LD: 100-300 U/kg CRI: 10-50 U/kg/hr (dog) 5-10 U/kg/hr (cat)	D: Any IV fluid I: Any drugs that are unstable in an acidic environment†	Adjust dose based on activated partial thromboplastin time; clinician should aim for increase of 1.5-2.5 times original rate
Hetastarch 6 g/100 mL	Synthetic colloid; used for its oncotic properties and as a volume expander	1-2 mL/kg/hr	Available as a 6% solution in 0.9% NaCl	Should not be used if brown in color or precipitate present
Hydrocortisone sodium phosphate 100, 250, or 500 mg vials	Treatment of addisonian crisis and of adrenal insufficiency induced after adrenalectomy	0.625 mg/kg/hr	D: Any IV fluid; should be diluted to 0.1-1.0 mg/mL I: Mixing with other drugs should be avoided†	Proper dilution volume should be used to avoid precipitation; should not be administered if discolored
Insulin (regular) 100 U/mL	Lowers blood glucose, used in diabetic ketoacidotic patients and for adjunctive treatment of hyperkalemia	1.1-2.2 U/kg/day (use lower doses for cats)	D: 0.9% NaCl I: Sodium bicarbonate; mixing with other drugs should be avoided†	Binds to IV tubing; tubing should be flushed with insulin solution prior to IV infusion
Isoproterenol 0.2 mg/mL (1 mg/5 mL)	Beta-adrenergic agonist, causes positive inotropy and chronotropy; also vasodilator and bronchodilator; used in advanced heart block	0.02-0.1 µg/kg/min	D: 5% Dextrose or 0.9% NaCl; dilute to 1 mg in 500 mL (1:500,000 solution) I: Sodium bicarbonate	Causes peripheral vasodilation
Ketamine 100 mg/mL	Neuroleptanalgesia; may be used as an adjunct to opioid therapy to ease severe pain	1-3 µg/kg/min; clinician should prepare a 1-2 mg/mL solution (500 mg added to 500 mL)	D: 5% Dextrose or 0.9% NaCl I: Diazepam, barbiturates	Should be used with opioid or tranquilizers
Lidocaine 20 mg/mL (2%)	Class IB ventricular antiarrhythmic	LD: 2-4 mg/kg (dog) CRI: 50-100 µg/kg/min (dog) LD: 0.25-0.75 mg/kg (cat) CRI: 10-20 µg/kg/min (cat)	D: 5% Dextrose; 0.9% saline less preferred I: Alkaline solutions; mixing with other drugs should be avoided†	Adsorption to polyvinyl chloride bags; stable in IV fluids for 24 hours; cats are very sensitive to the drug (may seizure)
Magnesium sulfate (parenteral) 4.06 mEq/mL 50% (500 mg/mL)	Used as a source of magnesium in hypomagnesemia and refractory hypokalemia	Up to 1 mEq/kg/day	D: 5% Dextrose diluted to <20% I: Many drugs,† including those containing calcium, vitamin B complex, sodium bicarbonate	Use with caution with impaired renal function; overdose causes bradycardia, muscle weakness; treat with calcium

Continued

Table 147-1

Drugs Administered Via Constant Rate Infusions—cont'd*

DRUG NAME AND FORMULATION	ACTIONS AND INDICATIONS	CONSTANT RATE INFUSION (CRI) DOSE	RECOMMENDED DILUENT (D) AND INCOMPATIBILITIES (I)	COMMENTS
Mannitol 25% (250 mg/mL)	Osmotic diuretic; free radical scavenger; has a role in treatment of oliguric renal failure, glaucoma, cerebral edema	0.5-1 g/kg/hr for 2-6 hr	D: 5% Dextrose to 8%-10% solution I: Blood, strongly acidic or alkaline solutions; mixing with other drugs should be avoided	Clinician should warm to remove crystallization of high (25%) concentrations; easier in glass containers than plastic
Methylprednisolone sodium succinate 40 mg/mL	Treatment of head/spinal cord trauma	LD: 30 mg/kg followed by 15 mg/kg at 2 and 4 hrs CRI: 2.5 mg/kg/hr for 42 hours reducing dose gradually	D: 5% Dextrose or 0.9% NaCl I: Normosol-R, Normosol-M, selected drugs†	Precipitation may occur if dilution is too small; reconstituted solution should be used within 48 hours
Metoclopramide 5 mg/mL	Antiemetic; gastrointestinal (GI) stimulant	1-2 mg/kg/day or 0.7-1.4 µg/kg/min or 0.01-0.02 mg/kg/hr (dog) and 0.01 mg/kg/hr (cat)	D: Any IV fluid without calcium I: Sodium bicarbonate; mixing with other drugs should be avoided†	Should be protected from light
Midazolam 5 mg/mL	Anticonvulsant, sedative; similar to diazepam	LD: 0.1 mg/kg (dog) CRI: 0.35 µg/kg/min (dog)	D: 5% Dextrose, 0.9% NaCl I: Mixing with other drugs should be avoided	Does not adsorb to plastics and therefore can be dosed more reliably than diazepam
Morphine 15 mg/mL	Opiate agonist; used in treatment of acute pain	LD: 1-10 mg/hr CRI: 0.01-0.1 mg/kg/hr	D: 5% Dextrose; should be diluted to 0.1-1 mg/mL I: Mixing with other drugs should be avoided†	Lower dose should be used in cats; cats may show CNS excitability
Norepinephrine 1 mg/mL	Potent adrenergic vasopressor; used for short-term blood pressure support	0.05-1.0 µg/kg/min to effect	D: 5% Dextrose or 0.9% NaCl I: Mixing with other drugs should be avoided	Initial systolic pressure should not be raised by >40 mm Hg; extravasation should be treated with phentolamine
Nitroprusside 200 µg/mL	Venous and arterial vasodilator; used in acute, congestive heart failure to treat fulminant pulmonary edema or systemic hypertension	0.5-10 µg/kg/min (dog) 0.1-0.3 µg/kg/min (cat); clinician should start low and increase slowly; BP should be monitored	D: 5% Dextrose; must use with infusion pump only I: Mixing with other drugs should be avoided†	Should be used with extreme caution; overdose results in cyanide toxicity; should not be used in oliguric patients; solution must be shielded from light
Oxytocin 20 U/mL	Used for enhancement of uterine contractions at parturition	5-10 U over 30 min (dog) 2-5 U over 30 min (cat)	D: 5% Dextrose or 0.9% NaCl I: Mixing with other drugs should be avoided†	Should be used when cervix is open; normal glucose and calcium levels should be ensured first

Continued

Table 147-1

Drugs Administered Via Constant Rate Infusions—cont'd*

DRUG NAME AND FORMULATION	ACTIONS AND INDICATIONS	CONSTANT RATE INFUSION (CRI) DOSE	RECOMMENDED DILUENT (D) AND INCOMPATIBILITIES (I)	COMMENTS
Pancuronium 1 mg/mL	Neuromuscular blockade as an adjunct to anesthesia or mechanical ventilation	LD: 0.04-0.1 mg/kg CRI: 0.06-0.1 mg/kg/hr	D: 5% Dextrose or 0.9% NaCl, by syringe pump I: Drug insert should be consulted	Cardiovascular and respiratory monitoring must be used
Pentobarbitol 65 mg/mL	GABA-mimetic; used as an anticonvulsant and for chemical restraint during mechanical ventilation	LD: 3-30 mg/kg to effect CRI: 0.2-1 mg/kg/hr	D: 5% Dextrose or 0.9% NaCl I: Mixing with other drugs should be avoided†	Respiratory activity should be monitored; ventilatory support may be required
Phenylephrine 100 mg/mL	Causes vasoconstriction via alpha-adrenergic effects; used to treat hypotension under anesthesia	1-3 µg/kg/min	D: 5% Dextrose or 0.9% NaCl I: Sodium bicarbonate	Extravasation injuries must be treated with phentolamine locally
Potassium chloride 2 mEq/mL	Used to treat serum potassium deficits	In IV fluids: 28-80 mEq/L	D: Any IV fluid I: Diazepam	IV administration should not exceed 0.5 mEq/kg/hr
Potassium phosphate 3 mM/mL phosphorous, 4.4 mEq/mL potassium	Used in correction of hypophosphatemia	0.01-0.03 mM/kg/hr for 6 hr or 0.03-0.12 mM/kg/hr for DKA patients	D: 0.9% NaCl I: Dobutamine, lactated Ringer's solution	50%-75% of potassium supplied using KCl, the rest as KPO_4; phosphorous levels checked every 12 hours in DKA patients, until >2.5 mg/dl
Procainamide 100 or 500 mg/mL	Class IA antiarrhythmics; used in treatment of ventricular arrhythmias	LD: 2-20 mg/kg over 5 min (dog) CRI: 20-50 µg/kg/min LD: 1-2 mg/kg (cat) CRI: 10-20 µg/kg/min (cat)	D: 0.9% NaCl I: Decomposes if admixed with dextrose	Light yellow (but not amber) discoloration does not affect potency; should not be used if dark yellow; stable in fluids for 24 hours
Propofol 10 mg/mL	Short-acting hypnotic	0.05-0.2 mg/kg/min	D: 5% Dextrose I: Should not be mixed with other drugs	Propofol supports bacterial growth; should be used as strict asepsis
Sodium bicarbonate 1 mEq/mL	An alkalinizing agent; used to treat metabolic acidosis; adjunctive therapy in hyperkalemic crises	50% of calculated dose (based on deficit) IV over 4-6 hours	D: 5% Dextrose or 0.9% NaCl I: Mixing with other drugs should be avoided†	Deficit calculation: 0.3 × kg body weight × base deficit
Verapamil 2.5 mg/mL	Calcium channel blocker; used for supraventricular tachyarrhythmias	LD: 0.05-0.15 mg/kg CRI: 2-10 µg/kg/min	D: 5% Dextrose or 0.9% NaCl I: Mixing with other drugs should be avoided	Loading dose not always used
Vitamin B complex (injectable)	Provides B complex supplementation	2-4 mL/L at maintenance fluid rate	D: Any IV fluid I: Sodium bicarbonate	Compatible with IV fluid and TPN solutions

*Data compiled from references listed.
†See package insert for details.
IV, Intravenous; *LD*, loading dose; *CRI*, constant rate infusion; *TPN*, total parenteral nutrition; *GABA*, gamma aminobutyric acid; *CHF*, congestive heart failure; *DIC*, disseminated intravascular coagulation; *BP*, blood pressure; *mM*, millimoles.

To calculate number of minutes each bag will last:

500 mL at 100 mL/hour = 5 hours

5 hours × 60 minutes/hour = 300 minutes

To solve the equation:

60 µg (required dose) × 40 kg × 300 minutes = 720,000 µg

To convert µg to mg:

720,000 µg/1000 = 720 mg

To calculate the amount of drug needed per 1000 mL bag, the clinician should divide the amount of drug needed by the concentration of drug being used (in this case, 2% lidocaine or 20 mg/mL):

720 mg/20 mg/mL = 36 mL of lidocaine

Note: 36 mL of Normosol R should be removed from the 1000 mL bag prior to the addition of 36 mL of 2% lidocaine.

Drug manufacturers provide specific diluent recommendations based on drug trials providing stability information. Drugs should be added to small volumes of diluent (usually 60, 100, or 250 mL) and administered separately from the patient's maintenance needs to allow for dose titration, through changes in CRI volume, without affecting the patient's other fluid dose. CRI solutions should always be labeled with the amount of drug added, the date, and the volume of diluent. Solutions should be changed every 24 hours. Drug admixtures should be avoided; when necessary, specific package insert and other recommendations should be consulted.

Drug Delivery Systems

The accurate delivery of parenteral drugs is dependent on the use of sophisticated infusion device technology. The traditional gravity delivery systems (using in-line drip chambers) have been shown to have wide variations in the accuracy of delivery due to factors such as length and diameter of infusion set tubing, distance from the patient, and resistance to flow. These devices are acceptable for intravenous fluid therapy but are not advised for the provision of minute doses of vasoactive drugs. Mechanical devices such as *volumetric infusion pumps* generate positive pressure to achieve the delivery of small and precise volumes. Those that deliver fluid by continuous flow are preferred because the intermittent delivery of vasoactive drugs, particularly when at high concentrations with low flow rates, can cause adverse pharmacodynamic effects. As an example, variable delivery of epinephrine can result in blood pressure variations, whereas variable delivery of nitroprusside may cause toxicity.

Infusion pumps may be classified, according to mechanism of operation, into peristaltic systems, cassette systems, and syringe pump systems. Peristaltic systems (linear or rotary) use a motor-driven mechanism to squeeze the tubing and move fluid toward the patient (Baxter Flo-Gard 6200, Travenol Flo-Gard 6200, Sigma 6000). These systems tend to be less expensive but slightly less accurate than the cassette systems. Cassette systems (Travenol 8000 series, IMED pumps) use an administration set that contains an in-line chamber of a measured volume. Syringe pumps (Baxter 150XL, IVAC 700, Medfusion 3010A) may use motor- or nonmotor-driven mechanisms to move the syringe plunger and cause fluid delivery in eithera continuous or intermittent fashion. When an infusion or syringe pump is not available, CRIs may be delivered through a burette type of administration set. This allows the infusion to be limited to a small volume (100 mL). Inherent inaccuracies exist with this system; for drugs with narrow therapeutic-to-toxic ratios, such as nitroprusside, infusion pump use is essential.

CHAPTER • 148

Hyperbaric Medicine

Jennifer J. Devey

Hyperbaric medicine is performed under conditions of greater than 1 atmosphere absolute (ATA) of pressure (Figure 148-1). A specially designed chamber is used, and variable pressures and concentrations of oxygen are delivered based on the condition being treated. In hyperbaric therapy, concentrations of oxygen greater than 21% typically are delivered. However, a recent study examined the use of pressurized air versus pressurized oxygen. Outcomes were similar between the treatment groups, suggesting that pressure, not just oxygen, may be an important factor in hyperbaric oxygen therapy.

PHYSIOLOGIC EFFECTS

The primary effect of hyperbaric oxygen is to increase the amount of oxygen dissolved in plasma. At 2 ATA and 100% oxygen concentration, the amount of dissolved oxygen in the blood is increased by up to 15 times.

In normoxic tissues, except the heart and lungs, hyperoxic conditions cause vasoconstriction, which helps reduce edema. This in turn improves oxygen delivery to tissues by reducing the barrier to gas diffusion. The decrease in cerebral blood flow also helps reduce intracranial pressure. Decreases in cerebral blood flow have not been noted to be a problem clinically until pressure is greater than 3 ATA. If the tissues are hypoxic, vasoconstriction does not occur.

In neurologic tissue, the increase in oxygen delivery also helps reduce the ischemic penumbra seen in traumatic brain injury and transient ischemic attacks. In traumatic spinal injuries, hyperbaric oxygen has been shown to decrease ischemia, edema, and lactic acidosis and to directly reverse damage associated with bruising.

Hyperbaric oxygen enhances wound healing by promoting the growth of new capillaries, enhancing fibroblast proliferation, increasing collagen formation, and increasing the rate of epithelialization.

1 Bar = 15 psi = 100 kPa = 0.99 atm

psi – pounds per square inch, kPa – kilopascals, atm – atmospheres

Figure 148-1 Pressure conversion table.

Hyperbaric oxygen has been shown to improve immune function, which is impaired in the presence of tissue hypoxia. However, above 2.5 ATA, the immune system is inhibited. Oxygen has a direct bacteriostatic and bactericidal effect that is equivalent to some antibiotics. It is effective against gram-positive and gram-negative bacteria, mycobacteria, and fungi but is most effective in treating anaerobic infections.

Free radicals are produced; phagocytosis is stimulated; and the number of lymphocytes is increased. The levels of immunoglobulin G (IgG) and immunoglobulin E (IgE) decrease, which may be of benefit in the treatment of allergic reactions.

The elasticity of red blood cells is improved and platelet aggregation is reduced, which improves rheology. Hemoglobin synthesis is upregulated after acute blood loss. Hyperbaric oxygen has been used for 25 years as a treatment when blood transfusions have not been readily available.

Hyperbaric oxygen increases the affinity of endorphins for receptor sites, improving analgesia. By improving the microcirculation and decreasing edema, it may help reduce the degree of pain the patient experiences.

Hyperbaric oxygen has been shown to enhance the sensitivity of neoplastic cells to radiation therapy as long as the tumor cells are hypoxic. It does not seem to be effective as an adjunct to radiation therapy if metastases are present. Currently there is no proof that hyperbaric oxygen therapy increases the likelihood of recurrence of the cancer.

Box • 148-1

Partial List of Conditions Approved for Medicare Reimbursement That Apply to Veterinary Medicine

Actinomycosis
Birth asphyxiation
Brown recluse spider bite
Cyanide poisoning
Carbon monoxide poisoning
Cerebral edema
Compromised skin graft flaps
Crush injury/compartment syndrome
Diabetic wounds/ulcers
Hypoxic nonhealing wounds
Exceptional blood loss anemia
Frostbite
Gas embolism
Gas gangrene
Near-drowning
Near-hanging
Necrotizing soft tissue infections
Peripheral ischemia
Radiation necrosis
Refractory osteomyelitis
Refractory mycoses
Stroke (transient ischemic attack)
Thermal burns
Traumatic brain injury

INDICATIONS IN HUMAN MEDICINE

A number of conditions have been approved for U.S. Medicare reimbursement of hyperbaric oxygen therapy. Box 148-1 presents a partial list of these conditions, those that are relevant to veterinary medicine. Based on clinical experience, research findings, and anecdotal reports in human medicine, some other conditions also may respond to hyperbaric oxygen therapy (Box 148-2).

CONTRAINDICATIONS

The only absolute contraindication for hyperbaric oxygen therapy is untreated tension pneumothorax. Veterinary patients with evidence of any kind of pneumothorax are not placed in the hyperbaric chamber unless a chest tube attached to a relief valve (i.e., Heimlich valve) has been inserted.

Some relative contraindications in human medicine are upper respiratory infections; the presence of pulmonary lesions, even if they are not symptomatic; heart failure; a history of ear or thoracic surgery; and uncontrolled high fever. High fever is a contraindication because of the increased likelihood of seizures; however, this does not appear to be a concern in veterinary medicine. In fact, febrile veterinary patients often experience a reduction in temperature in 100% hyperbaric oxygen environments as long as they are not anxious (see above). Pregnant patients should not receive hyperbaric oxygen because experimental evidence suggests an increased incidence of congenital defects. Epilepsy is not considered a contraindication, but pressure should be kept below 2 ATA.

Box • 148-2

Conditions That May Benefit from Hyperbaric Oxygen Therapy

Cardiac surgery postoperatively
Cranial nerve lesions
Post cardiopulmonary resuscitation
Degenerative myelopathy
Gastrointestinal ulcers
Geriatric vestibular disease
Glaucoma
Head trauma
Hepatotoxins that cause damage after oxidative transformation
Ileus
Methemoglobinemia
Myocardial contusions
Organophosphate toxicity
Osteomyelitis
Pancreatitis
Perianal fistulas
Peripheral neuropathies
Snakebite
Spinal cord injuries or ischemia

COMPLICATIONS IN HUMAN MEDICINE

Complications primarily relate to oxygen toxicity; however, pressure-related problems, such as sinus pain, middle ear barotrauma, and pulmonary barotrauma, have been reported in human medicine. Complications related to oxygen toxicity are rare, especially if pressure does not exceed 1.5 ATA.

Oxygen-induced seizures can occur in the dog if the pressure exceeds 2.2 to 2.5 ATA. The mechanism is unknown but may relate to the presence of oxygen free radicals, inactivation of nitric oxide, alterations in gamma-aminobutyric acid (GABA), and changes in the levels of biologically active peptides. Seizures normally cease as soon as the oxygen levels drop and/or the pressure decreases. Oxygen-induced seizures are not a contraindication for further treatment; however, the pressure and time of exposure to hyperbaric oxygen should be decreased.

Oxygen-induced lung injury should not be a problem if the lung tissue has sufficient time to recover between episodes. Pulmonary dysfunction has not been noted in humans exposed to prolonged hyperbaric oxygen therapy.

COMPLICATIONS IN VETERINARY MEDICINE

The complications listed above presumably can occur in all species; however, in more than 5000 hyperbaric treatments, none of them have been observed in clinical veterinary medicine. In veterinary medicine the most common complications are hypothermia in small, sedated, or depressed patients and anxiety, sometimes accompanied by hyperthermia.

HYPERBARIC CHAMBERS

Chambers can be multiplace or monoplace. High-pressure chambers deliver oxygen concentrations of 100% and pressures up to 6 ATA. The oxygen concentration in lower pressure chambers typically is approximately 30%, and pressures reach a maximum of 1.25 ATA.

Spontaneous combustion, although rare, can occur in hyperbaric chambers that deliver 100% oxygen under pressure. Certain precautions should be taken when using 100% oxygen; electrical devices should not be permitted in the chamber; no nylon should be allowed in the chamber; and the patient must not have an oil-based product on its skin.

Portable hyperbaric chambers compress entrained room air. As a result, the temperature of the room air and the air in the hyperbaric chamber are the same. If the room air is hot, it should be cooled by running the air hose through an ice bath before it reaches the chamber. This prevents overheating of the patient.

Variable levels of oxygen can be provided to patients being treated in lower pressure hyperbaric chambers. When an oxygen source is attached to the chamber, an inspired oxygen concentration of approximately 30% is provided. Alternatively, an oxygen hood can be placed on the patient, in which case the inspired oxygen concentration may be as high as 80%.

TREATMENT PROTOCOL

Currently no consensus exists on the best regimen for hyperbaric oxygen therapy, although administration within 4 hours of injury appears to be critical in the treatment of neurologic disease. Research indicates that the effects of a single treatment last at least 6 hours.

Current human recommendations are to treat patients for 1 hour at 1.5 to 2 ATA, consisting of 10 minutes of compression, 45 minutes of treatment at the designated pressure, and 5 minutes of decompression time. The time in the chamber is doubled if infections are present.

The author's clinical experience with dogs and cats suggests that pressures of up to 1.25 ATA generally are well tolerated and appear to provide beneficial effects. Treatments last 1 hour and are performed twice daily in the acute stages of the injury or illness and then once daily after the first 3 to 5 days. The twice daily treatments are continued if the patient appears to respond better to treatments at 12-hour rather than 24-hour intervals. With chronic conditions, owners are encouraged to continue treatments two or three times weekly on an outpatient basis if clinical improvement still is noted or if there is concern that relapse will occur if treatment is discontinued.

The vast majority of patients do not object to hyperbaric oxygen therapy, as evidenced by dogs' willingness to walk voluntarily into the chambers repeatedly and by the lack of any outward signs of distress in cats. Anxious patients are provided with anxiolytics. Depending on the patient, this may include narcotics, benzodiazepines, or acepromazine. If any concern arises that the patient is not tolerating the hyperbaric oxygen, the session is discontinued.

Hyperbaric oxygen therapy should not replace approved treatments; however, cats and dogs are affected by a number of disease conditions that appear to benefit from adjunctive therapy with hyperbaric oxygen.

SECTION VII

Dietary Considerations of Systemic Problems

CHAPTER 149

Nutritional Assessment

Kathryn E. Michel

The purpose of nutritionally assessing a patient is to allow the clinician to answer the question, "Is intervention for this patient necessary?" and to aid the clinician in selecting the most appropriate nutritional intervention for that patient. The process involves evaluating both subjective and objective information regarding the patient and its dietary practices. In addition to aiding in the selection of a suitable diet and feeding management for the patient, it will also help the clinician to anticipate potential problems or complications and to devise strategies to avoid or monitor such developments.

TAKING A DIET HISTORY

The more information that is available about the patient's diet and feeding management, the better the clinician will be able to assess the adequacy of nutrient intake, the suitability of feeding practices, and the urgency for nutritional intervention. At the core of a dietary history is the careful gathering of information that will give an accurate picture of the foods that the patient consumes. Ideally the person who is most responsible for feeding the patient should be questioned; however, it is important to find out who else resides in the household or has regular contact with the patient, including other pets. The patient's caregiver should be questioned about all foods that the patient receives (Box 149-1) and asked whether the information reflects what is typical for this pet, whether changes have occurred, and if so when they happened.

In addition to particulars about the patient's diet, the history should also include information regarding appetite, documented or perceived changes in body weight or condition, level of physical activity, and occurrence of any gastrointestinal (GI) signs. Again, the patient's caregiver should be queried as to whether the information reflects what is typical for this pet or whether (and if so when) changes have occurred. Although it is often the case that a pet owner cannot precisely recount an exact weight change, he or she may have an impression of the period of time over which the change occurred. Rapid weight loss and deterioration in body condition, particularly if associated with muscle wasting, suggests a greater degree of metabolic derangement or reduction in food intake (or both) and greater potential for significant malnutrition than a more gradual loss of weight.

Box • 149-1

Information to Be Included in a Diet History

- Commercial pet foods (brand and daily portion; dry foods should be weighed or measured with an 8 oz measuring cup; canned foods should be measured by can size and portion used)
- Commercial treats (brand, size, and frequency of use)
- Table foods or scraps (detailed information about type of food, portion size, and frequency of use)
- Treats for chewing (e.g., rawhide, pig's ears; size and frequency of use)
- Dietary supplements (brand and daily portion)
- Foods used for medication of the patient (type of food, portion size, and frequency of use)
- Pet's access to garbage
- Pet's ability to scavenge or roam

PATIENT ASSESSMENT

Evaluation of body condition is the chief consideration in the assessment of the animal. Although some sophisticated techniques are currently being used in human patients or in a research setting (e.g., multiple-frequency bioelectrical impedance, dual-energy radiographic absorptiometry (DEXA), neutron activation), they have either not been sufficiently validated in companion animals or do not lend themselves to a clinical setting because of logistic considerations or expense. Body condition scoring, although subjective, is simple to learn, requires no special equipment, and has been shown to be repeatable and consistent among multiple observers.[1] The body condition scoring systems that have been published for companion animals are principally based on characterization of body silhouette and palpation of body fat. These systems are useful, particularly for identification of patients that have an overweight body condition; however, they may misclassify some malnourished patients. It is important to recognize that catabolism of lean body tissue can occur very rapidly and may account for a disproportionate amount of the body mass lost in sick patients. Although the purpose of adipose tissue is to serve as an energy reserve, no analogous reserve of endogenous protein exists. Because all endogenous protein is serving some function, the result of continuous catabolism will eventually have deleterious consequences for the patient. Therefore the process of body condition assessment should include not only the standard evaluation of body silhouette and evaluation of adipose tissue as assessment of energy reserves but also a separate evaluation of muscle mass as a subjective means of assessing lean tissue status. This can be accomplished by palpation of skeletal muscle over the axial skeleton and other bony prominences.

Other aspects of the physical examination of a patient that should be taken into consideration include haircoat quality and skin condition, evidence of peripheral edema or ascites (which may indicate hypoproteinemia), and clinical signs that may indicate specific micronutrient deficiencies such as neck ventroflexion or tetany.

SPECIAL CONSIDERATIONS REGARDING ASSISTED FEEDING

No definitive tests are available for establishing a patient's nutritional status. However, based on the information gathered from the patient's medical and dietary history and physical examination (as described previously), the clinician should be able to classify broadly the patient as being well nourished, mildly malnourished, or severely malnourished. The decision whether or not to intervene with some form of nutritional support for a patient has to balance the anticipated benefits with the potential risks and costs of the proposed intervention. Therefore the intent of nutritional assessment should not simply be to diagnose inadequate food intake or malnutrition, but rather to identify patients that are at risk of a poor outcome as a result of their compromised nutritional status. Investigations of human patients have found increased risk of morbidity and mortality associated with various objective markers of nutritional status including hypoalbuminemia, lymphopenia, and attenuated delayed hypersensitivity reactivity. Other investigators have found that clinical assessment of patients based on a carefully performed history and physical examination, as described previously, has predictive value similar to that of objective markers of nutritional status such as serum albumin concentration.[2] Furthermore, investigations of the effect of nutritional support on improving clinical outcome suggest that it is the most significantly malnourished patients that are likely to show benefit from nutritional support.[3]

There has been only limited investigation of the prognostic value of nutritional assessment in veterinary patients. Admission serum albumin concentration has been shown to correlate with risk of poor clinical outcome in critically ill dogs, and elevation of serum creatine kinase activity has been found to be associated with anorexia in feline patients.[4,5] To date there have not been any investigations of the prognostic value of subjective nutritional assessment or the impact of nutritional support on clinical outcome in companion animals; however, it is not unreasonable to expect results similar to those found in human patients. Therefore it is recommended that patients assessed to be significantly malnourished on presentation or that are at risk of becoming significantly malnourished in the course of their illness due to decreased food intake, malassimilation of diet, or metabolic derangement, should be considered candidates for assisted feeding.

MONITORING NUTRITIONAL INTERVENTIONS

Once a dietary recommendation has been made, the patient should be reassessed after an appropriate interval of time. The actual timing of reassessment depends on the severity of the patient's illness and the type of nutritional intervention it has received. One should determine whether the prescribed recommendations are being followed if problems with diet acceptance or tolerance are seen, if the desired outcomes have been achieved, or if any adverse events associated with the diet or feeding management have occurred. A thorough nutritional assessment at the outset will often identify potential problems or complications and thereby determine what parameters should be monitored in the patient. At the least, body weight and condition should be reassessed regularly to ascertain that the patient is maintaining, gaining, or losing weight appropriately.

CHAPTER 150

Nutrition of Healthy Dogs and Cats in Various Stages of Adult Life

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Although both dogs and cats are classified as carnivores, their nutrient requirements are not identical. The metabolism and nutritional needs of dogs approach those of omnivores, whereas the metabolism of cats is consistent with that of a strict meat-eating mammal.[1-3]

Dogs have the capability to use plant sources for synthesizing taurine, arachidonic acid, and vitamin A from their metabolic precursors, cysteine, linoleic acid, and beta-carotene, respectively. Cats, by contrast, either have diminished enzyme activities for synthesizing these nutrients (taurine and arachidonic acid) from their metabolic precursors, or they do not possess the enzyme (vitamin A). Cats must therefore obtain these nutrients from their diet. Both dogs and cats possess some similar metabolic characteristics such as an obligation to conjugate bile acids with taurine and an inability to synthesize vitamin D. However, the cat digests uncooked starch somewhat better than the dog, so not all evidence is fully consistent with the cat being a strict carnivore and the dog simply being an omnivore.

FOOD INTAKE AND PALATABILITY

The diet of feral cats is based largely on small mammals, birds, lizards, and insects. When domesticated cats are fed free choice, they eat 10 to 20 meals per day (12 mice per day provide the energy requirement of a normal cat) about equally divided between the light and dark period. Significant breed differences are seen in the feeding behavior of dogs: beagles have feeding patterns similar to cats, whereas basenjis and poodles eat only during the daylight hours. The number of meals can vary

widely from 5 to 20. Adult dogs adapt to one meal a day, and cats at maintenance can adapt to a similar regimen. During gestation and lactation, however, performance is enhanced by feeding several times a day or by feeding free choice. During the latter part of gestation and lactation, bitches should be offered food at least twice a day and preferably fed free choice. Both cats and dogs prefer meat-based canned products rather than dry expanded diets, in part owing to the higher moisture content of canned products and in part because blood and fluids contain positive palatability factors. Texture is important; cats and dogs both prefer soft, moist foods to dry, powdery foods. Dogs respond positively to protein, peptides, certain free amino acids, sugar, and mononucleotides, together with certain electrolytes. The response of cats is neutral to protein and sugar, positive to peptides and certain free amino acids, and negative to mononucleotides. Good-quality animal fats enhance palatability for both cats and dogs. Medium chain triglycerides are strongly aversive to cats but not to dogs. Both dogs and cats respond positively to fresh meat extracts, whereas cats but not dogs generally show strong negative palatability to oxidized or rancid fats and breakdown products of trinucleotides or mononucleotides. In summary, cats are more sensitive to adulteration, oxidation, and rancidity in foods than are dogs. Uncooked or cooked meat extracts (broth) are the most palatable natural ingredients to use to enhance the palatability of unpalatable foods for both dogs and cats.

Food intake of cats and dogs fed diets of low or high palatability is quite well controlled. The level at which the animal controls its weight is complex and depends on factors such as genetics (breed and strain), life stage, physical activity, food availability, food palatability, and whether or not the animal is neutered. Both dogs and cats maintain their weight and stay healthy if their diet is complete and balanced, even if the diet has poor palatability. Highly palatable high-fat diets increase the risk for obesity. Nevertheless, dogs and cats control their food intake, albeit at a higher level of body weight, even when fed highly palatable high-fat diets. It is always easier to prevent obesity by selecting or manipulating the aforementioned factors before obesity occurs rather than to try to limit food intake to affect weight loss. In herbivores and omnivores, food intake is depressed, and strong avoidance of a particular diet is exhibited when animals are fed diets with various nutrient deficiencies or excesses (e.g., deficiencies of thiamine, sodium, phosphate, protein, specific essential amino acids). In most species, including cats and dogs, emetics (e.g., lithium chloride, apomorphine) induce an aversion to the taste of the food just previously eaten. This behavior is called a *learned taste aversion*. In cats there appears to be a neural disassociation between the neural response to the nutrient deficiency and feeding behavior. For those deficiencies and excesses that have been examined (protein deficiency and excess, individual essential amino acid deficiency and excess, sodium deficiency), no learned taste aversions have been demonstrated, despite the fact that food intake may have been depressed.[3,4] Thus palatability may override nutrient metabolic effects in cats, whereas nutrient metabolic effects (caused by nutrient deficiencies and excesses) override palatability effects in herbivores and omnivores (Figure 150-1). It is notable that even though cats do not appear to develop learned aversions to simple nutrient deficiencies or excesses, it has been shown that cats do avoid diets that cause hyperammonemia[5] or metabolic acidosis.[6]

GENERAL FEEDING RECOMMENDATIONS

Practitioners should advise clients to choose a commercial diet that has passed an Association of American Feed Control Officials (AAFCO) animal protocol test for the particular life stage of the cat or dog. This ensures that the diet has undergone an animal feeding test. An AAFCO nutrient profile label means only that a diet meets a calculated nutrient profile. In most cases it is safest to feed a diet that has passed an AAFCO all-stages protocol. The exception would be if a particular dog or cat has a medical problem; then a specific therapeutic diet should be fed. In selecting an appropriate therapeutic diet, one should always select a diet that has been tested for the intended purpose. If no particular diet has been tested clinically for the particular medical condition, a clinical nutritionist should be consulted for advice or to formulate a balanced homemade diet that is appropriate. It is prudent to check whether a commercial diet (regular or therapeutic) has been properly tested in animals for the intended purpose. No reason exists not to feed a diet that has large built-in safety factors in nutritional requirements, but likewise no reason exists to pay for extra nutrients if they have not been shown to be of extra benefit to the cat or dog. When a diet is complete, balanced, and tested and has been shown to be fully adequate in animals, no reason exists to feed a diet containing even more of one or more essential nutrients. Nevertheless, a paucity of information is available on specific nutrient requirements in adult life stages, including maintenance. There has been considerable research on the nutrient requirements for dogs and cats for growth, because it is the easiest life stage for which to determine requirements. Therefore requirements for growth have been used to formulate requirements during pregnancy. Additional information from epidemiologic evidence and from other species has been used to formulate requirements for maintenance.

MEETING ENERGY NEEDS

About 80% of the food eaten by mature cats and dogs is used to provide their energy needs. The requirements for protein, minerals, and vitamins can be met in the remaining dry matter. Therefore meeting energy needs is the first consideration in feeding cats and dogs. Energy, unlike individual amino acids, vitamins, and minerals, is not supplied by any single nutrient but is provided by the oxidation of substrates, primarily fats, carbohydrates, and proteins. The energy needs of dogs or cats may be supplied by diets with varying ratios of these three nutrients. The only avenue an animal has for disposal of excess energy is by oxidation to produce adenosine triphosphate or to store the excess energy in the form of adipose tissue. Mature dogs and cats that are in energy balance convert all the available or metabolizable energy (ME) from food into heat. To calculate the amount of food required by dogs or cats, the ME value of the food should be known.

The energy requirements of mature, nonpregnant cats and dogs are not constant but decrease on a unit-body-weight basis with age, which is related to the reduction in general activity with age. As indicated, many individual cats and dogs adjust their energy intake from food to balance their energy needs. However, in some adults, this balance is not maintained, leading either to body weight loss, resulting in catabolism of body energy stores, or to obesity and body weight gain owing to excessive energy intake.

The maintenance energy requirements of adult cats and dogs may be estimated from formulas relating ME requirements to body weight. Because mature dogs have about a fiftyfold range in body weight, and because ME requirements per unit of body weight decrease with body weight, formulas generally include some power function of body weight (e.g., body weight raised to three-fourths power). A common linear formula used for dogs is $ME = 30\ W + 70$,

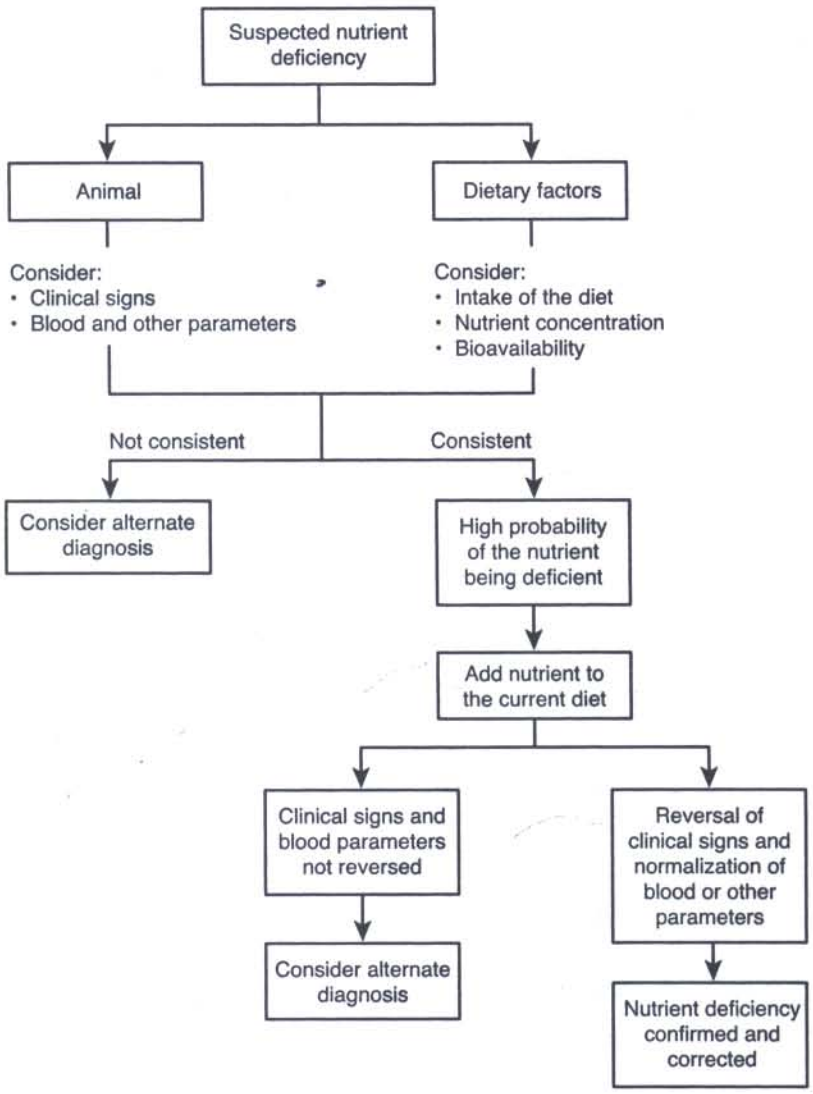

Figure 150-1 Algorithm for solving a nutrient deficiency in an adult dog or cat.

and an exponent formula is ME = 132 $W^{3/4}$, where W is body weight in kilograms and ME is kilocalories per day. The first equation approximates the relationship for small dogs such as beagles but overpredicts energy requirements for large breeds. Because the body-weight range of adult cats is much less than that of adult dogs, a power function is not used with cats. The formula ME = 80 W has been used for active cats and ME = 70 W for inactive cats.

Although these formulas are useful starting points, they are not absolute requirements because considerable individual animal variation exists. It has been shown that a large variation exists in the prediction interval of maintenance energy requirement.[8] However, when enteral or parenteral nutritional support is necessary, a requirement estimate must be made. Similarly, when a weight reduction program is undertaken, an estimate of maintenance energy requirements is desirable. All adult cats and dogs that are voluntarily consuming food should be fed relative to their body condition and not by a formula. If an adult dog or cat is fed free choice and becomes obese, either the amount of food offered or the energy density (available caloric density) of the food should be reduced. When an adult cat or dog is not maintaining body weight, either more food or a more palatable food should be fed to increase intake or a diet of a higher caloric density should be fed (or both should be done).

Pregnancy causes a demand for energy greater than normal adult maintenance requirements. Different responses to pregnancy occur in the ingestive behavior of bitches versus queens, even though the length of gestation is similar. Queens increase food intake soon after conception and have an almost linear increase in body energy stores with duration of gestation. In contrast, bitches normally do not increase food and energy intake until the latter stages of pregnancy. Queens and bitches in normal body condition may be given food free choice during pregnancy to allow for the increase in body tissue that will be mobilized during lactation and by fetal energy demands. Whereas the latter stages of pregnancy increase energy requirements by about a third, lactation places a huge demand on the bitch and queen and can result in energy intakes three to four times above maintenance. Depending on the number of kittens or pups, queens or bitches sustain a loss of body weight during lactation. This tissue loss should be largely the tissue gained during the prepartum period; with a good diet and normal litter size the weaning body weight of the mother should not be less than the body weight at conception.

PROTEINS AND AMINO ACIDS

Proteins are added to diets to provide essential amino acids and nitrogen. Nitrogen requirements are usually expressed as the crude protein requirement, because crude protein is defined as the quantity of nitrogen times 6.25. Nitrogen is used for the biosynthesis of dispensable amino acids, heme, purines, pyrimidines, and so forth. Both essential and dispensable amino acids are necessary at the cellular level for protein synthesis. Several amino acids are precursors for hormones and neurotransmitters. If the amino acid and crude protein requirements are known for each life stage, the clinical nutritionist can formulate a diet using amino acid composition tables for particular proteins and ensure that both essential amino acid and nitrogen requirements are met. However, a weakness of diet formulation using nutrient composition tables is that the bioavailabilities of amino acids and nitrogen from food sources are usually not known, or the effect of processing on the particular food (or food combinations) is not known. The most accurate way to tell if the diet is adequate in protein is to evaluate plasma amino acid concentrations during the absorptive state after feeding a particular diet. Amino acid patterns can be used not only to verify that essential amino acid requirements have been met but also to diagnose various nutritional problems (e.g., protein-energy malnutrition, essential amino acid deficiency) and metabolic problems (e.g., liver or kidney disease).

Carnivores have no problem meeting their protein or amino acid requirements if they eat other animals, because the body composition of various animals is quite similar and is high in good-quality protein. Nutritional problems arise only if a client attempts to feed a carnivore a vegetarian diet or a diet that has poor-quality ingredients (e.g., by-products that are high in collagen, such as skin and bone) or products that have been excessively processed. Quality control of ingredients in pet foods is a problem in the pet food industry, because large quantities of animal by-products do not always have a constant composition; thus these by-products may have variable digestibilities and bioavailabilities for nitrogen and amino acids. Specific amino acid deficiencies or excesses can cause a variety of problems, such as cataracts, dermatitis, hair loss or reddening of black hair or both, irritability, neurologic deficits, hyperammonemia, fatty liver, low glutathione, and emesis. After reviewing the literature and using our experience in feeding dogs and cats, we have developed an estimate of dietary nutrient allowances (Table 150-1). These allowances include an approximate 25% to 50% in excess of the minimal requirement to allow variation in bioavailability. Our estimate of minimal requirement is undoubtedly high for several of the amino acids, because so many data are missing, especially for the adult life stages. Nevertheless, these values may be used as guidelines until more refined data are available. It is possible, using diet composition tables, that these recommendations may be too low owing to poor-quality ingredients with low digestibility coefficients. Most cat and dog foods are formulated to meet or exceed these recommendations. Major pet food companies have competent nutritionists who take digestibility and bioavailability values into account in formulating diets, and most of the major diets have been tested. Therefore veterinarians should be confident in recommending any pet food that has passed the AAFCO feeding protocol for the life stage in question. The bottom line is simple for adult dogs and cats: feed a commercial diet for the appropriate life stage from a reputable company. The only other safe course is consultation with a small animal nutritionist to attempt to evaluate a diet or to formulate a homemade diet. The latter is not recommended because of the difficulty in predicting bioavailability of ingredient nutrients and the difficulty in getting good compliance in making and feeding such a diet.

Table • 150-1

Suggested Nutrient Allowances* for Adult Dogs and Cats at Maintenance (Nutrient Per 1000 kcal of Dietary Metabolizable Energy)

NUTRIENT	UNIT	ADULT DOG	ADULT CAT
Protein†	g	37.5	75.0
Arginine	g	1.43	3.13
Histidine	g	0.54	0.90
Isoleucine	g	1.05	1.75
Leucine	g	1.80	3.75
Lysine	g	2.25	3.00
Methionine + cysteine	g	1.50	2.75
Methionine	g	0.75	1.50
Phenylalanine + tyrosine	g	2.10	2.50
Phenylalanine	g	1.05	1.25
Threonine	g	1.20	2.00
Tryptophan	g	0.35	0.50
Valine	g	1.28	1.75
Calcium	g	1.6	1.2
Phosphorus	g	1.2	1.2
Potassium	g	1.2	1.25
Sodium	g	0.40	0.40
Chloride	g	0.20	0.20
Magnesium	g	0.11	0.08
Iron	mg	20.0	20.0
Copper	mg	0.8	1.1
Manganese	mg	1.4	1.1
Zinc	mg	9.7	11.0
Iodine	mg	0.16	0.07
Selenium	mg	0.03	0.02
Vitamin A (retinol)	mg	0.3	0.21
Vitamin D (cholecalciferol)	µg	2.75	2.6
Vitamin E (alpha-tocopherol)	mg	6.1	7.0
Vitamin K	µg	—	21.0
Thiamine	mg	0.3	1.1
Riboflavin	mg	0.7	0.9
Pyridoxine	mg	0.3	0.9
Niacin	mg	3.0	10.0
Pantothenic acid	mg	2.7	1.0
Folic acid	mg	0.54	0.17
Vitamin B_{12}	µg	7.0	4.0
Biotin	µg	—	15.0
Choline	mg	340.00	500.00

*These values are not minimal nutrient requirements, but nutrient allowances. Requirements have been increased to accommodate variation in digestibility and bioavailability of nutrients in natural foods and individual animal variation.

†For a protein of good quality. The requirement for protein and amino acids needs to be increased for proteins of lower quality or lower digestibility.

MINERALS AND VITAMINS

Adult cats and dogs require the same minerals and vitamins that are essential to growing kittens and puppies. Although the requirements for growing kittens and puppies are fairly well defined, those for adults are not known with the same precision.

The dietary concentration for growth satisfies adult requirements, even though the food intake of adults on a unit-body-weight basis is less than that during growth. The function and clinical role of vitamins have been reviewed.[8]

Minerals

Mineral requirements for adult cats and dogs for maintenance (expressed per 1000 kcal dietary ME) are given in Table 150-1. These requirements are based on published values[9,10] with updated information. Expression on an equivalent energy basis shows that the requirements of adult cats and dogs are similar. The requirements given in Table 150-1 are for minerals with a high bioavailability, such as from mixtures of the salts of these minerals or from bone. Applying these values to practical diets requires bioavailability values to be taken into account. Although these have not been determined in cats and dogs, values originating in other simple-stomached species give useful approximations. The bioavailability of calcium, phosphorus, and magnesium from plant sources is considerably less than that from mineral salts or bone and should be discounted by 50%. In contrast, sodium, potassium, and chloride are readily exchangeable, and no adjustments are necessary concerning their source.

Bioavailability of trace elements, especially as they pertain to cats and dogs, is not known, but observations indicate that the availability of zinc and copper in diets containing high proportions of plant products is compromised. Zinc deficiency has not been uncommon in dogs fed some of the lower-quality dry diets containing a high proportion of plant products. Clinical signs of copper deficiency have been reported in newborn kittens from queens given diets containing copper oxide as a supplementary source of copper. Reproductive performance of the queens was also reduced. The requirements for many of the major minerals (e.g., calcium, potassium, sodium) increase greatly in lactation. However, because food intake is also increased about twofold, the percentage in the diet need not change.

Diagnosis of mineral deficiencies should be based on specific clinical signs, blood, plasma, or tissue concentrations for the species, as well as on reversal of clinical signs after supplementation with the specific mineral while the cat or dog is maintained on the same diet.

Vitamins

Vitamin requirements of adult cats and dogs expressed based on 1000 kcal of ME are given in Table 150-1. The values are based on published data[9,10] that have been modified when newer information was available. For the fat-soluble vitamins A, D, and E, the requirements are similar for adult cats and dogs. Cats, unlike dogs, are unable to use beta-carotene as a precursor for retinol, so they depend on preformed vitamin A in the diet. The values for vitamin A and D are in excess of minimal requirements, and further supplementation in normal animals is unwarranted. Neither cats nor dogs are capable of synthesizing vitamin D from ultraviolet (UV) light.[11] Although vitamins A and D are regarded as the most toxic of all the vitamins when given in excess, adult cats can tolerate large excesses (50 times requirement) of these two vitamins with no discernible deleterious effects. In normal cats and dogs, in contrast to most other animals, large concentrations of retinyl esters occur in plasma. Requirements for vitamin E are a function of the total polyunsaturated fatty acids (PUFAs) in the diet. Because cats frequently consume diets high in PUFAs, the requirement to prevent steatitis in cats is higher than that for dogs that are subjected to lower dietary inputs of PUFAs. Both cats and dogs require an exogenous source of vitamin K, but intestinal synthesis appears to be adequate to supply this need in dogs. When cats are fed some high-fish diets, they have a prolongation of clotting time and require supplemental vitamin K.

In contrast to the fat-soluble vitamins, the requirements for the water-soluble vitamins for cats versus dogs are different. Cats have a higher requirement than dogs for thiamine (vitamin B_1) and are exposed to dietary ingredients that often contain both thiaminases (e.g., fish) and to canned diets that have sustained extensive processing, causing loss of thiamine. As thiamine stores are rapidly exhausted, thiamine deficiency can readily occur in cats given deficient diets. Cats, unlike dogs, are unable to use tryptophan as a precursor for niacin synthesis, so niacin is an absolute essential dietary nutrient for cats. Niacin is normally obtained from foods by hydrolysis of nicotinamide adenosyl dinucleotide (NAD) and nicotinamide phosphodinucleotide (NAPD) in the gut. Meats contain high levels of these nucleotides and thus are a principal source of this vitamin.

The published vitamin requirements[9,10] for growing kittens and puppies appear to satisfy the requirements of mature cats and dogs. However, in applying these values, it is necessary to take into consideration the bioavailability of the vitamin and its stability in the product. The bioavailability of the fat-soluble vitamins is high in the absence of most fat malabsorption syndromes, whereas the bioavailability of most of the B vitamins in natural products is variable and can be quite low.

TAURINE

Taurine, a beta-sulfur amino acid, occurs in all animal cells and is virtually the sole conjugate of the bile acids in cats and dogs. Taurine is synthesized de novo by dogs and cats from the sulfur amino acids cysteine and methionine. Although cat diets contain a higher level of sulfur amino acids than do dog diets, the rate of taurine synthesis by cats is low; cats given a low-taurine diet are readily depleted of this amino acid. This very low rate of taurine synthesis in cats is a consequence of low activities of two enzymes in the pathway of synthesis. Taurine depletion is associated with a wide range of clinical conditions, including feline central retinal degeneration, reversible dilated cardiomyopathy, reproductive failure in queens, and developmental defects and growth retardation in kittens. The amount of dietary taurine required for cats to maintain adequate blood concentrations varies twofold with the type of diet. For expanded (dry) diets, 1250 mg taurine/kg dry matter is adequate. Canned diets, which promote higher intestinal degradation of taurine exposed in the enterohepatic circulation, require 2500 mg/kg dry matter to maintain blood concentrations in the normal range.

Until recently, diet-associated taurine deficiency in dogs has not been recognized. However, low blood taurine concentrations and dilated cardiomyopathy (DCM) has recently been identified in dogs that do not have a genetic predilection to this disease. A common finding among the cases was the consumption of commercial dry diets containing lamb meal, rice, or both as the primary ingredients. Cardiac parameters and blood taurine concentrations improved with treatment and taurine supplementation. Dogs that survived longer than 1 year were able to be removed from all cardiac mediations except taurine, suggesting that these were not typical cases of DCM. Suggested mechanisms for taurine deficiency in these dogs were considered to be (1) insufficient synthesis of taurine, (2) extraordinary loss of taurine or its precursors in urine, (3) extraordinary gastrointestinal (GI) loss of taurine in bile acid conjugates (as found in cats), or (4) a reduction in protein digestibility. Based on clinical findings, blood taurine concentrations, and common diet histories, it appears that the consumption of diets with inadequate or unavailable sulfur amino acid taurine precursors, plus rice bran increasing GI loss, results in taurine deficiency and low blood taurine concentrations in these dogs. The low

plasma taurine concentrations can lead to the development of abnormal cardiac function and DCM.

ESSENTIAL FATTY ACIDS

The diets of healthy dogs and cats, like those of other animals, must contain polyunsaturated fatty acids (PUFAs). Because these fatty acids cannot be synthesized de novo by animals, they are designated as essential fatty acids (EFAs). Dogs require two EFAs in the diet: linoleic acid C18:2 n-6 and linolenic acid C18:3n-3. The letter followed by the number (e.g., n-6 or ω-6, n-3 or ω-3) refers to the location of the first double bond in the fatty acid from the methyl (or omega) end of the fatty acid. Animals cannot insert double bonds further than 9 carbons from the carboxyl end of a fatty acid. In addition to linoleic and linolenic acids, cats under certain conditions may require arachidonic acid, a member of the n-6 family of fatty acids in the diet. The activity of the hepatic delta-6-desaturase enzyme required in one of the pathways for the synthesis of arachidonic acid from linoleic acid is low in cats. This limited activity appears to be sufficient for growth and reproduction in male cats (where the testis also has delta-6-desaturate activity) but may be inadequate for sustained reproduction in queens. Other fatty acids, particularly those of the n-3 series, may also limit reproduction in queens.

Fatty acids function as precursors of eicosanoids, which include prostaglandin, leukotrienes, and thromboxanes. These extremely active biologic compounds have both paracrine and endocrine activity. As a group the eicosanoids of the n-6 series tend to be involved in a more proinflammatory role, whereas those of the n-3 have an anti-inflammatory or only a mildly inflammatory role.

Of the EFAs, the quantitative requirement of cats and dogs is greatest for linoleic acid. A deficiency of linoleic acid results in hyperkeratosis of skin, fatty degeneration of the liver, and degeneration of the testis. In addition, increased water loss through the skin occurs. Cats and dogs require about 1% to 2% of the calories as linoleic acid to prevent clinical signs of deficiency, though higher levels of total fat in the diet may result in better coat condition. The n-3 fatty acid, linolenic acid, occurs in high concentration in some plant oils such as linseed (flaxseed) oil, and higher homologues of this fatty acid occur in animal fats, particularly marine oils such as herring and tuna. In cats, the production of these higher n-3 homologues also appears to be limited, which may contribute to the poor reproductive performance of queens given some vegetable fat diets.

Clinical signs of arachidonate deficiency in cats are associated with eicosanoid dysfunction and include defective reproduction in queens and changes in blood platelet aggregation. The requirement of cats for arachidonic acid has not been defined but appears to be of the order of 200 mg/kg dry matter. Arachidonate in natural diets comes from animal tissue membranes. Recently a fungal source of arachidonate has become commercially available, so it is possible to add this fatty acid to diets for cats without the inclusion of animal fat.

OTHER NUTRIENTS AND NUTRACEUTICALS

Choline is often included among the "essential" vitamins because it supplies labile methyl groups. Methionine and betaine can also supply methyl groups. A lack of total methyl groups in the diet leads to fatty liver because of an inability to mobilize hepatic fat.

Ascorbate, or vitamin C, is synthesized de novo by dogs and cats from glucose, and no substantiated evidence exists (except anecdotal reports in liver disease) to indicate that dogs or cats benefit from the addition of ascorbate to the diet. In contrast, some breeds of dogs have a limited capacity to synthesize adequate carnitine and benefit from its supplementation. Synthetic antioxidants are frequently added to human and animal diets to prevent lipid peroxidation during storage. Substantial evidence contraindicates the consumption of lipid peroxides. It is debatable whether these synthetic antioxidants are deleterious when used at the recommended concentrations in the diet. Natural antioxidants such as alpha-tocopherol, though less effective than the synthetic antioxidants, can also be used. A number of human foods such as onions and chocolate cause adverse effects in cats and dogs, respectively; thus some human foods should not be fed to cats and dogs indiscriminately. Food faddism in human nutrition has resulted in malnutrition, toxicities, and deficiencies.[12] These same practices occur in dog and cat nutrition and should be avoided.

CHAPTER • 151

Neonatal and Pediatric Nutrition

Johnny D. Hoskins

The nutritional requirements, feeding, and care of puppies and kittens from birth to early adulthood are substantially different during their different stages of growth. The growth phase is a critical time in the life of a puppy or kitten; some will fail to grow to the size determined by their hereditary factors unless they consume appropriate food of adequate quality.

FEEDING THE PUPPY

Healthy puppies, during the first 2 to 3 weeks of life, should only eat and sleep. Nursing should be vigorous and active, with each puppy receiving sufficient milk from its mother. If the mother is healthy and well nourished, the puppy's nutritional needs for its first 3 to 4 weeks of life should be provided completely by her. Indications that the puppy is not receiving sufficient milk are constant crying, extreme inactivity, or failure to achieve weight gains in accordance with the general guidelines that a puppy should gain 1 to 2 g/day/lb (2 to 4 g/day/kg) of anticipated adult weight (or at least 10% gain per day).[1] For example, if the adult dog is expected to weigh 30 lb, as a puppy it should gain 30 to 60 g/day during its first 5 months of life.

The transition from mother's milk to solid food should be a gradual process beginning at about 3 weeks of age (4 weeks of age for toy breeds); however, if necessary, supplemental feeding may be started as soon as the puppy fails to show sufficient weight gain. During the changeover to solid food, the puppy can be offered a thick, gruel-like mixture of good-quality puppy food designed for growth and water (one part dry food blended with three parts water, or two parts canned food blended with one part water). To get the puppy eating, the gruel is placed in a shallow food dish, the puppy is encouraged to lap the gruel by touching its lips to the food, or the feeder can put a finger in the gruel and then into the puppy's mouth. It can also be force-fed using a commercial dosing syringe. Once the puppy accepts the gruel, the amount of water is gradually reduced until it is omitted.

By 6 weeks of age, the puppy should be receiving at least 25% of its requirements from the weaning diet. The puppy may be permanently separated from the mother as soon as it learns to eat readily and drink satisfactorily. Most puppies are completely weaned at 7 to 8 weeks of age, depending somewhat on size and breed. Early weaning and separation from littermates, prior to 6 weeks of age, however, can cause malnutrition or numerous behavioral problems later in life. Because of this, complete weaning should not be attempted until puppies are at least 6 weeks old and close human contact has been established.

Feeding the weaned puppy should always be directed to attaining the appropriate growth rate for the breed.[1] Instead of making food available to the puppy at all times (free-choice feeding), time-limited meal feeding is recommended. At each feeding, the puppy should be given 15 to 20 minutes to eat all that it wants; then the remaining food should be removed. From the time of weaning to 4 to 6 months of age (9 months for giant breeds), puppies are best fed at least three times a day at regular intervals. Thereafter, puppies should be fed twice a day on a regular schedule.

Some large and giant breeds of dogs (those over 30 kg body weight at maturity) have the genetic capacity to grow rapidly and will do so if provided with a food that meets or exceeds their nutrient and energy needs. However, a rapid growth rate is not compatible with normal skeletal growth and may result in certain types of developmental bone disease.[2,3] Beginning at weaning and continuing until they reach maturity, large and giant breeds of dogs should be fed for a moderate growth rate. This can be accomplished by limiting food intake or, even better, by feeding a growth-formulated puppy food for large and giant breeds. If osteochondrosis or hypertrophic osteodystrophy occurs, nutritional management should be aimed at reducing caloric intake by decreasing the amount of food that is fed or feeding a growth-formulated puppy food for large and giant breeds.

FEEDING THE KITTEN

Healthy kittens, during their first 4 weeks of life, should nurse vigorously and actively. If the mother is healthy and well nourished, the nutritional needs of the kittens during this time should be filled completely by her. Each kitten should receive sufficient milk from its mother. Kittens not receiving sufficient milk cry constantly, are restless or extremely inactive, or fail to achieve the expected weight gain of 10 to 15 g/day.[1]

Kittens should be encouraged to begin eating solid food at 4 weeks of age. At this time, the kitten can be offered a thick, gruel-like mixture of good-quality kitten food designed for growth and milk or water (one part dry food blended with three parts milk, or two parts canned food blended with one part milk). The gruel is fed to kittens from a shallow bowl or force-fed by using a commercial dosing syringe. The feeder can encourage the kitten to eat the gruel by smearing some of the gruel on the kitten's lips, being careful not to get any in the nose, or placing a finger in the gruel and then into the kitten's mouth. This usually encourages the kitten to eat from a bowl at an early age. Once the kitten is eating the gruel well, the amount of milk or water in the gruel is gradually reduced until the kitten is consuming only solid food. The kitten may be permanently separated from the mother as soon as it learns to eat readily and drink satisfactorily. Most kittens are completely weaned at 6 to 8 weeks of age. Early weaning and separation from littermates before 6 weeks of age can result in behavioral problems such as slowness to learn and more suspicious, cautious, and aggressive actions.[4]

Food given to weaned kittens should be one specifically formulated for growth. Feeding between 3 to 3.5 oz of dry food per day or 8 to 10 oz of canned food per day usually meets the growth requirements of most kittens. Because the kitten's eating habits are still in the formative stage after weaning, it is important that easily digested, high-quality,

calorically dense food is provided. Cow's or goat's milk is often fed to kittens after weaning and is a good food, provided that it does not cause diarrhea. Milk should never be given in place of fresh water.

Kittens should be fed all the food they will consume. Excessive caloric intake and excessively rapid growth rate are seldom problems in growing kittens. Most kittens are not voracious. When food is always available, they nibble at it frequently. Kittens fed unlimited amounts of food (free-choice feeding), regardless of the form of food (dry or canned), eat every few hours. Free-choice feeding, or at least three-times-a-day feeding, is preferred during growth.

At 12 weeks of age the kitten's energy needs are three times greater than those of an adult cat, or more than 200 kcal/kg of body weight. As kittens mature past 6 months of age, their growth rate slows and their food needs decrease. Their energy needs are still greater than adult cats, or approximately 90 kcal/kg of body weight.

REARING NURSING PUPPIES AND KITTENS

Newborn puppies and kittens are unable to effectively control their body temperature.[5] During their first 4 weeks of life, they gradually progress from being largely poikilothermic to being homeothermic. That is, for the first week of life their body temperature is directly related to the environmental temperature, and a steady ambient temperature of 30° to 32° C (86° to 90° F) is needed. Over the next 3 weeks, the ambient temperature can be gradually lowered to 24° C (75° F). Humidity should be maintained at 55% to 60%. It is equally important that sudden changes of environmental conditions be avoided.

The most obvious alternative to a mother rearing her own young is for another nursing mother to act as a foster mother. If a foster mother is not available, it is necessary to hand-feed the puppies or kittens a replacement food that is a prototype of nutritive substance formulated to meet the optimum requirements of the puppy or kitten. Mother's milk is the ideal food. Various modifications of homemade and commercially prepared formulas simulating mother's milk have been used with good success.[5-7] Commercially prepared formulas are preferred, because they closely compare to mother's milk. These formulas generally provide 1 to 1.24 kcal of metabolizable energy per milliliter of formula. The caloric needs for most nursing-age puppies and kittens are 22 to 26 kcal per 100 g of body weight. Therefore the average puppy or kitten should daily receive approximately 13 mL of formula per 100 g of body weight during the first week of life, 17 mL of formula per 100 g of body weight during the second week, 20 mL of formula per 100 g of body weight during the third week, and 22 mL of formula per 100 g of body weight during the fourth week. These amounts of formula should be given in equal portions three or four times daily. For the first 3 weeks of life, the formula should be warmed before each feeding to about 100° F (37.8° C) or to a temperature near the animal's body temperature.

After each feeding, the abdomen should be enlarged but not overdistended. When a formula is used, less than the prescribed amount should be given per feeding for the first feedings. The amount should then be gradually increased to the recommended feeding amount by the second or third day. The amount of formula should then be increased accordingly as the puppy or kitten gains weight and a favorable response to feeding occurs. Puppies should gain 1 to 2 g/day/lb (2 to 4 g/day/kg) of anticipated adult weight for the first 5 months of their lives. At birth the kitten should weigh 80 to 140 g (most weighing around 100 to 120 g) and gain 50 to 100 g weekly.[1]

When preparing formula the clinician should always follow the manufacturer's directions for its proper preparation and keep all feeding equipment scrupulously clean. A good way of handling prepared formula is to prepare only a 48-hour supply at a time and divide this into portions required for each feeding. Once formula is prepared, it is best stored in the refrigerator at 4° C.

The easiest and safest way of feeding prepared formula to nursing-age puppies and kittens is by nipple bottle, dosing syringe, or by tube.[1] Nipple bottles made especially for feeding orphan puppies or kittens or bottles equipped with preemie infant nipples are preferred. When feeding with a nipple bottle, the clinician or other staff member should hold it so that the puppy or kitten does not ingest air. The hole in the nipple should be such that when the bottle is inverted, milk slowly oozes from the nipple. It may be necessary to enlarge the nipple hole with a hot needle to get milk to ooze from the bottle when inverted. When feeding, a drop of milk should be squeezed onto the tip of the nipple and the nipple should be inserted into the animal's mouth. Milk should never be squeezed out of the bottle while the nipple is in the animal's mouth; doing so may result in laryngotracheal aspiration of the milk into the lungs. In addition, prepared formula should never be fed to a puppy or kitten that is chilled or that does not have a strong sucking reflex. Only when the sucking reflex is present should feeding with nipple bottle be attempted.

Tube feeding is the fastest way to feed orphaned puppies or kittens. Most owners can do it easily with a little training. The following may be used: a No. 5 French (F) infant feeding tube for puppies or kittens weighing less than 300 g, a No. 8 to 10 F infant feeding tube for puppies or kittens weighing over 300 g, or an appropriately sized, soft, male urethral catheter. Once weekly, the feeding tube should be clearly marked to indicate the depth of insertion to ensure gastric delivery (that is, the distance from the last rib to the tip of the nose can be measured and marked off on the feeding tube as a guide). The animal should never be fed into the distal esophagus. When feeding, a syringe should be filled with warm, prepared formula and fit it to the feeding tube. The clinician or staff member should be sure to expel any air in the tube or syringe. The animal's mouth should be opened slightly and, with the animal's head held in the normal nursing position, the feeding tube should be gently passed to the marked area. If an obstruction is felt, or coughing occurs, before reaching the mark, the tube should be assumed to be in the trachea. If this does not happen, the prepared formula should be slowly administered over a 2-minute period to allow sufficient time for slow filling of the stomach. Regurgitation of formula rarely occurs; but if it does, the feeding tube should be withdrawn and feeding interrupted until the next scheduled meal.

A vital aspect of tending orphaned puppies and kittens is to simulate after feeding, the mother's tongue action on the anogenital area, which provokes reflex micturition and defecation. Application of this stimulus has to be taken over by the person tending the puppies or kittens. The clinician can achieve the necessary result by swabbing the anogenital area with moistened cotton or dry, soft tissue paper to manually stimulate the reflex elimination. It is sometimes possible to effect the same response simply by running a forefinger along the abdominal wall. This stimulation should be regularly provided after each feeding using nipple bottle or tube. After they reach about 3 weeks of age, puppies and kittens are usually able to relieve themselves without simulated stimulation.

Most puppies and kittens benefit from gentle handling before feeding to allow for some exercise and to promote muscular and circulatory development. In addition, at least once a week the orphaned puppy or kitten should be washed gently with a soft moistened cloth for general cleansing of the skin, simulating the cleansing licks of the mother's tongue.

CHAPTER 152

Nutrition-Related Skeletal Disorders

Herman A.W. Hazewinkel

INTRODUCTION

Some skeletal diseases can be linked to unbalanced nutrition (alimentary hyperparathyroidism, rickets). The incidence of many hereditary, developmental skeletal diseases (hip dysplasia [HD], osteochondrosis) may be enhanced by inappropriate nutrition. More than 99% of body calcium (Ca) is stored in the skeleton, giving it rigidity. The extracellular Ca concentration ($[Ca^{2+}]$) is also of paramount importance for different cellular, contractive, and enzymatic processes. Plasma $[Ca^{2+}]$ is maintained in a relatively narrow range with the aid of physiochemical processes: increase in $[Ca^{2+}]$ causes Ca transport to cell organelles, storage of Ca in the labile Ca-pool of bone, and increased glomerular Ca excretion with fine tuning by a variety of regulators, including the calciotropic hormones parathyroid hormone (PTH), calcitonin (CT), and vitamin D (vitD). These hormones have direct or indirect actions (or both) on the skeleton, kidneys, and gut[1] (Figure 152-1). The skeleton includes both bone and cartilage cells and their matrix. Appositional growth of bones occurs by osteoblasts originating from the periosteum; growth in length takes place via endochondral ossification, whereas bone remodeling is controlled by osteoclasts.

ALIMENTARY HYPERPARATHYROIDISM

Chronic insufficient Ca intake or absorption results in increased PTH synthesis and secretion. PTH, in turn, increases osteoclast activity (deliberate Ca and phosphorous [P] from the skeleton), increases calcitriol synthesis in the kidney (thus increasing intestinal Ca and P absorption), and decreases P reabsorption from renal tubuli (thus causing hyperphosphaturia)[2,3] (see Figure 152-1). Consequently, hyperparathyroidism will normalize the extracellular $[Ca^{2+}]$. When the increase in Ca absorption in the intestine is not covering the daily requirements, the skeleton is the only remaining source of Ca. Ca will be resorbed at the endosteal surface of the diaphyses and in the areas of cancellous bone. Mineralization of osteoid and cartilage will be undisturbed.[4,5]

Clinical and Radiologic Examination

The most commonly affected dogs and cats are young and raised on foods that are extremely low in Ca content. Usually this includes meat or by-products. Therefore this metabolic bone disease is sometimes referred to as "all-meat syndrome." However, food of low quality binding Ca to phytate may also cause chronic Ca deficiency, especially in young dogs of large breeds. Affected dogs and cats are reluctant to stand and walk and can even be paralyzed due to spinal compression by pathologic fractured vertebrae. Blood investigation will not reveal hypocalcemia, although elevated PTH and calcitriol ($1,25[OH]_2$vitD) levels can be detected[3,5] (see Figure 152-1). Radiographs may reveal thin cortices, wide medullary cavities, folding (green stick) fractures, normal height of growth plates with relatively white metaphyseal borders, as well as compression fractures of cancellous bone of epiphyses and vertebrae.[4,5]

Differential Diagnosis

Ca deficiency can be complicated with vitD deficiency when solely lean meat (which is low in Ca and vitD) is fed. Bone disease due to an inborn error may resemble alimentary hyperparathyroidism, including osteogenesis imperfecta, mucopolysaccharidosis, and other rare diseases.

Therapy

It is extremely important to prevent more pathologic fractures (especially of the vertebrae). The skeleton is too fragile for bandages, splints, or implants. Analgesics will facilitate early mobility, which is not desirable. Changing to a balanced diet with a Ca content up to 1.1% on a dry-matter basis will allow the skeleton to mineralize within 3 to 4 weeks, because almost 100% of the ingested Ca will be resorbed due to the hyperparathyroid-induced high calcitriol levels.[3] Extra Ca as Ca-carbonate or Ca-lactate (and not Ca-phosphate or bone meal) at 50 mg Ca/kg body weight might even accelerate osteoid mineralization. Corrective osteotomies can be planned, when necessary, after the skeleton is normally mineralized. Even pets with compression fractures of the spinal cord may have a full recovery.

RICKETS

Hypovitaminosis D in young animals is known as *rickets*, whereas in adults it is called *osteomalacia*. Dietary vitD is absorbed by the intestine and transported to the liver where it is hydroxylated into 25-OHvitD.[1] Dogs and cats are not able to synthesize vitD in their skin under the influence of sunlight, unlike many other species.[1,4] A second hydroxylation takes place in the kidney, either to $24,25(OH)_2$vitD or to $1,25(OH)_2$vitD (calcitriol).[1] Calcitriol is the active metabolite that stimulates active absorption of Ca and P in intestine and renal tubular cells. Both metabolites are necessary for osteoid and cartilage mineralization.[1] Rickets is characterized by poor mineralization of newly formed osteoid and cartilage and a thickening of metaphyseal areas of bone.[4] Hypovitaminosis D in adult animals may be more common than the condition in young dogs and cats, but it does not cause obvious clinical signs. It might play a role in chronic renal insufficiency due to decreased capacity of hydroxylation of 25-OHvitD, despite renal secondary hyperparathyroidism. Normal vitD intake together with high Ca intake starting at an early age (3 weeks of life) may cause hypercalcemia, secondary hypoparathyroidism and tertiary decreased calcitriol formation. Rickets is the result.[5,6]

Clinical and Radiologic Examination

An unbalanced diet (either low in animal fat or enriched with calcium salts) fed from an early age onward is the most common problem. Thus a diet history is quite important.

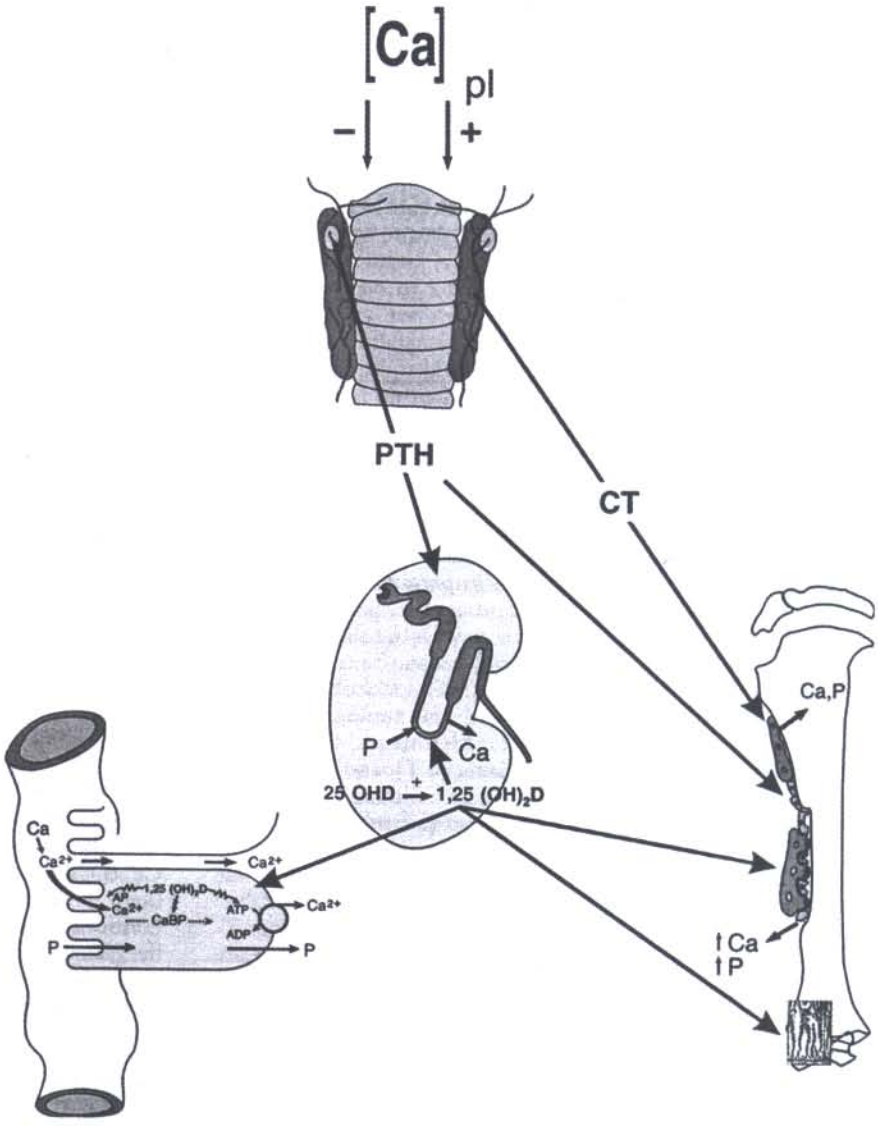

Figure 152-1 Calcium homeostasis regulated by calciotropic hormones. An increase (+) of plasma calcium concentration $[Ca]_{pl}$ stimulates secretion of calcitonin (CT) from the thyroid glands with consequently retraction of the ruffle boarder of osteoclasts (OCL) with—in case of long duration—disturbance of skeletal remodeling and endochondral ossification. A decrease (–) of $[Ca]_{pl}$ stimulates parathyroid hormone (PTH) secretion from the parathyroid glands causing (1) shrinkage of osteoblasts, allowing OCL to resorb bone, and (2) increased reabsorption of Ca and excretion of P and increased formation of $1,25(OH)_2$vitD in the kidney. As a result of the latter, active absorption of Ca and P is increased, renal Ca and P reabsorption is increased, and mineralization of newly formed osteoid and cartilage is stimulated.

Radiographs demonstrate thin long bone cortices and extremely thickened growth plates. Plasma $[Ca^{2+}]$ can be normal or low-normal due to hyperparathyroidism, also causing hypophoshatemia together with hyperphosphaturia (see Alimentary Hyperparathyroidism).[1,6] Determination of circulating vitD concentrations will reveal decreased levels of 25-OHvitD, whereas normal 25-OHvitD but low $1,25(OH)_2$vitD indicates alimentary induced hypoparathyroidism or renal disease.[1]

Treatment

First the diet has to be changed to a major commercial dog or cat food. These foods are known to contain sufficient vitD to resolve and prevent rickets.[1,4] Mineralization of bone cortices, callus, and growth plates will occur within 3 weeks. If the dog or cat fails to respond to a balanced diet, vitD therapy can be recommended.

HIP DYSPLASIA

Environment, including nutrition, plays a role in the expression of HD. Dogs raised on a diet with high Ca content instead of the recommended level of 1.1% Ca on dry-matter base, have retarded secondary ossification centers.[7] Delayed ossification of the skeleton at a given age, weight, and activity might allow for skeletal deformation when compared with dogs with a more advanced stage of skeletal development. In addition, excessive Ca intake will induce hypercalcitoninism, which may cause decreased skeletal modeling (see Figure 152-1). Changes in femoral neck angle during growth may result from osteoclast activity and can thus be hampered in animals with excess Ca intake.[8] Osteoclast activity can also be influenced by a change in base excess.[9] It has been suggested, but not proven, that an excess of cations (Na, K, Ca, Mg) and the expected compensatory alkalosis lowers bone cell activity and thus skeletal modeling.[9] Hypervitaminosis C can also cause hypercalcemia-induced hypercalcitoninism, contributing to the development of HD.[9,10] Excessive energy intake–induced excess in body weight has negative influences on hip joint development in dogs prone to HD.[9-11] Subluxation of the femoral head together with excess body weight causes the acetabular rim to deform as is seen in young dogs with severe HD. In addition, subluxation causes a corresponding increase in pressure on joint cartilage, which might cause irreversible cartilage

damage and thus osteoarthrosis.[9] Excessive dietary protein per se has not proven to influence hip joint development.[3] High calorie intake may result in more rapid rate of growth of young dogs, both in length and in weight, and thus increase the risk of HD to develop.[9,12]

Treatment

Proper nutrition can help prevent HD. Proper nutrition in adult dogs can also serve as a conservative treatment of the osteoarthrosis due to HD. It is advocated to raise young dogs on a balanced diet with appropriate calories but without mineral excess. Nutritional treatment of osteoarthrosis should focus on weight reduction. Omega-3 fatty acids originating from fish may stimulate the synthesis of noninflammatory leukotrienes-5 (LTB_5) rather than the proinflammatory LTB_4. Combinations of chondroitin sulfate and glucosamine may be of benefit for treatment of osteoarthrosis when chronically administered at a dose of sufficient magnitude. In those cases where conservative treatment (activity reduction, appropriate diet and analgesics) is not sufficient in treating osteoarthrosis, surgery may be indicated. Diets restricted in calories (30% to 50% of the current quantity) might be used to assist in weight loss. However, these "light diets" should only be fed to overweight adult dogs and not to growing young dogs, because the danger exists that such low-energy but complete dog foods fed to a young dog may cause excessive mineral uptake.[9,12]

OSTEOCHONDROSIS

Growing cartilage is present in the growth plates and around the bony ends. Growth and closure of growth plates depends on age, breed, location, as well as on humoral and nutritional factors.[7] Overnutrition diets with excess Ca, diets with limited energy, and balanced foods with excessive vitD content[13] have all been proven to be important factors in the development of osteochondrosis (OC).[2-4,6,8,13] OC is a disturbance in the process of endochondral ossification of growth plates and joint cartilage. Ossification of cartilage will become clinically evident whenever fissure lines cause a cartilage flap (i.e., osteochondritis dissecans [OCD]). Not relative, but absolute amounts of mineral consumed per kilogram of body weight (or per kilogram of metabolic body weight) have to be taken into account.[6] Dietary Ca diffuses passively through the intestinal wall of the growing dog when dietary Ca content is larger than 1.0% on dry matter basis (dmb); therefore the absolute amount of ingested Ca determines the daily Ca absorption.[14] Ca excess causes hypercalcitoninism with decreased osteoclast activity, decreased skeletal remodeling, and (in large breed dogs) disturbed endochondral ossification.[2,3,8]

Clinical and Radiologic Examination

OC is considered to be a hereditary disease, seen most often in large breed males and rapidly growing females during their developmental growth phase. In case of retained cartilage

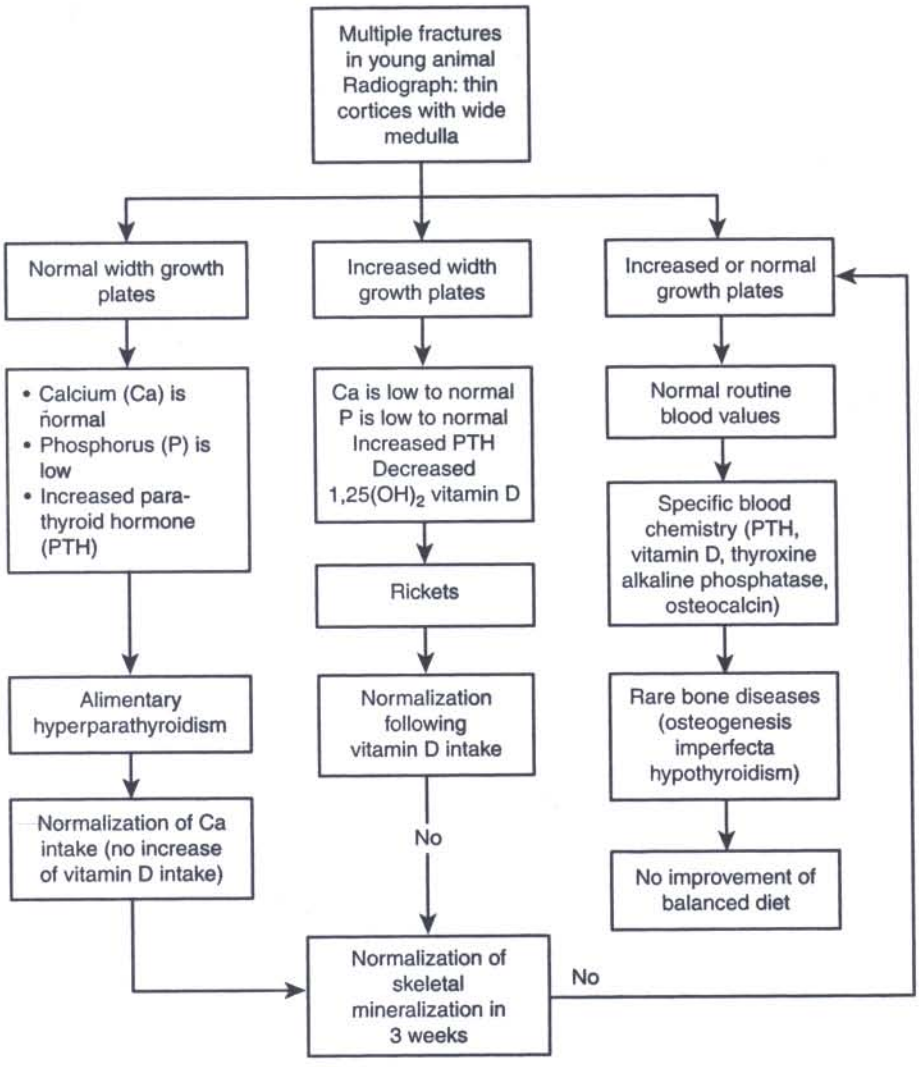

Figure 152-2 An algorithm for multiple pathological fractures in young dogs and cats.

cones, inspection of the front and rear legs may demonstrate bilateral valgus deformation.[4] In dogs with OCD, palpation and extension of shoulder, elbow, stifle, and tibiotarsal joints may demonstrate overfilling, pain reactions, or both. Measurement of circulating concentrations of Ca, P, calcitonin, and calcitriol may not provide insight into the dietary content or absorption rates of these elements.[5,6,13] Radiographs of growth plates or affected joints may reveal an abnormality in the alignment, whereas other imaging techniques, including arthroscopy, may support the diagnosis.[4,6-8]

Treatment

Young dogs of large breeds should be raised with limited amounts of food, preferably a food of good quality and containing ingredients according to the requirements of growing dogs.[9] Overfeeding and oversupplementation must be avoided. The increased level of protein in puppy food will not cause these skeletal disturbances[12,3] Surgery is indicated in case of malalignment or OCD.

PANOSTEITIS (= ENOSTOSIS = EOSINOPHILIC PANOSTEITIS)

Intake of food, and especially of Ca, causes the release of gastrointestinal (GI) hormones, some of which will cause calcitonin release from the thyroid glands. Increased plasma calcitonin concentrations prevent Ca release from the skeleton by influencing osteoclasts (see Figure 152-1). High Ca intake in young dogs leads to hyperplasia of calcitonin-producing cells with reduced osteoclastic activity, even months after an episode of high Ca intake.[2,6,8] In immature dogs, a large blood supply to the metaphyseal area (bordering the growth plates) exists. This network of arteriolae receives blood from branches of the periosteal side (i.e., the epiphyseometaphyseal arcade) and the medullary arteries. The latter enter the bone mainly in the foramen nutritium. The direction of efferent blood flow is through the diaphyseal cortex, centrifugal from medulla to periosteum, and runs through rigid bone canals including Volkmann's canals.[15] When, during growth, widening of the bony canals lags behind the growing vessels, vessel occlusion will result in edema formation inside the medullary cavity. Ultimately, new bone formation will take place on the fibrous tissue formed. Increased pressure and finally new bone formation is first seen near the foramen nutritium. Edema may also accumulate underneath the periosteum and thus make the periosteum painful in response to pressure or muscle activity, causing extra lamellar bone formation.[5] So far, no causes other than high food[8] and Ca[6] intake have been demonstrated.

Clinical and Radiologic Investigation

Panosteitis is mainly seen in medium and large-breed dogs (especially German shepherd dogs), starting at 6 months of age with a sudden onset of shifting lameness showing pain reaction upon deep palpation at several long bones. An increased body temperature may be present. Blood investigation or culture of blood or bone is negative, although electrophoresis of plasma proteins may reveal abnormalities.[16] Radiographs demonstrate a blurring of the trabecular pattern and well-defined subperiosteal cortical thickening can be noticed.

Therapy

Because the disease is self-limiting and is not diagnosed in dogs over 22 months of age, treatment is limited to analgesics and nursing of the dogs. Analgesics can relieve pain. Dietary corrections include a decrease in the amount of Ca to the minimal requirements for dogs. The role of dietary proteins is suggested by some[16] and rebutted by others.[2,3]

CHAPTER • 153

Adverse Reactions to Foods: Allergies versus Intolerance

Philip Roudebush

An adverse reaction to food is a clinically abnormal response to an ingested food or food additive. In general, the pathogenic mechanisms that cause adverse food reactions include ingestion of the inciting agent followed by interaction of the agent with a biologic amplification system that leads to inflammation and clinical signs.

In view of the number of diverse foods that are routinely ingested by animals, it is not surprising that adverse reactions develop to dietary substances. The fact that food-related reactions appear relatively infrequently is testimony to the effectiveness of the intestinal mucosal barrier and oral tolerance. Adverse reactions to food have been blamed for a variety of clinical syndromes in cats and dogs, usually involving the skin and gastrointestinal tract.

TERMINOLOGY

Adverse reactions to food comprise a variety of subclassifications based on pathomechanisms. The following terms and definitions are recommended by the American Academy of Allergy and Immunology (Figure 153-1).[1,2] *Food allergy (food hypersensitivity)* is an adverse reaction to a food or food additive with a proven immunologic basis. *Food anaphylaxis* is an acute food allergy with systemic consequences, such as respiratory distress, vascular collapse, and urticaria. *Food intolerance* is a nonimmunologic, abnormal physiologic response to a food or food additive. Food intolerance can be further classified as food idiosyncrasy, food poisoning, and pharmacologic reactions to food. *Food idiosyncrasy* is an abnormal response that

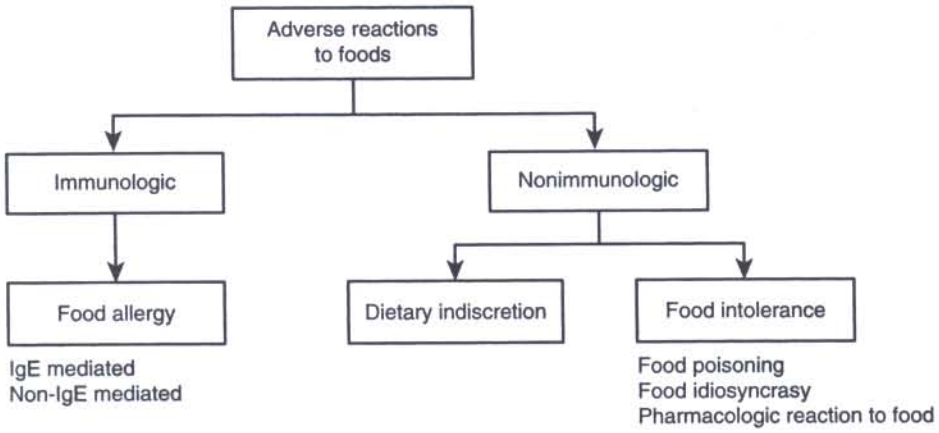

Figure 153-1 Classification of adverse reactions to food.

resembles food allergy but that does not involve immune mechanisms. A direct nonimmunologic action on the host of food or a toxin in food is termed *food poisoning.* Adverse reactions due to a druglike or pharmacologic effect of a food substance on the host are called *pharmacologic reactions to food.* When adverse reactions result from such behaviors as gluttony, pica, or ingestion of indigestible materials, the term *dietary indiscretion* is used. Traditionally, the term *food allergy* has been used to describe all adverse reactions to food in dogs and cats, including reactions that were actually food intolerance.

FOOD ALLERGENS

The specific food allergens that cause problems in animals have been poorly documented. In general, the major food allergens that have been identified in human beings are water-soluble glycoproteins that have molecular weights ranging from 10,000 to 70,000 daltons and that are stable when treated with heat, acid, or proteases.[3,4] Other physiochemical properties that account for their unique allergenicity are poorly understood.

Twelve different studies, representing a total of 265 dogs, have described cutaneous lesions associated with adverse reactions to specific foods or ingredients.[5] These studies reported findings from a wide geographic area, including the United States, United Kingdom, France, Australia, and Japan. Adverse reactions to beef, dairy products, and wheat accounted for two thirds of reported cases in dogs. Adverse reactions to chicken, chicken eggs, lamb, or soy accounted for approximately 25% of reported canine cases. Adverse reactions to corn, pork, rice, or fish ingredients are rarely reported in dogs.

In cats, 10 different studies, representing a total of 56 animals, have described cutaneous lesions or gastroenteric signs associated with adverse reactions to specific foods or ingredients.[5] These studies have also reported findings from a wide geographic area, including the United States, United Kingdom, France, New Zealand, and Japan. Adverse reactions to beef, dairy products, and fish accounted for more than 80% of reported cases.

Human allergy reference books often have phylogenetic tables of animal and vegetable foods so that food-allergic individuals can avoid other closely related foods. Cross-reactivity among food allergens has been only briefly investigated in pet animals.[6]

FOOD INTOLERANCE

Nonimmunologic, abnormal physiologic reactions to food include food intolerance and dietary indiscretion (see Figure 153-1). Like the term *food allergy,* the term *food intolerance* has been applied inappropriately to any and all adverse reactions to food. Food intolerance mimics food allergy except that it can occur with the first exposure to a food or food additive, because nonimmunologic mechanisms are involved. The incidence of food intolerance versus food allergy in animals is unknown.

Idiosyncratic adverse reactions to food additives often occur in human beings. Although food additives are frequently cited as the cause of problems in dogs and cats, few data confirm this perception. Propylene glycol and onion ingredients have been documented to cause hematologic abnormalities in cats.[7,8]

Another cause of food intolerance is pharmacologic reactions to substances found in food. Vasoactive or biogenic amines such as histamine cause clinical signs when present in excessive levels in food. Adverse reactions to histamine in scombroid fish (e.g., mackerel, tuna) have been observed in cats and dogs.[9] Vasoactive or biogenic amines may not be present in levels high enough to cause clinical signs, but they may lower the threshold levels for allergens in individual dogs and cats.

The diarrhea, bloating, and abdominal discomfort that occur when animals with lactose intolerance ingest milk are relatively common metabolic adverse reactions in dogs and cats. Osmotic diarrhea often occurs when excessive levels of lactose are consumed. Puppies, kittens, or adult animals may develop diarrhea when given cow's or goat's milk because these milk sources contain more lactose than either bitch's or queen's milk.

Intolerance to disaccharides commonly occurs secondary to enteritis or rapid food changes. Loss of intestinal brush border disaccharidase activity contributes to the diarrhea associated with enteritis. Inadequate intestinal disaccharidase activity is another factor responsible for diarrhea subsequent to rapid food changes. Several days are required for intestinal disaccharidase enzyme activity to adapt to changes in food carbohydrate sources.

CLINICAL FEATURES IN DOGS AND CATS

Dermatologic Responses in Dogs

Reports of adverse food reactions in dogs with cutaneous disease did not document a gender predisposition, and ages ranged from 4 months to 14 years. However, up to one third

of canine cases may occur in dogs less than 1 year old. Because many adverse food reactions occur in young dogs, the index of suspicion for food allergy may rise above that for atopic dermatitis when intense pruritus occurs in dogs less than 6 months old. Most investigators have not found a breed predilection, whereas others have found that cocker spaniels, springer spaniels, Labrador retrievers, collies, miniature schnauzers, Chinese Shar Pei, West Highland white terriers, wheaten terriers, boxers, dachshunds, Dalmatians, Lhasa apsos, German shepherds, and golden retrievers are at increased risk.

Adverse food reactions in dogs typically occur as nonseasonal pruritic dermatitis, occasionally accompanied by gastrointestinal (GI) signs. The pruritus varies in severity. Lesion distribution is often indistinguishable from that seen with atopic dermatitis; the feet, face, axillae, perineal region, inguinal region, rump, and ears are often affected. Many dogs with adverse food reactions have lesions only in the region of the ears. This finding suggests that adverse food reactions should always be suspected in dogs with pruritic, bilateral otitis externa, even if it is accompanied by secondary bacterial or yeast infections.

Adverse food reactions often mimic other common canine skin disorders, including pyoderma, pruritic seborrheic dermatoses, folliculitis, and ectoparasitism. Twenty percent to 30% or more of dogs with suspected adverse food reactions may have concurrent allergic disease, such as flea-allergy or atopic dermatitis.

Food anaphylaxis is an acute reaction to food or food additives with systemic consequences. The most common clinical manifestation in dogs occurs in localized form and is referred to as *angioedema* or *facioconjunctival edema*. Angioedema is typically manifested by large, edematous swellings of the lips, face, eyelids, ears, conjunctivae, and/or tongue, with or without pruritus. Most veterinary practitioners attribute angioedema solely to insect envenomation (biting or stinging insects); however, a number of other common causes are food, drugs, vaccines, infections, atopy, and blood transfusions. Urticarial reactions (hives) are characterized by localized or generalized wheals, which may or may not be pruritic. They usually occur within minutes of allergen exposure and generally subside after 1 to 2 hours.

Dermatologic Responses in Cats

Gender predisposition has not been documented in adverse food reactions in cats, and ages have ranged from 6 months to 12 years. Siamese and Siamese-cross cats may be at increased risk, because they have accounted for nearly one third of cases.

Dermatologic signs include several different clinical reaction patterns, such as (1) severe, generalized pruritus without lesions; (2) miliary dermatitis; (3) pruritus with self-trauma centered around the head, neck, and ears; (4) traumatic alopecia; (5) moist dermatitis; and (6) scaling dermatoses. Angioedema, urticaria, and conjunctivitis occur commonly in cats with adverse food reactions. Adverse reactions to food may also cause self-inflicted alopecia (psychogenic alopecia, or neurodermatitis), eosinophilic plaques, and indolent ulcers of the lips in some cats. Concurrent flea-allergy or atopic dermatitis may occur in up to one third of cats with suspected adverse food reactions.

Moderate to marked peripheral lymphadomegaly and absolute eosinophilia are commonly found in cats with dermatologic manifestations of food allergy.

Gastrointestinal Responses in Dogs and Cats

Gender predilections have not been established for GI disease resulting from adverse reactions to foods. Similarly, there are no well-documented breed predispositions to GI food allergy, but Chinese Shar Peis and German shepherds are commonly affected. Gluten-sensitive enteropathy has been well documented in Irish setters. A wide age range of patients can be affected, including dogs and cats as young as weaning age.

Every level of the GI tract can be damaged by food allergies. In cats and dogs, clinical signs usually relate to gastric and small bowel dysfunction, but colitis can also occur. Vomiting and diarrhea are prominent features. The diarrhea can be profuse and watery, mucoid or hemorrhagic. Intermittent abdominal pain is occasionally observed. Concurrent cutaneous signs may be seen. GI disturbances occur in 10% to 15% of dogs and cats with cutaneous manifestations of food sensitivity.

The role of food allergy in canine and feline inflammatory bowel disease is unknown. Hypersensitivity to food is probably involved in the pathogenesis of this syndrome; at least some affected animals could be more appropriately diagnosed as suffering from food protein-induced enterocolitis.[2]

Irritable bowel syndrome is a disease of dogs characterized by chronic recurrent abdominal pain and large bowel diarrhea. Feeding changes often alleviate the signs of irritable bowel disease, implying that food allergy or food intolerance plays a role in this syndrome.

DIAGNOSIS

Dietary elimination trials are the main diagnostic method used in dogs and cats with suspected adverse food reactions. At the present time, intradermal skin testing, radioallergosorbent tests (RASTs), and enzyme-linked immunosorbent assays (ELISAs) for food allergy are considered unreliable in animals.[10,11]

The ideal elimination food should (1) include a protein hydrolysate or reduced number of novel, highly digestible protein sources; (2) avoid protein excesses; (3) avoid additives and vasoactive amines; and (4) be nutritionally adequate for the animal's life stage and condition.[12] Excess protein levels should be avoided so as to reduce the amount of potential allergens to which the dermatologic patient is exposed. However, a higher protein level may be necessary to counteract protein losses from the GI tract or impaired absorption in patients with hypoproteinemia and weight loss associated with severe GI disease. Although elimination trials are performed only for several weeks to months, the food used in the trial should be nutritionally complete and balanced for the intended species, age and lifestyle of the animal. Elimination trials are often performed with young animals, in which nutritionally inadequate foods are more likely to result in nutritional disease.

Homemade Elimination Foods

Homemade foods are often recommended as the initial test food for dogs and cats with suspected food allergy. Homemade test foods usually include a single protein source or a combination of a single protein source and a single carbohydrate source. However, many homemade foods fail to meet nutritional requirements because they are made from a minimum of ingredients.[12] In general, homemade foods lack a source of calcium, essential fatty acids, certain vitamins, and other micronutrients and contain excessive levels of protein, which are contraindicated in animals with food allergy. Feeding nutritionally inadequate homemade foods for more than 3 weeks may result in nutritional disease, especially in young animals.

Commercial Elimination Foods

A variety of foods with limited and different protein sources are manufactured by several companies. These commercial products are attractive because they are convenient and nutritionally complete and balanced for either cats or dogs. The newest concept for managing animals with suspected

adverse food reactions is use of commercial foods containing hydrolyzed protein ingredients. Veterinary therapeutic foods containing protein hydrolysates offer several hypothetical advantages over traditional commercial or homemade elimination foods. Protein hydrolysates of appropriate molecular weight (less than 10,000 daltons) do not elicit an immunologically mediated response and may be regarded as truly "hypoallergenic" ingredients. Novel or unique protein sources are less important with protein hydrolysates. Protein hydrolysates have been used for many years in human infant formulas and for human patients with various gastrointestinal diseases.

Few commercial foods have been adequately tested in dogs and cats with known adverse food reactions; only a few commercial foods have undergone the scrutiny of clinical trials using patients with dermatologic or GI disease. In published

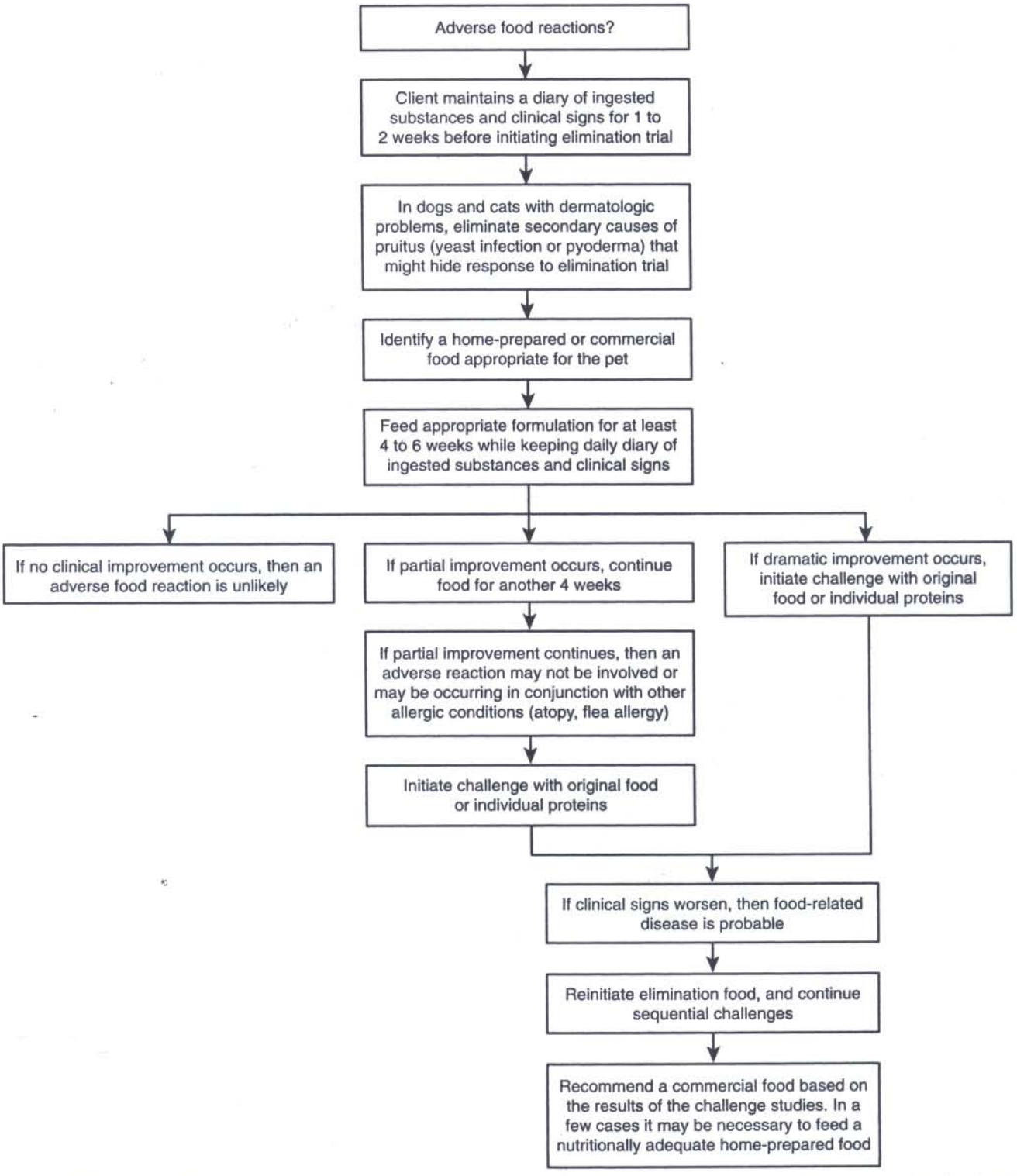

Figure 153-2 Protocol for elimination-challenge trials for the diagnosis of adverse reactions to food. (From Hand MS, Thatcher CD, Remillard RL, et al [eds]: Small Animal Clinical Nutrition, 4th ed. Topeka, Kansas, Mark Morris Institute, 2000.)

clinical trials, two thirds to three fourths of patients with suspected adverse food reactions showed significant improvement in clinical signs when fed commercial foods.

Performing an Elimination Trial in Patients with Dermatologic Disease

Before an elimination trial is initiated, the client should feed the animal its usual food for several days. During this time, the client should record the type and amount of food ingested, any other ingested food items (e.g., table scraps, treats, and snacks), and the occurrence and character of adverse reactions. The patient is then fed a controlled elimination food for 4 to 12 weeks. During the elimination trial, no other substances should be ingested, including treats, flavored vitamin supplements, chewable medications, fatty acid supplements, or chew toys. The client should document daily the type and amount of food ingested and the occurrence and character of adverse reactions. A daily food diary helps document progression of clinical signs during the elimination trial and whether a strict elimination trial was performed in the home environment. Examples of food diaries can be found in other publications.[12]

A tentative diagnosis of an adverse food reaction in dermatologic patients is made if the level of pruritus markedly decreases. This improvement may be gradual and may take 4 to 12 weeks to become evident.

A diagnosis of an adverse food reaction is confirmed if clinical signs reappear 10 to 14 days after the animal's former food and other ingested substances are offered as a challenge.

Elimination trials are often difficult to interpret because of concurrent allergic skin disease. Patients with other allergic diseases may only partially respond to an elimination trial. Flea-allergy and atopic dermatitis are the most common canine and feline allergies and should be eliminated through other diagnostic testing.

Performing an Elimination Trial in Patients with Gastrointestinal Disease

Elimination-challenge trial designs for patients with GI food disease are similar to those for patients with dermatologic problems (Figure 153-2). However, shorter elimination periods (2 to 4 weeks) are usually satisfactory. In chronic relapsing conditions, the elimination period chosen must be greater than the usual symptom-free period of the patient to allow reliable assessment of how food sensitivity contributes to the patient's signs.

As with skin disease, the degree of clinical improvement during the elimination trial will be 100% only if food allergy or food intolerance is the sole cause of the patient's problems. For instance, resolution of allergies acquired as a result of GI disease will not eliminate the clinical signs due to the primary GI disease process. Recrudescence of GI signs after challenge of a food-sensitive patient with the responsible allergen usually occurs within the first 3 days but may take as long as 7 days, particularly if the responsible allergen was removed from the food for longer than 1 month.

TREATMENT

For most food allergies, avoiding the offending foods is the most effective treatment. How selective or meticulous an avoidance diet must be depends on the individual animal's sensitivity. Some dogs and cats may suffer adverse reactions to even trace amounts of an offending food, whereas others may have a higher tolerance level. Concurrent allergies influence the threshold level of clinical signs in some animals. Symptomatic therapy in pruritic animals can also include corticosteroids and antihistamines. Corticosteroids, along with dietary change, are often used in cats with inflammatory bowel disease.

Both homemade and commercial foods can be used for long-term maintenance of patients with suspected food allergy. It is very important that any homemade recipe for long-term maintenance ensures a nutritionally adequate ration. An attempt should always be made to find an acceptable commercial food that will increase owner compliance with the dietary change and ensure a nutritionally adequate ration.

CHAPTER 154

Nutritional Management of Gastrointestinal Conditions

Debra L. Zoran

The gastrointestinal (GI) tract is a complex system primarily responsible for acquiring and digesting food, absorbing nutrients and water, and expelling wastes from the body in the form of feces. A proper diet and normally functioning GI tract are integral to the delivery of nutrients, the prevention of nutrient deficiencies and malnutrition, the repair of damaged intestinal epithelium, the restoration of normal luminal bacterial populations, the promotion of normal GI motility, and the maintenance of normal immune functions (e.g., both tolerance of and protection from pathogens).[1] Dietary characteristics, such as the amount of food, its form, the frequency of feeding, and the composition of the diet, also have important effects on GI function and may be used to help ameliorate signs of disease. Both nutrients and non-nutritional components of a diet support normal GI functions, but they also may cause or influence the development of GI pathology (e.g., antibiotic-responsive diarrhea [ARD], inflammatory bowel disease [IBD], and dietary intolerance or sensitivity/allergy). In chronic or severe GI disturbances, diet may have a profound

effect on intestinal recovery and successful management of the disease.

ROLE OF CONSISTENCY, FREQUENCY, AND MEAL SIZE

For many acute, non-life-threatening GI disturbances, treatment customarily includes the withholding of food and water for 24 to 72 hours, along with correction of fluid and electrolyte deficits. This approach often is an effective treatment for vomiting or diarrhea due to dietary indiscretion or for mild forms of infectious or toxin-induced gastroenteritis.[2] After this short fasting period, the dog or cat should be fed a highly digestible diet (i.e., minimal fat and easily digested protein and carbohydrate [CHO] sources). This should be followed by gradual reintroduction of the original diet. In previously healthy animals, fasting would not be expected to be harmful nutritionally, systemically, or to the GI tract. However, the traditional approach of "resting" the GI tract (i.e., extended fasting) may be harmful or may prolong recovery, especially in injured or sick animals fasted longer than 3 to 4 days or in any nutritionally compromised animal. Deficiency of protein and calories leads to immune system dysfunction, reduced availability of antioxidants and free radical scavengers, reduced energy for vital cellular functions, lack of precursors for repair of injured or diseased tissue and, ultimately, loss of lean body mass.[3] Prolonged fasting also deprives the GI epithelium of its primary metabolic fuel source, the glutamine present in chyme.[4] This metabolic fuel is necessary not only for replacement of the GI mucosal cells lost in normal turnover (every 3 to 5 days), but also for repair of mucosal injury.[4]

One alternative is to provide an oral rehydration solution containing CHO, peptides, and electrolytes to "feed through the diarrhea" in animals that are not vomiting or severely dehydrated (including glutamine).[5] However, if the animal is vomiting or the gut is not functional, the animal's protein (including glutamine) and calorie needs, can and should be met through parenteral nutritional support.[6] Whatever route is chosen, feeding should be instituted as soon as possible. A good rule of thumb for induction of nutritional support is the 3-5-7 day rule: On day 3 of anorexia, planning should begin for implementation of nutritional support, and the plan should be implemented by day 5; otherwise, by day 7 protein and calorie malnutrition will occur, requiring an immediate response.

A major consideration in choosing a diet to feed an animal with GI disease is nutrient digestibility. Typical maintenance pet foods have protein and CHO digestibilities ranging from 70% to 85% on a dry matter (DM) basis.[7] Pet foods formulated for dietary therapy of GI disease have CHO and protein digestibilities of 90% DM or higher.[7] Therapeutic diets also have low levels of fat (less than 15% DM in cats and less than 10% to 15% DM in dogs), are lactose free, and have reduced amounts of dietary fiber and other poorly digestible CHO. Many different, highly digestible, therapeutic diets are available. Each formula is unique and therefore can elicit a different individual response. For example, these diets have different protein or CHO sources and varying levels and types of fat (e.g., some add omega 3 fatty acids), and some are formulated with ingredients designed to enhance GI health, such as fructo-oligosaccharides (FOS). Although the benefits of these individual additives have not been proven in large clinical trials, feeding highly digestible diets to pets with both acute and chronic GI diseases is widely accepted as beneficial.

The amount of a diet fed should be calculated based on the energy needs of the individual animal. Although there is ongoing discussion among nutritionists regarding the best equation for determining the energy requirements of sick animals, at the very least, the resting (or basal) energy requirements (RER) should be met.[8] One generally accepted equation for determining resting energy requirements in dogs and cats is 70 $(BW_{kg})^{0.75}$. Once energy requirements have been determined, meal size, frequency, and consistency are considered. Generally, small meals (e.g., less than one third of stomach capacity) are fed several times per day (three to six meals). The feline stomach has a smaller capacity (approximately 60 mL/kg) and is less distensible than the stomach of a dog (nearly 80 to 90 mL/kg), which is designed for greater storage.[9] Feeding small meals reduces gastric distension, decreases gastric acid secretion, and may reduce nausea, vomiting, and gastroesophageal reflux.[1,7] Furthermore, the larger the volume of food ingested, the less that can be effectively assimilated. In general, liquid diets empty faster from the stomach than canned foods, and canned foods empty faster than dry.[7] Therefore if liquid diets are fed too quickly or in large volumes, diarrhea may occur. In veterinary medicine, liquid diets are primarily used in specialized circumstances (e.g., for nasoesophageal or jejunostomy tube feeding) or with certain GI conditions (e.g., esophageal stricture, selected cases of megaesophagus, or gastric outflow disturbances) because they may reduce regurgitation or vomiting.

NUTRIENT COMPOSITION

A variety of nutritional and non-nutritional diseases affect the GI tract; however, treatment of most GI disease is enhanced by appropriate diet selection. Numerous therapeutic diets are available for treatment of GI disease, including highly digestible diets, novel antigen or so-called hypoallergenic diets, hydrolyzed protein diets, and diets with increased dietary fiber. Each of these diets may be used in the management of various GI disturbances; however, selection of the most appropriate diet requires an understanding of the differences in the nutrient composition of these formulations. Furthermore, under some circumstances, specific diets (e.g., homemade or novel) are required for successful dietary management of severe GI disease.

PROTEIN

The effects of protein on the GI tract are subtle and often less clinically obvious than those of fat or CHO, but they are no less important. Protein in the GI tract increases lower esophageal sphincter pressure; is a potent stimulus for the secretion of hormones, including gastrin and pancreatic hormones; and increases both gastric emptying and intestinal transit.[1,7] Despite this, protein malassimilation is not a major stimulus for diarrhea; for example, dogs with protein-losing enteropathies (PLE) often do not have diarrhea unless they have concurrent fat malabsorption. However, intact protein reaching the distal small intestine and colon increases bacterial ammonia production, alters bacterial numbers and species, and may contribute to colitis or colonic hypersensitivity.[10] Furthermore, protein antigens in food are responsible for the development of most food hypersensitivity reactions in dogs and cats (see Chapter on food hypersensitivity). In animals with severe mucosal disruption (e.g., IBD, lymphoma), intact proteins cross the mucosa, exposing the mucosal immune cells of the lamina propria to these antigens. This results in the development of hypersensitivity to that protein and perpetuation of the aberrant immune response. For this reason, feeding a "sacrificial" diet during the initial stages of therapy of severe GI disease, until the inflammation is under control, has been recommended.[11] Once the inflammatory disease has been suppressed, a new, highly digestible or novel antigen diet can be introduced for long-term therapy.

Feeding hydrolyzed diets (e.g., peptides of less than 15,000 daltons) in this situation may be beneficial as there is no intact protein to stimulate animal response. However, epitopes may still exist on these peptides that can be recognized as foreign, and thus may not eliminate the possibility of immune stimulation, nonetheless, anecdotal evidence suggests many dogs and cats benefit from this dietary approach.

Protein-losing enteropathies are a group of severe intestinal diseases that occur as primary enteropathies (e.g., lymphangiectasia) or familial enteropathies (e.g., soft-coated wheaten terriers, basenjis, Irish setters[12]). Alternatively, they occur secondary to infectious, neoplastic, or inflammatory diseases that infiltrate the GI mucosa and result in loss of mucosal function, including malassimilation of nutrients, motility disturbances, and loss of normal gut functions.[12] Protein loss may also occur from a lack of available or functional enzymes, such as exocrine pancreatic insufficiency (EPI). Regardless of the cause, nutritional therapy is an essential aspect of successful management of PLE. In mild forms of PLE, feeding a highly digestible, low-fat diet, in addition to specific therapy for the primary disease, may be sufficient. However, when severe intestinal disease results in significant loss of serum proteins (serum albumin less than 1.5 g/dL), subsequent development GI mucosal edema causes further nutrient malassimilation. In these animals, hydrolyzed diets or elemental diets (e.g., diets containing no intact nutrient sources) may be required. In animals with severe PLE, a combination of parenteral and enteral nutrition may also be needed to replace lost oncotic proteins, resolve gut edema, and correct protein-calorie malnutrition. Once serum albumin concentrations are more stable (greater than 1.75 g/dL) highly digestible, low-fat diets containing intact protein may be tolerated. However, some dogs with PLE may require feeding of ultra-low-fat homemade diets (e.g., nonfat cottage cheese, egg whites, rice, cooked potatoes) or combinations of hydrolyzed, ultra-low-fat (less than 10% fat DM), or elemental diets indefinitely.[11]

FATS AND FATTY ACIDS

Generally, the higher the density of nutrients, the slower the food empties from the stomach. This is primarily because most nutrient-dense foods are higher in fat, which slows gastric emptying in both dogs and humans but not in cats.[1,7] In contrast to the effects of protein, increased levels of dietary fat decrease the tone of the lower esophageal sphincter and may lead to an increased risk of gastroesophageal reflux or vomiting.[13] Because digestion and absorption of fat is a complex process, malassimilation of fat in animals with GI disease is common. Fat or fatty acids reaching the distal ileum or colon increase the fermentation of bacteria (especially nonbeneficial species), result in the formation of proinflammatory and prosecretory hydroxy fatty acids, and can cause osmotic diarrhea.[10,13] Nevertheless, the complete absence of fat from the diet is also undesirable and may lead to a deficiency of essential fatty acids. Essential fatty acids must be supplied to provide the phospholipid and cholesterol building blocks for cellular growth and repair and for synthesis of prostaglandins, leukotrienes, and thromboxanes.[13] Dietary fat is also important because it enhances the palatability and acceptance of food, and it is an essential energy source for sick or injured animals that cannot effectively utilize CHO.

Recently, attention has been focussed on the addition of anti-inflammatory omega 3 fatty acids (fish oils) to diets used for therapy of GI disease. In humans with ulcerative colitis, the addition of fish oils to the diet resulted in a reduction in inflammatory mediators, improved mucosal function and fluidity, and reduced the use of anti-inflammatory drugs to maintain control of the disease.[14] The clinical benefit of fish oils in the treatment of inflammatory skin disease in dogs is well recognized; however, studies specifically assessing a reduction of intestinal inflammation in dogs and cats fed omega 3 fatty acids are lacking. Nevertheless, some therapeutic diets have omega 3 fatty acids added to their formulations.

CARBOHYDRATES

There are no requirements for CHO in the diet of dogs or cats. The CHO present in pet foods are primarily plant starches, such as rice, potato, corn, wheat, and barley.[13] Another type of CHO present in some diets are the beta-linked polysaccharides (i.e., those not readily broken down by mammalian amylases), which include the dietary fibers.[13] CHO digestibility is determined by its origin and the degree of cooking; for example, rice and wheat are generally highly digestible, whereas uncooked maize or potato starch is less digestible.[13] CHO malassimilation results in the development of osmotic diarrhea, the production of increased intestinal gas (flatus), loss of water and electrolytes, increased fermentation of bacteria in both the small intestine and the colon, overgrowth of pathogenic bacteria, and acidification of the colonic luminal environment, promoting the formation of hydroxy fatty acids and other potentially toxic intermediates.[7,13] White rice is the CHO of choice for most dogs (and is the most commonly used CHO in therapeutic diets), because it is gluten free (some dogs, especially Irish setters and soft-coated wheaten terriers, are sensitive to gluten or may develop sensitivity to gluten, which is present in wheat, oats, and barley), highly digestible, and nonantigenic.[1,2,7,12] Other gluten-free CHO sources include potato, corn, and tapioca, but potato and tapioca are less digestible, and corn may be antigenic to animals prone to develop food sensitivity.

Dietary fibers are a large, complex group of CHO that include starch and nonstarch polysaccharides found in plants; they are readily digested by bacterial enzymes but less well digested by mammalian enyzmes.[13] Traditionally, fibers were classified as *soluble* (highly fermentable) or *insoluble* (poorly fermented or nonfermentable) based on their digestion by amylase; however, a physiologically relevant classification, based on their activity in the GI tract, is currently recommended. Fibers are soluble if they form gels in solution (thus attracting water), delay gastric emptying and slow intestinal transit, inhibit the absorption of cholesterol and some other nutrients, are poor bulking agents, are highly fermentable in the colon (i.e., increase the numbers of bacteria and increase short chain fatty acids, especially butyrate, an essential colonic fuel source), acidify the lumen, and stimulate colonic cellular proliferation.[1,15] Examples of soluble fibers include FOS, pectins, psyllium, oats, barley, guar gum, fruits, and some legumes.[13] Insoluble fibers do not form gels, have no effect on gastric emptying, increase or "normalize" intestinal transit, have no effect on nutrient absorption, are good bulking agents (i.e., dilute colonic content and thus bind noxious agents in the colon), are fermented less and therefore produce fewer short chain fatty acids, and increase fecal weight.[1,15] Typical examples of insoluble fibers are cellulose, wheat and rye fibers (most cereal fibers), and the woody parts of plants (e.g., lignins).[13]

FOS are kestose or nystose sugars present in a variety of fruits, vegetables, and grains that behave in the GI tract like soluble fibers. These sugars have generated considerable interest in both human and veterinary medicine, because they are preferentially fermented by beneficial bacterial species (e.g., *Lactobacillus* and *Bifidobacteria* spp.) and prevent the

Table 154-1

Vitamin Deficiencies Caused by Severe Intestinal Disease

VITAMIN	SIGNS OF DEFICIENCY	COMMENTS
A	Impaired growth, loss of epithelial integrity	Stored in liver; deficiency is rare
D	Osteomalacia, nutritional secondary hyperparathyroidism	Stored in liver; cats more likely to be deficient
E	Dermatoses, pansteatitis	Caused by malabsorption
K	Hemorrhage, increased PT	Caused by fat malabsorption
Thiamin (B_1)	CNS dysfunction, anorexia, muscle weakness	Cats more likely to be deficient; thiaminase
Riboflavin (B_2)	CNS dysfunction, dermatitis	Important cofactor in energy metabolism
Niacin (B_3)	Oral/mucosal disease	Cannot be synthesized by cats, which have a greater requirement for B_3
Pyridoxine (B_6)	Microcytic, hypochromic anemia	Greater requirement for B_6 in cats
Pantothenic acid	Anorexia, weight loss	Part of coenzyme A; deficiency is rare
Biotin	Dermatitis	Eggs a rich source
Choline	Neurologic dysfunction, fatty liver	Methyl donor; synthesized in the body
Cobalamin (B_{12})	Anemia (cofactor for energy metabolism)	GI disease may cause deficiency; some of the vitamin is stored.
Folic acid	Anemia, leukopenia	DNA synthesis, bacteria can synthesize
C		Not required

growth of pathogenic species.[16] In studies of humans with IBD or colitis, adding FOS to the diet greatly improved the response to therapy, clinical disease was reduced, and relapses were fewer.[17] Only a few studies in dogs (and even fewer in cats) have evaluated the role of FOS in the dietary therapy of GI disease. However, preliminary evidence supports the finding in humans that FOS increases the numbers of beneficial bacteria in the colon of both dogs and cats[18,19] and may prove beneficial in controlling bacterial overgrowth, ARD, or other inflammatory diseases believed to have a bacterial origin (e.g., IBD).

NUTRITIONAL DEFICIENCIES RESULTING FROM GASTROINTESTINAL DISEASE

Nutritional deficiencies commonly occur as a consequence of GI disease.[20] Protein and calorie malnutrition is the most common nutritional deficiency in severe or chronic GI disease. Not surprisingly, deficiencies of electrolytes (e.g., sodium, potassium, chloride, and bicarbonate) and divalent cations (e.g., magnesium, zinc, and calcium) are also common and should be corrected.[20] A variety of vitamin deficiencies may occur as a result of severe intestinal disease (Table 154-1). Deficiencies of B vitamins, especially cobalamin, and of some of the fat-soluble vitamins (E and K) are the most common and clinically important micronutrient deficiencies recognized in dogs and cats.[1,7,20] Little is known about deficiencies of microminerals; however, it is reasonable to assume that levels of copper, selenium, zinc, and others may be affected and deficiencies thus corrected by nutritional support.

CHAPTER 155

Nutritional Management of Hepatic Conditions

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The objectives of nutritional therapy in dogs and cats with liver disease are to provide optimal conditions for hepatic repair and regeneration and to prevent or manage complications of hepatic failure, such as hepatic encephalopathy. Hepatic healing and maintenance require a positive caloric balance and nitrogen intake with some consideration given to particular nutrients in certain types of hepatic disease.

CALORIES AND FEEDING FREQUENCY

The major consequences of malnutrition in any animal are decreased immunocompetence, decreased tissue synthesis and repair, and altered intermediary drug metabolism.[1] The foundation of adequate nutritional management of a dog or cat with hepatic disease is the provision of adequate calories. It is prudent first to provide for the total caloric need and then to consider the protein requirement. When sufficient calories are supplied as fat or carbohydrate, less endogenous or dietary protein is catabolized for energy, resulting in a decrease in the demand to metabolize nitrogen to urea. Enteral nutritional support is preferred to parenteral nutrient administration because it provides antigenic stimulation to the gut-associated lymphoid tissue (GALT) and stimulates secretion of IgA, which helps maintain an intact gut barrier to prevent bacterial translocation into the portal circulation. The method and quantity of food fed must be adjusted according to the animal's ability to handle metabolites. Small, frequent meals (three to six per day) help optimize blood flow through the liver, manage fasting blood glucose, and minimize episodes of hepatic encephalopathy. In the dog, blood glucose concentrations are maintained through glycogenolysis, which begins within 4 to 5 hours of the last meal. The liver exports glucose in order to maintain blood glucose concentrations. In a normal liver, blood glucose concentrations can be maintained through glycogenolysis for another 12 to 28 hours without food. A diseased liver with fewer functioning cells cannot store normal amounts of glycogen and adequately maintain blood glucose concentrations between meals. In the cat, blood glucose concentrations are maintained through gluconeogenesis from fat and protein stores because hepatic glycogen stores are normally minimal. Hepatic glycogen storage in cats is relatively small compared with dogs due to lower glycogen synthase and glucokinase activities. Nonprotein calories should come from highly digestible carbohydrate and fat sources. Most dogs and cats with liver disease can adequately digest and absorb dietary long chain fats; hence, fats should not be routinely restricted unless there is clinical evidence of steatorrhea.

PROTEIN QUANTITY AND QUALITY AND AMINO ACID PROFILE

Body protein content is not static, but rather is always in a flux between anabolism and catabolism. Protein degradation involves deamination of amino acids. The resulting carbon skeleton is oxidized for energy, and the amino group enters the urea cycle. Under normal metabolic circumstances, about 15% of the daily energy expenditure occurs through the oxidation of amino acids.[2] Protein intake should be balanced with calories consumed. Sufficient calories must be available from fat or glucose before amino acids are used for tissue synthesis and repair. Hence, every effort should be made to minimize protein catabolism in any animal with hepatic disease. Excessive protein feeding requires energy expenditure to rid the body of excess nitrogen, which may not be handled well by the liver and kidneys. Feeding excess nitrogen can result in azotemia or hyperammonemia and accompanying clinical signs of encephalopathy. Conversely, insufficient protein intake has been linked to a low serum albumin concentration, poor immune response, poor healing, and increased risk of dehiscence and muscle wasting. Hospitalized animals with hepatic disease receiving parenteral nutrition do well clinically with 3 to 5 g of protein per 100 kcal at resting energy requirements (RER). Therapeutic diets well tolerated by dogs contain 3 to 4 g/100 kcal, but feline diets should contain 6 to 7 g/100 kcal. Protein recommendations per 100 kcal of energy are not the same as per kilogram of body weight (BW). Administration of 5 to 6 g of protein on a BW basis delivers 40% more than on a per calorie basis and has resulted in encephalopathic signs in sensitive animals. The protein intake for a particular dog or cat should be adjusted according to the animal's ability to handle these initial protein recommendations.

VITAMINS, CARNITINE, AND CHOLINE

Water-soluble vitamins are coenzymes that are vital to optimal hepatic metabolism. Folic acid, thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, and B_{12} are essential for hepatic metabolism of glucose, fat, and protein. They are essential coenzymes in the Krebs cycle and for adenosine triphosphate (ATP) production and red blood cell metabolism. They are required in small amounts relative to other nutrients but are required daily and are not optional if tissue energy metabolism is to operate efficiently. These vitamins are easily and inexpensively replaced and should be included in all forms of nutritional support. Few dogs or cats require fat-soluble vitamin supplementation unless there is a history of prolonged weight loss, inappetence, and decreased fat absorption. Animals with long-standing liver disease may benefit from fat-soluble vitamin supplementation because vitamins A, D, and K are primarily stored in the liver. In these cases, it is much simpler and more cost-effective to administer 1 mL of a vitamin A, D, and E product* intramuscularly every 3 to 4 months.

*Vital E-A+D, containing 100 kIU vitamin A, 10 kIU vitamin D, and 300 IU alpha tocopherol per milliliter (Schering-Plough Animal Health Corp., Kenilworth, New Jersey).

Intramuscular or subcutaneous administration of vitamin K_1 (1 to 5 mg/kg body weight/day) may be required for several days.

Carnitine is an essential cofactor in mitochondrial transport of fatty acids and in subsequent long chain fatty acid beta-oxidation in all cells. Carnitine, residing in the mitochondrial intermembranous space, binds and transports fatty acyl-CoA into the mitochondrial matrix, where beta-oxidation takes place. Carnitine requirements are met by de novo hepatic synthesis using lysine and methionine, but carnitine is viewed as a conditionally essential nutrient when de novo synthesis is inadequate. There is no stated minimum carnitine concentration for pet foods. Beginning in 2002, carnitine supplementation of cat foods was allowed under the regulations of the Association of American Feed Control Officials (AAFCO) at levels not to exceed 1000 ppm on a dry matter basis (DMB).

Choline is an important methyl donor that is required for de novo synthesis of phosphatidyl choline, which is essential in the packaging of very low density lipoprotein (VLDL) in the liver and, therefore, hepatic exportation of triglycerides. A choline deficiency with concurrent lipolysis may slow VLDL export and promote hepatic lipid accumulation. In humans and rats, choline deficiency has been shown to result in triacylglyceride (TG) accumulation, depress VLDL synthesis, and cause liver dysfunction.[3] There is clearly a relationship between carnitine and choline. Tissue levels of carnitine are decreased in choline-deficient rats; conversely, adding choline to a choline-deficient diet has been shown to increase hepatic carnitine levels. Although there is evidence and a rationale for the importance of carnitine and choline as separate cofactors in hepatic lipid metabolism, a synergistic relationship may actually be the key. All complete and balanced cat foods should contain at least 60 mg choline/100 kcal, according to AAFCO regulations. Hepatic recovery diets should contain choline and carnitine, although the efficacy levels are not known.

ANTIOXIDANT SUPPLEMENTATION

There is evidence of free radical damage in certain types of liver disease. Two endogenous antioxidant systems exist to scavenge free radicals, a cytosolic system and a membrane-bound system, but they often require a nutritional cofactor. Adding antioxidants to the diet, although the exact effective dose is truly unknown, appears to be reasonable. These "antioxidant" nutrients are known to be part of the body's antioxidant system (directly and indirectly) and may ultimately help minimize the tissue damage. Antioxidant nutrients—vitamin A as beta carotene (5000 IU), vitamin C (250 to 1000 mg), vitamin E as alpha tocopherol (200 to 500 IU), zinc (7.5 mg), selenium (15 µg), copper (1 mg), and manganese (1.5 mg)—are reasonable daily dosages per os with food for a 10 to 30 lb dog or cat. Supplements carrying a United States Pharmacopeia (USP) label are recommended, and the product must be stored at refrigerator temperatures in a container protected from light.

A plethora of herbal remedies have been touted for hepatic patients; however, only two are currently worth consideration: S-adenosyl-L-methionine (SAMe) and milk thistle. Herbal remedies are not nutritional supplements. Taken orally, they should be viewed as compounds with pharmacologic properties.

NUTRITIONAL CONCERNS IN SPECIFIC HEPATIC CONDITIONS

Feline Hepatic Lipidosis

Hepatic lipidosis (HL), a well-recognized syndrome that occurs in several companion animal species, is characterized by the accumulation of triacylglycerides, which causes hepatic dysfunction and cholestasis. HL historically has been associated with anorectic, obese cats; however, cats with a normal or thin body condition also can be afflicted. Prolonged inappetence is the common denominator, often resulting from a stressful event or occurring secondary to another disease (e.g., diabetes, pancreatitis, cholangiohepatitis). The changes in liver metabolism that occur during HL are similar to those that occur during food deprivation. In the adaptation from the fed to the starved state, fuel usage by the animal shifts from primarily a mixture of fuels to one in which the primary fuel is fatty acids. In cats, lipolysis delivers fatty acids as triglycerides to the liver within hours of fasting because glycogen stores are normally small. The exact metabolic or biochemical aberration or aberrations responsible for the accumulation of fat in the liver during HL are not known. Protein deficiency, lipid oxidation abnormalities, and decreased VLDL exportation are under consideration.

Regardless of the biochemical derangement, it is clear from clinical responses that in feline hepatic lipidosis, adequate caloric and protein intake is the key to recovery. The provision of calories and protein in a complete and balanced formulation, delivered as small, frequent meals or as a continuous rate infusion (CRI), is the only known treatment. Overfeeding must be avoided. Hence, a balanced formulation sufficient to meet the cat's RER (20 kcal/lb BW) at its current weight is a safe starting food dose. However, grossly obese cats with a body condition score of 8/9 or 9/9 may be carrying 35% or more fat; these cats should not be fed at their current body weight, but rather at a lower, estimated optimal weight. If clinical signs of hepatic encephalopathy should begin with feeding, the food dose should be reduced by 50% until signs resolve. Serum phosphorus and potassium levels should be monitored daily during the first few days of refeeding to avoid a clinically relevant decrease caused by the intercellular electrolyte shift that occurs with refeeding. If electrolyte abnormalities occur, the feeding dose should be reduced by 50% and corrective fluid therapy must be instituted. If electrolyte abnormalities persist or become difficult to correct, measurement of and supplementation with magnesium should be considered.

Cats with HL appear to metabolize both enterally and parenterally administered lipids in the form of chylomicrons without exacerbation of clinical signs. The key to the hepatic derangement may lie in the differences between how various types of fat are metabolized in cats. When enteral feeding is not possible due to vomiting or encephalopathy, parenteral nutrition (PN) administration using fat, dextrose, and amino acids (4 g/100 kcal) is possible and should be instituted until a feeding tube can be placed. Fewer (1 g/100 kcal) or no amino acids may be required with hepatic encephalopathy (HE). Administration of a 20% lipid product* at RER through a peripheral catheter for 24 to 48 hours has worked well, as evidenced by improved hepatic serum profiles, when no better feeding alternative is possible. When a feeding tube of any type has been successfully placed, cats with small bowel atrophy due to prolonged anorexia (longer than 5 days) should be fed a monomeric diet with glutamine at RER for the first 24 to 48 hours.† Bolus feeding often can begin as three to six (30 ml) meals per day in a 4.5 kg cat. Initially, feeding via CRI (5 to 10 mL/hour) using a pump or gravity and a liquid product works very well for cats intolerant of bolus feedings and does not cause refeeding diarrhea.‡

*LipoSyn II (Abbott Laboratories, Abbott Park, Illinois); IntraLipid (Baxter Healthcare Corp., Deerfield, Illinois).

†Perative (Ross Products, a division of Abbott Laboratories); Peptamen (Baxter Healthcare Corp.).

‡Feline CliniCare (Ross Products).

In cats with HL, the plasma, liver, and skeletal muscle concentrations of carnitine are increased relative to normal cats.[4] Despite this generalized increase in synthesis, the overall carnitine levels attained are still inadequate to meet the body's demands when dietary intake is poor or nonexistent. When a cat is fed enterally, carnitine-supplemented cat foods should be fed to aid the animal's recovery. Choline, like carnitine, may become deficient in anorectic cats; however, the roles of dietary choline and carnitine in feline HL have not been investigated.

Cholangitis, Cholangiohepatitis, Hepatitis, and Cirrhosis

Nutritional strategies are intended to control the complications of hepatic failure. This goal is met by (1) reducing ammonia and ascites formation; (2) compensating for altered dietary lipid, essential fatty acid, and fat-soluble vitamin absorption; and (3) reversing hypoalbuminemia if present.[5] In the refeeding of an anorectic, catabolic animal, provision of calories above the resting energy expenditure, particularly as glucose, may result in metabolic and septic complications.[6] The liver plays a central role in blood glucose homeostasis through the processes of glycogenolysis and gluconeogenesis. Insulin resistance with subsequent glucose intolerance, as evidenced by hyperglycemia, hyperglucagonemia, and hyperinsulinemia, may develop in dogs or cats with liver disease.[7] Liver and, in some cases, muscle glycogen stores are depleted in chronic liver disease, leaving body fat as the main source of energy between meals. In comparison to a dog with normal liver function, glycogen stores may provide substrate only for 10 to 12 hours in a dog with cirrhosis. As a result of impaired glycogen stores, protein catabolism is accelerated.

There is no consensus regarding the level and sources of carbohydrate or fat calories appropriate for patients with compromised liver function. In theory, an adequate supply of highly digestible carbohydrate would reduce muscle and dietary protein catabolism for energy. Provision of at least 30% to 50% of dietary calories as highly digestible grain (cooked starch) is consistent with these metabolic changes. Dextrose should comprise 20% to 40% of the caloric admixture when a dog or cat is supported with PN. Animals with hepatobiliary disease may benefit from fermentable fiber sources. Dietary fiber enables nitrogen fixation by enteric bacteria, reduces the nitrogenous waste substances available for absorption, binds endotoxins and bile salts, and alters the colonic pH. Dietary soluble fiber can be incorporated into commercial diets using psyllium husk fiber (1 teaspoon per 5 to 10 kg of body weight).[8]

Dietary fats supply a dense form of calories, provide essential fatty acids, and aid in fat-soluble vitamin absorption. Fat is also a palatability enhancer to help inappetent animals. Appropriate dietary fat levels for most animals with hepatic disease range from 15% to 30% DMB. Complications of cholestasis can be associated with reduced excretion of bile salts, resulting in fat malabsorption and steatorrhea.[9] In these cases, dietary fat levels should be lowered. If necessary, an alternate fat source, such as medium chain triglycerides (MCT), could be considered. MCT is reported to be useful for malnourished people with cirrhosis and advanced cholestatic hepatic disease, but reports of clinical trials in animals are not yet available. Therapeutic diets containing MCT can be slowly worked into the diet, which is preferable to adding the oil to food directly. MCT oil alters the palatability of any diet, may result in food refusal, and does not contain essential fatty acids; hence MCT should not exceed 25% of the daily caloric requirement. The inflammatory component of hepatic disease, particularly that associated with hepatitis, may be attenuated by omega 3 (n-3) fatty acid supplementation. Although a specific dosage and the optimal ratio of omega 6 (n-6) to omega 3 fatty acids is not known, n-3 fatty acids have been shown to moderate various aspects of immune cell function. Several therapeutic veterinary diets formulated for the management of liver disease are n-3 enhanced.[10] When parenteral nutrition is necessary, lipid should comprise 60% to 80% of the calories in an admixture.

The liver processes both endogenous and exogenous amino acids; therefore altered protein metabolism may be the most clinically significant metabolic disturbance in an animal with hepatic disease. Increased protein catabolism occurs in early cirrhosis, and protein deficiency generally worsens with progression of liver disease. Addressing the protein needs of an animal with liver disease is a challenge, especially if the pet is critically ill or if signs of HE are apparent. In the absence of HE, protein should not be restricted because many animals with chronic hepatitis or advanced cirrhosis are catabolic and hypoalbuminemic, and most can tolerate standard enteral protein formulas.[11] Protein restriction and an increased branched chain to aromatic amino acid ratio should be limited to HE patients and those clinically unable to tolerate standard formulations.

Most therapeutic diets formulated for the management of dogs and cats with liver disease have a lower protein content (14% to 18% DMB) than the maintenance level (20% to 34% DMB). Recommendations on specific dietary protein concentrations have significant limitations. As the biologic value of a protein increases, less total protein is required to meet the amino acid requirements of the patient. In non-HE patients, a starting range for dietary protein would be 18% to 30% DMB. A more restricted protein level (8% to 15%, DMB) may be required for dogs exhibiting signs of HE postprandially. In all cases, protein ingredients of high biologic value (HBV) should be used so that the total nitrogen consumed may be minimized. Supplementation of the diet with HBV protein sources (e.g., cooked egg whites) provides essential amino acids while minimizing nitrogenous metabolites. It has been recommended that the proportion of branched chain amino acids (BCAA) to aromatic amino acids (AAA) be high in those diets. As liver disease progresses, the plasma concentration of BCAA decreases and AAA increases, because peripheral organs use BCAAs as a source of energy. There is increased cerebral uptake of AAAs, which may promote encephalopathy via synthesis of false neurotransmitters. To date, no data exist to suggest that BCAA formulations are superior to standard AAA formulations for animals with liver disease except when HE is present. Although dogs normally can synthesize sufficient amounts of taurine, in the case of severely compromised liver function, supplementation (250 to 500 mg/day) may be beneficial to choleresis. Additionally, taurine has some antioxidant action, which can help ameliorate the damage associated with excessive oxidative stress in liver disease.

Vitamin deficiency is common in chronic liver disease. The water-soluble B vitamins can be lost through vomiting or urinary losses or can become deficient as a result of anorexia, intestinal malabsorption, or decreased hepatic metabolism. High daily B vitamin intakes are recommended for patients with chronic forms of hepatic disease because excesses are excreted in the urine.* Nutrient malabsorption and the increased amounts of unconjugated bile salts associated with cirrhosis primarily alter absorption of fat-soluble vitamins, because absorption of vitamins A, D, E, and K depends on the availability of bile salts.

Gastrointestinal ulceration and hemorrhage associated with chronic hepatitis may result in iron (Fe) deficiency.

*B-Vitamin Complex, containing 50 mg thiamine, 2 mg riboflavin, 100 mg niacin, 2 mg pyridoxine, 10 mg pantothenic acid, and 0.4 ppm B_{12} per milliliter (Butler Co., Columbus, Ohio).

This deficiency can be addressed by altering dietary Fe concentrations or with oral supplementation or injectable Fe solutions. Supplementation should be approached with caution, because hemosiderosis is observed when liver disease has an inflammatory component; the hepatic Fe concentration should be assessed prior to supplementation. Diets supplying 80 to 140 ppm DMB of Fe should be adequate to meet daily Fe requirements. A zinc (Zn) deficiency results in abnormal ammonia metabolism, but diets containing more than 200 ppm DMB of Zn should be adequate. Diets can be supplemented with Zn gluconate (3 mg/kg body weight/day) or Zn sulfate (2 mg/kg body weight/day) divided into three doses. In cases of advanced hepatocellular damage with hypoalbuminemia and ascites, sodium restriction (0.01% to 0.25% DMB), with chloride at 1.5 times sodium, is recommended to help manage fluid balance and portal hypertension.

COPPER-ASSOCIATED HEPATOTOXICOSIS

Copper (Cu) storage disease impairs biliary excretion of Cu, resulting in signs of Cu toxicosis. The condition has been identified in the Bedlington terrier breed and is considered the canine counterpart of Wilson's disease in humans. These homozygous recessive individuals accumulate excessive amounts of Cu in the hepatocytes. If the condition is left untreated, the life expectancy is only 3 to 7 years.[12] With DNA technology, affected dogs can be identified and dietary changes can be initiated early in the disease process. The predominant feature is the progressive accumulation of Cu in hepatocytes, with hepatotoxicosis occurring at 2000 µg/g DMB. The time course can be as short as 8 to 12 weeks after birth, or Cu may accumulate for up to 1 year before clinical signs of toxicity become evident. Definitive diagnosis of Cu-associated hepatotoxicosis requires histochemical staining and quantitative assay of Cu in a liver biopsy sample.[13] Non-Bedlington terriers, cocker spaniels, and Doberman pinschers also can accumulate excess Cu in hepatocytes. Whether elevated hepatic Cu is the cause or consequence of the documented hepatitis and cirrhosis reported in these patients is not yet clear.

Copper-associated hepatotoxicosis is managed by feeding a low Cu diet and use of Cu-chelating agents. The AAFCO recommends 7.3 to 250 ppm DMB of Cu in both growth and maintenance canine foods. Therapeutic veterinary diets designed for liver patients contain 3 to 5 ppm DMB copper. Vitamin C and zinc supplementation are often used with copper hepatotoxicosis. Ascorbic acid augments urinary excretion of Cu and Zn and induces synthesis of intestinal metallothionein, which, because it has a much greater affinity for Cu than for Zn, binds excess dietary Cu. Elemental Zn can be supplemented in the acetate, sulfate, gluconate, or methionine forms. The recommended loading dose is 100 mg of elemental Zn per os given biweekly for 3 weeks, followed by a maintenance dose of 50 mg per os twice daily. Zn supplementation should be given between meals in a small amount of food to decrease the nausea and vomiting side effects.

CHAPTER 156

Nutritional Management of Endocrine Diseases

Kathryn E. Michel

With the exception of diabetes mellitus, the role of diet in the management of endocrine disorders of dogs and cats is largely uninvestigated. When abnormalities related to nutrient metabolism are seen, treatment of the primary endocrinopathy usually resolves the problem. Most of this chapter deals with the use of diet as a means of enhancing glycemic control in diabetics. A brief mention is made of dietary considerations in the management of endocrinopathy-associated hyperlipidemia and insulinomas.

DIABETES MELLITUS

With few exceptions, dietary management of diabetes mellitus in dogs and cats is done in conjunction with insulin or other pharmacologic treatment. Therefore it is important to stress that although appropriate dietary therapy can improve glycemic control, emphasis should be placed on adjustment of the insulin (or oral hypoglycemic) dosage and schedule and control of concurrent diseases. The objectives of dietary management of these animals are establishing and maintaining an optimal body weight, integrating feeding and insulin injection schedules, and optimizing glycemic control through diet composition. Beyond these goals, it is important to recognize that no single diet or dietary regimen fits all or even the majority of cases. To arrive at an appropriate dietary regimen, the practitioner must evaluate each dog or cat based on its body condition, on insulin therapy, and on whether coexisting diseases are a factor. Once a regimen is in place, it is critical that it be adhered to it as closely as possible, because alterations affect the efficacy of insulin therapy.

Body Condition

Obese dogs and cats can show insulin resistance that may resolve with weight loss.[1,2] In some cats with diabetes, the condition resolves naturally once loss of excess weight has been achieved. Many diabetic animals first have some form of medical crisis. Often, they have excess body fat but at the same time have also had some degree of muscle wasting. It is important that these animals be stabilized before any kind of caloric restriction for weight reduction is instituted. Many diabetic animals are underweight when first examined; after they have been stabilized, they should be fed a modest increase in calories to promote repletion.

Meal Timing and Diet Composition

The timing of meals is necessarily linked to the insulin dosage schedule. Ideally, the feeding timetable and the diet composition promote slow, steady absorption of nutrients from the gastrointestinal tract at times of peak insulin activity. Complex carbohydrates are generally absorbed in this fashion and should provide 50% to 60% of the calories in diets for canine diabetics. Soft, moist pet foods should be avoided, because they contain a high proportion of simple sugars.

Cats have evolved eating relatively little dietary carbohydrate. There are two major factors in which cats differ from more omnivorous species in their response to a carbohydrate-containing meal. The first is the lack of inhibition of hepatic gluconeogenesis. The activity of key gluconeogenic enzymes does not alter in the fed or fasted state, so that glucose will be synthesized from precursors, such as amino acids and glycerol, regardless of the extent of dietary carbohydrate intake. The second feature unique to feline carbohydrate metabolism is the lack of the enzyme glucokinase in both hepatic tissues and pancreatic islet cells. The maximal rate of this enzyme occurs when glucose concentrations are elevated; this facilitates the uptake and metabolism of glucose postprandially, both by serving as the "glucosensor" of the pancreatic beta cell for the release of insulin and by initiating the metabolism of glucose in the liver.

Some preliminary clinical trials have investigated the use of low-carbohydrate diets in diabetic cats.[3] The results have been encouraging, with the majority of cats responding with improved clinical signs, decreased insulin requirements (with some cats no longer requiring any insulin therapy at all), and improved serum glucose curves and fructosamine concentrations. One problem with interpreting the results of these investigations is the difficulty encountered in differentiating cats with insulin-dependent diabetes and those with transient disease. It may be that this type of dietary therapy is more or less indicated in a given cat, depending on the form of diabetes mellitus the animal has.

Increased dietary fiber has been recommended as an adjunct therapy for managing diabetes mellitus in dogs and cats. This recommendation was based largely on clinical studies involving humans, in whom fiber seems to aid in glycemic control by modulating glucose absorption from the gastrointestinal tract. There is a limited amount of experimental and clinical research involving dogs and one clinical trial in cats that suggest that high-fiber diets may aid in glycemic control in these species as well. Most of the data in human studies pointed to soluble fibers as being the effective fiber type for modulating glucose absorption. However, there is evidence that insoluble fibers are also effective in improving glycemic control in dogs with naturally occurring diabetes mellitus.[4] One published clinical trial investigating diabetic cats showed some benefits from feeding a diet that contained insoluble fiber over a low-fiber diet.[5] The diets also differed somewhat in protein and carbohydrate content (the fiber-containing diet was higher in protein and lower in carbohydrates). It is not entirely clear whether the improved glycemic control when cats consumed the fiber-containing diet was attributable to the fiber, the macronutrient makeup of the diet, or a combination of the two. Therefore currently there is no proven rationale for placing a nonobese diabetic cat on a commercial high-fiber diet.

It must be stressed that uniform caloric intake and normalization of body condition take precedence over the use of fiber-containing diets in the management of this disease. Many of the fiber-containing diets on the market today have been formulated as calorically restricted for the purpose of weight control and therefore would be contraindicated in an underweight or debilitated patient. In addition, "fiber" is a generic term, and one cannot simply expect any diet with additional fiber or even a specific category of fiber (e.g., insoluble, fermentable) to have the same physiologic effects a particular diet had in an investigation. Furthermore, increasing the amount of fiber in a diet generally decreases the digestibility and absorption of most nutrients. Many high-fiber diets are fortified with minerals and protein, but beyond the results of basic maintenance feeding trials conducted by the Association of American Feed Control Officials, data are lacking on the effects of these diets on nutrient availability. Caution should be used when supplementing a diet with fiber. If the diet contains marginal amounts of nutrients with respect to the nutritional requirements of the pet eating the diet, the addition of fiber may lead to deficiency of one or more nutrient.

Role of Ultra-Trace Elements

A brief mention should be made of the role of the ultra-trace elements chromium and vanadium in the management of canine and feline diabetes mellitus. Chromium appears to be involved in the maintenance of glucose tolerance. True dietary chromium deficiency has not been documented in companion animals. To date, clinical trials investigating whether pharmacologic amounts of chromium might improve glycemic control in diabetic dogs and cats are inconclusive.[6] Vanadium, when dosed in pharmacologic amounts, has insulin-like effects. Again, clinical trials in dogs and cats are lacking; however, vanadium has been documented to cause gastrointestinal side effects when administered orally, and chronic excessive intake may have toxic effects.[6] This element therefore should be used with caution.

HYPERLIPIDEMIA

A number of endocrinopathies can be associated with hyperlipidemia, including diabetes mellitus, hypothyroidism, and hyperadrenocorticism. Depending on the primary condition, hypertriglyceridemia, hypercholesterolemia, or both may be present. In general, therapy should be directed toward managing the underlying disease. Successful treatment often results in resolution of this condition. In some instances, dietary management can be used as an adjunctive therapy. The current diet should be evaluated, and if greater than 30% of the calories come from fat, a trial with a lower fat food should be considered.

INSULINOMA

Dietary therapy may aid in the management of the clinical signs that accompany an insulinoma. The goal is to minimize hypoglycemia by providing a highly digestible diet that contains low to moderate amounts of complex carbohydrates (as opposed to simple sugars and highly digestible starches) and to divide the daily feeding portion into three to six meals administered throughout the day. If signs of hypoglycemia do occur, the pet should be fed immediately and, if possible, foods or solutions containing simple carbohydrates should be avoided, because these may overstimulate the tumor and lead to another episode of hypoglycemia a short time later.

CHAPTER 157

Nutritional Modulation of Heart Disease

Lisa M. Freeman
John E. Rush

The goal of nutrition is no longer just to prevent deficiencies. It is now known that modification of diet can be an important part of medical therapy for heart disease. In the 1960s, the main nutritional recommendations for dogs with congestive heart failure (CHF) were to feed a low-sodium diet (for all stages of heart disease), to feed a restricted protein diet, and to provide supplemental B vitamins.[1] Few changes to these recommendations were made until the 1980s, when the question of how early to institute sodium restriction was raised and one of the first mentions of cardiac cachexia appeared in veterinary medicine.[2] It was also in the late 1980s that the discovery of the relationship between taurine deficiency and feline dilated cardiomyopathy (DCM) was published.[3] Now, research is beginning to show that nutrition may be able to modulate heart disease, either by slowing the progression, minimizing the number of medications required, improving quality of life or, in rare cases, actually curing the disease. There is potential for the use of diet as an important adjunct to medical therapy for animals with heart disease.

The main goals of diet therapy for heart disease are to maintain optimal body weight, to avoid nutritional deficiencies and excesses, and to take advantage of the potential benefits of pharmacologic doses of certain nutrients.

OPTIMAL WEIGHT MAINTENANCE

A key goal for the optimal management of heart disease is to maintain optimal body weight, because both obesity and weight loss can adversely affect health.

Obesity

Some patients with heart disease are overweight (i.e., over ideal body weight) or obese (i.e., more than 20% over ideal body weight). Endocrine disease, such as hypothyroidism and Cushing's disease, can be risk a factor for obesity and should be ruled out as an underlying cause; however, most obese animals simply suffer from overeating. Obesity has adverse effects on cardiac output, pulmonary function, neurohumoral activation, blood pressure, and heart rate in people and in experimental animal models, therefore it is likely to be similarly deleterious for companion animals with heart disease.[4] Owners often find that severely obese dogs and cats with cardiac disease that successfully lose weight appear less dyspneic and more active.

Successful weight reduction is a difficult and often unsuccessful endeavor. A careful dietary history is necessary to determine and control all sources of caloric intake as part of a successful weight loss program. Typically, the pet food is only one source of calories for the pet, and as many or more calories may be coming from treats and table food.[5] Additional sources of calories can be food intended for other household pets or food given by other people in the house, neighbors, or people delivering mail or packages. Because diets that are marketed as being reduced calorie vary tremendously in their caloric density, it is important to recommend a specific pet food and amount based on caloric requirements for weight loss, rather than making the general recommendation to switch to a "reduced calorie" pet food. Also, veterinarians should recommend a specific type and number of treats that can be fed to avoid overindulgence. Nonstarchy vegetables (fresh, frozen, or canned forms labeled "no salt added") are excellent, low-calorie treats for dogs that are obese and have heart disease. The practitioner should recheck the animal's body weight after 2 weeks on the diet, and if the animal is not losing weight, the owner should be questioned to find other potential sources of calories. If compliance appears to be good, the amount of food should be reduced further. The animal should be weighed every 2 weeks until consistent weight loss is achieved (1% to 2% per week) and then once monthly until the goal weight is achieved.

Cachexia

Cardiac cachexia is the muscle wasting commonly seen in patients with CHF. In one study of dogs with DCM, more than 50% of patients had some degree of cachexia.[6] The weight loss that occurs in animals with CHF is unlike that seen in a healthy dog or cat that loses weight. In a healthy animal receiving insufficient calories to meet requirements, metabolic adaptations allow fat to be used as the primary fuel source, thus preserving lean body mass. Conversely, the primary fuel source in animals with an acute or chronic disease, including heart disease, is amino acids from muscle, therefore these animals quickly catabolize muscle and lean body mass. Thus the distinguishing feature of cachexia is a loss of lean body mass, which has direct and deleterious effects on strength, immune function, and survival.[7] Cachexia is often mistakenly viewed as an end-stage syndrome manifested by an emaciated dog or cat. In fact, cachexia is a slowly progressive process of muscle loss that can be very subtle initially and can even occur in an obese animal. Recognizing the process of cachexia at an early stage may provide better opportunities to manage it effectively.

The loss of lean body mass in cardiac cachexia is a multifactorial process caused by anorexia, increased energy requirements, and metabolic alterations.[7] The anorexia may be secondary to fatigue or dyspnea or may be due to medication toxicity or feeding of an unpalatable diet.[7] Anorexia is present in 34% to 75% of dogs with heart disease.[5,8] However, increased production of inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukin-1 (IL-1), is the primary mediator of cachexia.[7] These inflammatory cytokines are known to directly cause anorexia, to increase energy requirements, and to increase the catabolism of lean body mass. Of particular pertinence to heart disease, TNF and IL-1 also cause cardiac myocyte hypertrophy and fibrosis and have negative inotropic effects.

Cardiac cachexia is typically recognized only after CHF has developed. It is more common in dogs than in cats and is most often seen in DCM or right-sided heart failure. Loss of lean body mass is most readily evident in the epaxial, gluteal,

scapular, or temporal muscles. Nutritional considerations for cardiac cachexia should include management of anorexia, if present. Nutritional modulation of cytokine production also may be helpful. One method of decreasing the production and effects of cytokines is omega 3 (n-3) polyunsaturated fatty acid supplementation (see below). Supplementation of fish oil, which is high in n-3 fatty acids, can decrease cytokine production in dogs with CHF and improve cachexia.[6] In some but not all dogs with CHF-induced anorexia, fish oil supplementation can improve food intake.[6] In addition, reduction of cytokines has been correlated with survival in dogs with CHF.[6]

MODULATION OF SPECIFIC NUTRIENTS

Nutritional deficiencies once were a common cause of cardiac disease in people and probably animals. In cats, taurine deficiency was a common cause of heart disease until as recently as the late 1980s. Identifiable nutritional deficiencies are now uncommon in dogs and cats but still could play a role in the etiology of some heart diseases. Nutritional deficiencies also may develop secondary to the disease or its treatment. A new area of nutritional research is that of nutritional pharmacology, the concept that supplementation of certain nutrients may provide benefits above and beyond their known nutritional effects. Therefore modulation of various nutrients by reducing or increasing their intake (either a small amount or to pharmacologic levels) may be recommended for animals with heart disease.

Protein and Taurine

Protein

In the 1960s authors recommended a restricted protein intake for dogs with CHF to prevent "metabolic stress" on the kidneys and liver.[1] There is no evidence that protein restriction is necessary for dogs and cats with CHF and, in fact, it probably is deleterious, because these patients are predisposed to loss of lean body mass. Many of the diets designed for dogs with cardiac disease are low in protein (3.6 to 4.2 g/100 kcal), and protein-restricted diets designed for renal disease are often recommended for animals with heart disease. Unless severe renal dysfunction is present (i.e., serum creatinine >3.0 g/dL), high-quality protein should be fed to meet canine (5.1 g/100 kcal) and feline (6.5 g/100 kcal) minimum levels according to Association of American Feed Control Officials (AAFCO).[9]

Taurine

Taurine is an amino acid found in high levels in the myocardium. Despite our knowledge of the role of taurine deficiency in feline DCM, a small number of cats still develop DCM.[3] Most current cases of feline DCM do not involve taurine deficiency, but it should be suspected in all cases of this disorder. A dietary history should be elicited from owners to determine whether the cat has been fed a poor quality, homemade, vegetarian, or otherwise unbalanced diet. Plasma and whole blood taurine levels should be measured, and treatment with taurine (125 to 250 mg given orally twice a day) should begin concurrently with medical therapy. If the taurine concentration is found to be normal, taurine supplementation can be discontinued.

Unlike cats, dogs are able to synthesize adequate amounts of taurine, which is not considered a requirement for canine diets. Most dogs with DCM do not have taurine deficiency, but low taurine concentrations have been found in some dogs with the disorder, particularly breeds in which DCM is not a common disease.[10] The most common breeds in which DCM has been reported to be associated with taurine deficiency are the American cocker spaniel, golden retriever, Labrador retriever, Newfoundland, Dalmatian, and English bulldog.[10-12] In one small study, cocker spaniels supplemented with taurine and carnitine showed clinical and echocardiographic improvement.[13] It is not known whether the response would be similar with either taurine or carnitine alone.

Taurine deficiency in dogs may be related to dietary factors, because it is thought to be more common in dogs eating high-fiber or certain lamb meal and rice-based diets. Taurine deficiency also may be the result of increased renal or fecal loss of taurine or other metabolic defects present in certain breeds. In a study of Portuguese water dog puppies, plasma taurine was low in all puppies tested, and DCM was diagnosed in eight of nine puppies.[14] Taurine supplementation was instituted in six of the puppies, and this significantly increased both circulating taurine concentrations and cardiac function.[14] A recent study showed that a low-taurine, very low protein diet fed to beagles for 48 months caused decreased whole blood taurine concentrations, and DCM developed in one of 16 dogs.[15]

In the authors' experience, although some dogs of atypical breeds with DCM have low circulating taurine concentrations, not all of them respond to taurine supplementation. In one small retrospective study, dogs that were taurine deficient and supplemented with taurine (with or without carnitine) did not show a significantly different response from that of dogs with DCM that were not taurine deficient and were not supplemented with taurine.[11] Dogs with DCM and taurine deficiency that respond to taurine supplementation generally do not have as dramatic a response as do taurine-deficient cats with DCM. Nonetheless, measurement of plasma and whole blood taurine concentrations is warranted in cocker spaniels and some other breeds of dogs with DCM. Supplementation with taurine (500 mg give orally two or three times a day), with or without carnitine (1 g given orally two or three times a day), is recommended in dogs with documented taurine deficiency. Some of the potential benefits of taurine in dogs with DCM may be due to the amino acid's positive inotropic effects or to its role in calcium regulation in the myocardium.

The AAFCO minimum for taurine for adult cats is 25 mg/100 kcal for dry food and 50 mg/100 kcal for canned foods.[9] Because taurine is a nonessential nutrient in dogs (i.e., it is not thought to be required in the diet), no minimum level has been established for commercial dog foods. The dietary taurine content of commercial dog foods, based on manufacturers' information, varies widely (less than 5 to over 50 mg taurine/100 kcal). To achieve a dose of 500 mg every 12 hours for a 40 kg dog (although this has not been determined to be the *optimal* dose of taurine for a dog with DCM), a diet would have to contain approximately 50 mg/100 kcal of taurine.

Fat

Fat provides calories and increases the palatability of pet foods, but it also can significantly affect immunologic, inflammatory, and hemodynamic parameters. The n-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are long chain fatty acids in which the first double bond is at the position of the third carbon from the methyl end (in the omega 6 [n-6] polyunsaturated fatty acids [i.e., linoleic, gamma linolenic, and arachidonic acids], the first double bond is at the sixth carbon). This minor chemical difference gives a different structure and characteristics to the fatty acid. Plasma membranes normally contain very low concentrations of n-3 fatty acids, but levels can be increased by a food or supplement enriched with n-3 fatty acids. Dogs with CHF have been shown to have plasma fatty acid abnormalities, including decreased concentrations of EPA and DHA, compared to normal dogs.[6,16] In one study of dogs with DCM and CHF, fish oil supplementation normalized these plasma fatty acid abnormalities.[6]

Another potential benefit of n-3 fatty acid supplementation is that breakdown products of the n-3 fatty acids (series 3 and 5 eicosanoids) are generally less potent inflammatory mediators than eicosanoids derived from n-6 fatty acids (series 2 and 4 eicosanoids). This decreases the production of cytokines and other inflammatory mediators, which may reduce cachexia.[6] The authors currently recommend a dosage of 40 mg/kg EPA and 25 mg/kg DHA for dogs and cats with anorexia or cachexia. With the exception of a few specially designed therapeutic diets, commercial diets do not achieve this level of n-3 fatty acids, therefore supplementation is usually necessary. Because the amount of EPA and DHA in individual fish oil supplements varies widely, it is important to know the exact amount in the brand of supplement recommended. The most common formulation of fish oil, however, is 1 gram capsules that contain approximately 180 mg EPA and 120 mg DHA; these can be purchased over the counter at most human pharmacies or health food stores. At this concentration, fish oil can be administered at a dose of 1 capsule per 10 pounds of body weight to achieve the authors' recommended EPA and DHA dosage. Fish oil with higher concentrations of EPA and DHA can be obtained from medical supply catalogs and may be more feasible for large dogs. Fish oil supplements should always contain vitamin E as an antioxidant, but other nutrients should not be included to avoid toxicities. Cod liver oil and flax seed oil should not be used as sources of n-3 fatty acids.

Minerals

Sodium

Even before clinical signs become apparent in cardiac disease, the renin-angiotensin-aldosterone (RAA) system is activated and sodium excretion is reduced. Based on this knowledge, authors in the 1960s and 1970s recommended changing to a severely sodium-restricted diet when a heart murmur was first detected, even before clinical signs were present. However, dietary sodium restriction can further activate the RAA system, therefore it is not clear whether sodium restriction in early heart disease is beneficial or harmful.[17] A study of low-sodium diets in dogs with CHF showed that measures of cardiac size decreased significantly on a low-sodium diet compared with a moderate-sodium diet, especially in dogs with chronic valvular disease, but the effect of low-sodium diets on survival was not studied.[16]

The optimal time to institute sodium restriction and the degree of sodium restriction is not known, but severe sodium restriction (i.e., near the AAFCO minimum of 20 mg/100 kcal for dogs and 50 mg/100 kcal for cats) is not currently recommended for early heart disease. For an animal with heart disease without CHF (e.g., a dog with chronic valvular disease with no clinical signs or an asymptomatic cat with hypertrophic cardiomyopathy), the authors recommend that the animal be fed a mildly sodium-restricted diet (i.e., sodium content less than 100 mg/100 kcal) and that the owner be instructed to avoid giving the pet high-sodium treats or table food. Most owners are unaware of the sodium content of pet foods and human foods and need very specific instructions regarding appropriate foods and acceptable low-salt treats (Table 157-1). When CHF first arises, additional sodium restriction is recommended (i.e., less than 80 mg sodium/100 kcal). This can be achieved with a therapeutic diet designed for animals with early heart disease or with some diets designed for use in older dogs.

If a diet designed for senior dogs is used, the characteristics of the individual product must be examined. There is no legal definition for a senior diet, therefore the levels of calories, protein, sodium, and other nutrients can vary dramatically. Diets designed for animals with renal disease are not recommended for most cardiac patients because of the protein restriction (unless severe renal dysfunction is present). As CHF becomes more severe, more sodium restriction may allow lower dosages of diuretics to be used to control clinical signs. To achieve severe sodium restriction, it is usually necessary to feed a commercial therapeutic diet designed for cardiac patients. Typically, these diets are severely restricted in both sodium and chloride; levels of other nutrients vary with the individual product.

Table 157-1

Examples of Low-Sodium Treats*

PRODUCT	kcal/Sodium (treat)/(mg/treat)
Dog Treats	
Science Diet Senior Treats (medium)	20/13
Milk-Bone Super Premium Chicken Meal & Rice Flavored Biscuits	10/10
Iams Original Formula Biscuits (small)	22/10
Hill's Prescription Diet Canine Treats	13/5
Stewart Fiber Formula Dog Biscuits (medium)	25/5
Baby carrots	4/4
Alpo Healthy Snacks Variety Snaps with Real Meat	13/6
Apple (raw, 1 slice) or orange (1 section)	10/0
Cat Treats	
Essentials Brand Overall Health for Cats	2/3
Purina Whisker Lickin's Crunchy Cat Treats— Tartar Control (all flavors)	2/2
Stewart Fiber Formula Cat Treats	1/1
Treats to Avoid	
Baby food; pickled foods; bread; pizza; condiments (e.g., ketchup, soy sauce); lunch meats and cold cuts (e.g., ham, corned beef, salami, sausages, bacon, hot dogs); most cheeses, including "squirtable" cheeses (unless specifically labeled as low sodium); processed foods (e.g., potato mixes, rice mixes, macaroni and cheese); canned vegetables (unless labeled as no salt added); snack foods (e.g., potato chips, packaged popcorn, crackers); soups (unless homemade without salt); and most other pet treats.	

*Even low-sodium treats, if fed in large quantities, can provide a large dose of sodium (this especially can be a problem in cats or small dogs).

Potassium

Hypokalemia causes muscle weakness, predisposes patients to digitalis toxicity, and potentiates arrhythmogenesis. In addition, Class I antiarrhythmic drugs (e.g., procainamide, quinidine) are relatively ineffective in the face of hypokalemia. Hypokalemia can be precipitated by the use of loop diuretics (e.g., furosemide), thiazide diuretics (e.g., hydrochlorothiazide), or by inadequate dietary intake (often associated with anorexia). In the past, when the mainstays of therapy were diuretics and digoxin, hypokalemia was recognized as a significant problem in people and dogs with CHF.

Angiotensin-converting enzyme (ACE) inhibitor therapy has gained widespread use in the management of dogs with CHF, and this class of drug results in renal potassium sparing. ACE inhibitors cause an increase in serum potassium, and some animals develop hyperkalemia. Spironolactone, now used

in some dogs and cats with heart disease, is an aldosterone antagonist and a potassium-sparing diuretic. Animals receiving ACE inhibitors and/or spironolactone can develop hyperkalemia, particularly if they eat a diet that contains high levels of potassium. Because some commercial cardiac diets contain higher potassium concentrations to counteract the theoretical potassium loss due to diuretics, these diets can contribute to hyperkalemia.

Commercial diets vary widely in potassium concentrations. Commercial reduced-sodium diets for dogs can have 143 to 381 mg potassium/100 kcal (the AAFCO minimum is 170 mg/100 kcal).[9] Commercial feline reduced-sodium diets can have 152 to 362 mg potassium/100 kcal (AAFCO minimum of 150 mg/100 kcal).[9] If hyperkalemia is present in a dog or cat with heart disease, a diet with a lower potassium content should be selected. Conversely, if an animal is hypokalemic, a diet higher in potassium may be indicated, or oral potassium supplementation may be instituted.

Magnesium

Magnesium plays an important role in normal cardiac function. Alterations in magnesium homeostasis can occur in people and dogs and can have deleterious effects in a variety of cardiovascular conditions, including hypertension, coronary artery disease, congestive heart failure, and cardiac arrhythmias. Some cardiac drugs, including digoxin and loop diuretics, are associated with magnesium depletion. Therefore animals with heart failure receiving these medications have the potential to develop hypomagnesemia. Hypomagnesemia can increase the risk of arrhythmias, decrease cardiac contractility, cause muscle weakness, and contribute to renal potassium loss and can potentiate the adverse effects of certain cardiac medications. Hypomagnesemia has not been a consistent finding in studies of animals with heart disease, but this may be because serum magnesium concentrations are a poor indicator of total body stores.[16,18,19] Therefore a normal serum magnesium level does not necessarily mean there are adequate total body stores. We currently recommend routine measurements of serum magnesium, especially in animals with arrhythmias or those on large doses of diuretics.

As with potassium, magnesium concentrations vary widely in commercial pet foods. Commercial reduced-sodium diets for dogs can have 9 to 40 mg magnesium/100 kcal (AAFCO minimum of 10 mg/100 kcal).[9] Commercial feline reduced-sodium diets can have 8 to 69 mg magnesium/100 kcal (AAFCO minimum of 10 mg/100 kcal).[9] A diet high in magnesium would be indicated for an animal with a low serum magnesium concentration. In some animals with low serum magnesium concentrations, diet adjustment alone does not correct the problem, and oral supplementation is required.

Vitamins

B Vitamins

Thiamine deficiency is known to be a cause of cardiomyopathy in humans, but there has been little investigation into the role of B vitamin deficiency as a cause of heart disease in dogs and cats. Anorexia and urinary loss of water-soluble vitamins can contribute to low B vitamin concentrations in patients with heart failure. Thiamine has been the B vitamin studied in greatest detail. In one study, more than 90% of people with CHF had low thiamine concentrations.[20] As with other nutrients, such as potassium, B vitamin deficiencies may have been much more common when furosemide was the primary means of therapy for patients with CHF. Recent research has shown that vitamin B_{12}, but not vitamin B_6 or folate, was significantly lower in cats with cardiomyopathy than in healthy controls, an effect that was unrelated to diet or furosemide use.[21] Based on information from other species, however, animals with cardiac disease (at least those receiving diuretics) may have higher B vitamin requirements. Most commercial cardiac diets have increased amounts of water-soluble vitamins to offset urinary losses, therefore supplementation usually is not required.

Other Nutrients

Carnitine

L-carnitine is concentrated in skeletal and cardiac muscle and is critical for fatty acid metabolism and energy production. Carnitine deficiency has been associated with primary myocardial disease in a number of species, including a family of boxer dogs.[22] Anecdotal reports exist regarding the efficacy of carnitine in canine DCM, but no blinded prospective studies have been done, therefore a causative role has not been established. Even if carnitine deficiency is not the inciting cause of DCM, carnitine supplementation could be beneficial by improving myocardial energy production. In human DCM patients, most studies of carnitine have not been well controlled. However, one randomized, double-blind, placebo-controlled study showed improved 3-year survival in human DCM patients receiving 2 g/day of carnitine.[23] It is not yet clear whether the carnitine deficiency seen in some dogs with DCM is the cause of the disease or occurs secondary to the development of CHF. A study of rapid pacing–induced heart failure in dogs showed that myocardial concentrations decreased in normal dogs after the onset of CHF.[24] Carnitine supplementation has few side effects, but the high cost is a deterrent for some owners. We currently offer the option of carnitine supplementation (50 to 100 mg/kg given orally every 8 hours) to owners of dogs with DCM.

Antioxidants

Much attention has been given to antioxidants for their potential role in the prevention and treatment of human cardiac diseases. Reactive oxygen species are a by-product of oxygen metabolism, for which the body normally compensates through the production of endogenous antioxidants. An imbalance between oxidant production and antioxidant protection, however, could increase the risk of heart disease. Antioxidants are produced endogenously but also can be supplied exogenously. The major antioxidants include enzymatic antioxidants (e.g., superoxide dismutase, catalase, glutathione peroxidase) and oxidant quenchers (e.g., vitamin C, vitamin E, glutathione, and beta carotene). Most of the research in human cardiology has been done on coronary artery disease; however, in dogs with DCM and CHF, oxidative stress increases and vitamin E concentrations decrease with more severe disease.[25] Additional research is required, but antioxidant supplementation may hold promise as a component of therapy for animals with heart disease.

Coenzyme Q10

Coenzyme Q10, like carnitine, is a cofactor in a number of reactions required for energy production; however, it also is an antioxidant. Although coenzyme Q10 supplementation has anecdotally been reported to be beneficial, controlled prospective studies are necessary to judge the efficacy of this product accurately. Most human studies of coenzyme Q10 supplementation have not been well controlled, and the results are conflicting. One study of experimentally induced CHF in dogs showed that serum coenzyme Q10 levels were not reduced in dogs with CHF.[26] Coenzyme Q10 supplementation increased serum, but not myocardial, concentrations in one canine study.[26] The current recommended dose in dogs is 30 mg given orally twice a day, although a dose of up to 90 mg given orally twice a day has been recommended for large dogs. Possible reasons for the purported benefits of supplementation include correction of a deficiency, improved myocardial metabolic efficiency, or increased antioxidant protection.

PRACTICAL ASPECTS OF FEEDING THE PATIENT WITH HEART DISEASE

There is no single "best" diet for managing heart disease. It is important to match the nutritional needs of an individual patient to the diet or diets that best suit those needs. Patients with heart disease vary in terms of clinical signs, laboratory parameters, and food preferences, all of which affect diet selection. For example, animals with asymptomatic heart disease require less severe sodium restriction than animals with CHF. Dogs with cardiac cachexia require a calorically dense diet, whereas an overweight dog should be fed a calorically restricted diet. Concurrent diseases also influence diet choice and, in one study, were present in approximately two thirds of dogs with heart disease.[5] For example, a cat with hypertrophic cardiomyopathy and a history of struvite urolithiasis would need a diet that is both sodium restricted and also nutritionally modified to reduce the risk of struvite urolith formation. Laboratory results, such as the presence of hypokalemia or hyperkalemia, also can alter diet selection.

Based on these and other patient parameters, diets can be matched to the individual patient. A number of commercial veterinary diets are specifically designed for animals with cardiac disease. The specific characteristics of these foods vary, but they are moderately to severely sodium restricted and generally have increased levels of B vitamins. Some cardiac diets may also have increased levels of taurine, carnitine, antioxidants, or n-3 fatty acids. Above all, the diet must be palatable enough that the animal eats it willingly. The authors typically determine several diets that would be appropriate for an individual animal, and these diets then are offered as choices for the owner and the pet. Having dietary choices is particularly beneficial for owners of more severely affected patients, because a cyclic or selective loss of appetite is common in these pets. All diet recommendations should include a discussion of treats, table food, and foods used for medication administration.

As mentioned earlier, anorexia is a common problem in animals with heart disease and can contribute to the syndrome of cachexia. Another important problem with anorexia is that it may affect survival by influencing an owner's decision to euthanize the pet. In one study of owners of dogs euthanized for CHF, anorexia was one of the most common contributing factors to the euthanasia decision.[8] Anorexia becomes more common as the heart disease becomes more advanced. Recommendations for managing anorexia are listed in Box 157-1.

A note of caution: For animals with an acute episode of CHF, the diet should not be changed until the patient's condition has been stabilized. Once the animal is home and has been stabilized on medications, a gradual change to a new diet can be made. Forced dietary changes when the animal is sick or starting new medications may induce food aversions.

In many cases, the desired nutrient modifications can be achieved through diet alone. However, supplementation of certain nutrients may be warranted if these nutrients are not included in a particular diet or if they are not present at high enough levels to achieve the desired effect. It is important to be aware that dietary supplements do not require proof of safety, efficacy, or quality control to be marketed. Therefore careful selection of type, dose, and brand is important to avoid toxicities or complete lack of efficacy. Recently, the United States Pharmacopeia (USP) established the Dietary Supplement Verification Program (DSVP) for human dietary supplements. Supplements with the DSVP certification mark on the label have been tested and verified by the USP for their ingredients, the finished product, and the manufacturing process. This voluntary program helps ensure the safety and quality of dietary supplements, but it does not test the overall safety of use of the product or of health claims made for it.

Box • 157-1

Keys to Managing Anorexia in Patients with Cardiac Disease

- Assess the patient for optimal medical control of heart failure.
- Assess the patient for side effects of medications (e.g., digoxin toxicity or azotemia).
- Feed more frequent but smaller meals.
- Warm the food to body temperature.
- Gradually introduce a more palatable diet (e.g., switch from a dry food to a canned food, change to a different brand, or have a nutritionist formulate a balanced homemade diet).
- Use flavor enhancers, such as cooked meat or fish or low-sodium tuna juice for cats, and cooked meat or sweeteners (e.g., yogurt, maple syrup, or honey) for dogs.
- Administer fish oil supplements if the diet does not contain high concentrations of omega-3 fatty acids.

Much additional information is needed to define the role of dietary supplements in heart disease, when they should be used, when they should not be used, and optimal dosages.

In addition to finding a diet that has the desired nutritional properties and palatability, the practitioner must construct an overall dietary plan that meets the owner's expectations. This involves finding a diet that the owner perceives the pet to enjoy, providing information about acceptable treats, and devising a satisfactory method of administering medications. In one study, more than 90% of dogs with heart disease received treats, and these are often high in sodium.[5] In addition, the majority of people who administer medications to their dogs use food as a means of achieving this (Box 157-2). To ensure success with nutritional modification, it is important to include information on how best to use food for this purpose in the overall diet plan.

Box • 157-2

Methods for Administering Medication to Dogs and Cats

1. Teach the owner to pill the animal without using foods.
2. Use a Pet Piller or Pet Pill Gun (Jorgensen Laboratories, Loveland, CO).
3. Use a compounded, flavored liquid medication instead of a pill (remember that compounding may alter the pharmacokinetics of a drug).

Caution: Always determine the sodium content of a compounded product.

4. Insert medications into appropriate foods, such as the following:
   - Fruit (e.g., grapes, banana, orange, melon)
   - Low-sodium cheese
   - Low-sodium canned pet food
   - Peanut butter (labeled as "no salt added")
   - Home-cooked meat (without salt); not lunch meats
5. Insert medication into a Canine Veterinary Tab Pocket (Waltham, Vernon, CA)

CHAPTER 158

Nutritional Management of Urinary Tract Conditions

India F. Lane

Dietary modifications can be used in managing urinary tract disease to influence excretory needs, acid-base status, fluid and electrolyte balance, and urine composition. Nutritional principles are described for acute and chronic renal failure, proteinuric renal disease, urolithiasis, and idiopathic feline lower urinary tract disease.

CHRONIC RENAL FAILURE

Chronic renal failure (CRF) is characterized by a progressive decline in renal function from renal insufficiency to azotemic renal failure to uremia to death or euthanasia.[1,2] Because diet can affect many consequences of renal failure, nutritional modification is a cornerstone of management. The most common derangements that occur with CRF include decreased ability to excrete nitrogenous wastes, phosphorus, and sodium; increased loss of potassium, and development of metabolic acidosis. Secondary hyperparathyroidism, systemic hypertension, and nonregenerative anemia are additional consequences of CRF. Dietary manipulation is designed to minimize protein precursors for urea and to minimize hyperphosphatemia and acid by-products; to provide an alkalinizing effect; and to supply adequate potassium while providing adequate calories to prevent further catabolism or malnutrition[1-3] (Table 158-1 and Chapter 260). The addition of soluble fiber to these diets has been recommended in an effort to provide fermentable substrate for bacteria in the large intestine. This may enhance both urea delivery and incorporation of ammonia generated into bacterial protein excreted in feces (nitrogen trapping).[4]

Dietary strategies also may help modulate progressive renal injury. In models of induced renal failure in dogs[5] and cats,[6] phosphorus intake has been linked to mortality, with increased mortality in animals consuming diets high in phosphorus. Phosphorus restriction appears to slow renal tubulointerstitial lesions, minimize secondary hyperparathyroidism and renal mineralization, and reduce development of hyperlipidemia.[1]

The influence of protein restriction is less clear, because an increased protein intake has not consistently hastened progression of renal failure in dogs or cats with induced renal dysfunction.[7] However, protein restriction decreases the nitrogenous solutes, phosphorus, and acid by-products that failing kidneys must handle. Protein restriction, therefore, is a feature of low-phosphorus diets designed for animals with moderate renal failure.

Modulation of dietary lipids may also be beneficial in slowing progressive renal failure. In dogs with induced renal insufficiency, supplementation of menhaden fish oil, which is high in omega 3 polyunsaturated fatty acids, resulted in reduced intraglomerular pressure, reduced proteinuria, and a slightly improved glomerular filtration rate (GFR) over a 20-week period. Dogs supplemented with safflower oil, which is high in omega 6 fatty acids, had progressive loss of

Table 158-1

Dietary Modifications Recommended in the Treatment of Urinary Diseases in Dogs and Cats

DISORDER	DIETARY RECOMMENDATIONS
Chronic renal failure	Reduced phosphorus Reduced protein Nonacidifying Potassium replete Reduced sodium Omega 3 fatty acid supplemented (dogs) +/– Increased soluble fiber
Proteinuric renal disease	Reduced protein Reduced sodium Omega 3 fatty acid supplemented (Additional modifications as above if animal is azotemic/uremic)
Struvite urolithiasis	Acidifying Increased moisture content (or induced diuresis) Reduced magnesium Reduced phosphorus Reduced protein
Calcium oxalate urolithiasis	Nonacidifying Reduced protein Adequate magnesium Adequate phosphorus Increased moisture content (or induced diuresis) Increased fiber (hypercalcemic cats)
Urate urolithiasis	Reduced protein (purines) Alkalinizing
Cystine urolithiasis	Reduced protein Reduced sodium Alkalinizing
Idiopathic lower urinary tract disease	Increased moisture Modifications as for struvite urolithiasis (if associated with struvite crystalluria)

Modified from Brown SA et al: Dietary considerations for urinary diseases. *In* Ettinger SJ, Feldman E (eds): *Textbook of Veterinary Internal Medicine*, 5th ed. Philadelphia, WB Saunders, p 269.

renal function.[8] In another group of dogs with naturally ocurring chronic renal failure, however, the measured GFR *increased* during a 6-week period in those dogs fed safflower oil.[9]

Dietary strategies may also be directed at other factors that may contribute to the progression of renal failure, including systemic hypertension, hyperparathyroidism, and renal ammoniagenesis (exacerbated by metabolic acidosis).

Studies of specific dietary components fed to dogs and cats with experimentally induced renal insufficiency have demonstrated the potential benefits of dietary modification. Recently, the overall benefit of "renal diets" has been investigated in cats and dogs with naturally occurring renal failure.[10-12] In a prospective study of cats with stable, azotemic chronic renal failure, feeding a canned renal failure diet resulted in significant reductions in plasma urea and phosphorus while prolonging survival times (median, 633 days) compared with cats that ate other diets (median, 264 days).[10] Unfortunately, diet groups were not randomized because they were determined by cat and owner preference. Consequently, cats with more advanced or complicated disease (potentially more selective about food) may have been more heavily represented in the non-renal failure diet group. Despite this limitation, the dramatic difference in survival times between the two groups supports the hypothesis regarding influence of diet on longevity.[10]

In a similar study, cats that ate low-protein/low-phosphorus diets had lower serum phosphorus concentrations and parathyroid hormone measurements than cats that ate other diets.[11] In a prospective, double-blind study of dogs with chronic renal failure, those fed a renal failure diet had delayed development of uremic crisis and a decrease in renal-related deaths as compared with dogs fed a diet formulated to mimic commercial adult maintenance diets.[12] In this study, other treatments were allowed as clinically necessary, such as phosphate-binding agents, potassium supplementation, and antihypertensive agents. Modification of the diet is recommended as soon as renal failure is detected.

ACUTE RENAL FAILURE

In acute renal failure (ARF), decline in renal function takes place over just a few days, limiting adaptability to loss of excretory function. In addition, insulin resistance, severe acidosis, release of stress hormones, and other metabolic derangements lead to a marked hypercatabolic state.[13] Optimal nutritional support in animals with ARF may minimize additional catabolism and azotemia, maximize chances for renal tissue repair, increase immunity against infectious complications, and improve survival.[13,14] Initial strategies (i.e., in the first 24 to 48 hours) are directed at managing fluid and electrolyte needs while avoiding large amounts of potentially damaging nutrients, such as amino acids or glucose. In maintenance and recovery phases after ARF, nutritional support should be provided as simple carbohydrates, fats, and protein, depending on the degree of uremia or malnutrition. Some authors recommend more protein for cats than dogs. Water-soluble vitamin supplementation is also recommended. Enteral or parenteral feeding often is required for animals with anorexia or vomiting. Aggressive, early use of antiemetics and gastrointestinal protectants is necessary to alleviate gastrointestinal erosion, hyperacidity, and reflux.[13,14]

PROTEINURIC RENAL FAILURE

A mildly to moderately reduced protein diet is recommended to limit protein loss in dogs with significant protein-losing nephropathy and normal albumin levels. If the serum albumin concentrations decrease below reference limits, protein supplementation may be necessary to improve hepatic albumin synthesis and to counter protein loss. Sodium restriction is also recommended because of the high incidence of hypertension associated with glomerular disease. In addition, omega 3 fatty acid supplementation may help modulate glomerular inflammation and decrease systemic hypertension, as well as hyperlipidemia, hypercholesterolemia, and platelet aggregation.[15]

MINIMIZING ANOREXIA ASSOCIATED WITH RENAL DISEASE

With worsening uremia, anorexia often complicates management of renal failure and compromises quality of life.[16] First, management of uremic gastroenteritis and other metabolic consequences of renal failure alleviates uremic anorexia. Dietary changes should be made gradually in the home environment, with food introduced that has a similar texture and flavor as the historical diet. Warming food, adding water or flavored (low sodium) broths or flavoring agents (butter, cottage cheese, clam juice, and garlic), and feeding small, frequent meals may increase palatability. It is important to avoid mixing unpalatable drugs with food, force feeding, or combining feeding with stressful, unpleasant, or painful procedures, such as injections or sample collection.[16]

Originally considered for preconditioning renal transplant patients, feeding by *percutaneous* or *surgically placed gastrostomy tubes* is a valuable tool in the management of some animals with renal failure.[3,17,18] Tube access also facilitates fluid intake and administration of medications. In 56 dogs with renal failure, gastrostomy tubes were used for a mean of about 2 months, and tubes in seven dogs were used for longer than 6 months. In these 56 dogs, increased gastric bleeding (transient), peristomal infection, and inadvertent tube removal were among the reported complications.[7] Preoperative gastrostomy tube feeding support is recommended for renal transplant candidates that have lost ≥10% of their body weight.[18]

UROLITHIASIS

Dietary strategies for the prevention or dissolution of uroliths are based on the principle of urine saturation.[19,20] Crystal precipitation occurs when urine becomes *oversaturated*. The amount, concentration, and types of ions and mineral present, as well as the urine pH, determine the overall solubility of a substance. When urine is *undersaturated* with such substances in a favorable pH, crystals do not precipitate or aggregate. In fact, some crystals or uroliths dissolve in such an environment. Dietary and other management strategies for urolithiasis, therefore, are designed to create a state of undersaturation for calculogenic minerals. Undersaturation is accomplished by (1) reducing the amount of dietary urolith precursors; (2) decreasing concentration of minerals by increasing urine volume; (3) modifying the urine pH to enhance solubility; and (4) providing optimal concentrations of crystallization inhibitors.[19,20] Using these principles, diets have been formulated to aid in the dissolution of magnesium ammonium phosphate (struvite), urate, and cystine uroliths and to minimize recurrence of other urolith types (see Table 158-1 and Chapters 266 and 267).

IDIOPATHIC FELINE LOWER URINARY TRACT DISEASE (OR IDIOPATHIC CYSTITIS)

Episodic or recurrent lower urinary tract signs related to a noninfectious inflammatory disorder of unknown etiology is still a common clinical disorder of cats. Because the obstructive

form of the disease was frequently associated with struvite crystalluria (and struvite crystals are still the predominant crystal found in urethral plugs), diets formulated for prevention or dissolution of struvite urolithiasis have traditionally been recommended.[21] However, many cats do not exhibit significant crystalluria along with the sterile hemorrhagic inflammation, therefore other dietary factors may be important. Dry cat food diets and decreased fluid intake appear to be significant risk factors for the development of both obstructive and nonobstructive disease, which may be reduced by maximizing moisture intake. In a prospective study of affected cats fed either a dry or canned formulation of mineral-controlled, acidifying diet for up to 12 months, fewer recurrences and significantly reduced urine specific gravities were seen in the cats that ate the canned preparation.[22]

Cats accustomed to dry food may not accept an exclusive canned food diet. Therefore other methods of increasing water intake must be considered, such as adding water to existing food; placing fresh, full water bowls near food; adding broths or juices to food or water; offering distilled or bottled water; leaving a faucet dripping slowly, or using pet water "fountains." Constancy of diet (i.e., limiting diet changes) also has been proposed as a protective measure in the management of idiopathic cystitis in cats.[23]

CHAPTER • 159

Parenteral Nutritional Support

Daniel Chan

Metabolic responses to illness or injury place critically ill animals at high risk for malnutrition and its deleterious effects. These problems include alterations in energy metabolism, compromised immune function, decreased wound healing, and, probably a negative impact on overall survival.[1-3] Whereas healthy animals lose primarily fat when they do not receive adequate calories (simple starvation), sick or traumatized patients catabolize lean body mass when they are not provided with sufficient calories (stressed starvation). Inadequate calorie intake is a common problem in critically ill animals due to anorexia, an inability to eat or tolerate feedings (e.g., vomiting), or decreased absorptive capabilities.[1,4]

Because malnutrition may occur quickly in these animals, it is important to provide nutritional support by either enteral or parenteral means if oral intake is not adequate. The goals of nutritional support are to prevent development of malnutrition and to treat malnutrition when present. Although unproven in dogs and cats, treatment or prevention of malnutrition is thought to decrease morbidity and mortality.[1,2,5-7] Whenever possible, nutritional support via the enteral route should be used because it is the safest, most convenient, most physiologically sound, and least expensive method. Although enteral nutrition is preferred in critically ill animals, parenteral nutrition (PN) is an established method of providing nutritional support to dogs and cats whose gastrointestinal tracts cannot tolerate enteral feedings.[3,5-6,8-9]

Although the use of parenteral nutritional support has certainly increased in recent years, there sometimes is a perception that this technique is technically difficult, associated with many complications, and limited to university hospitals and referral centers. In reality, parenteral nutritional support can be adopted in many practices and complications can be significantly reduced with proper management techniques. The goals of this chapter are to outline identification of dogs and cats most likely to benefit from PN; to review the process of formulating, implementing, and monitoring parenteral nutritional support; and to discuss how PN can be incorporated into various practice situations.

NUTRITIONAL ASSESSMENT

The first step in consideration of nutritional support is appropriate assessment. Assessing nutritional status via objective measurements of body composition (e.g., anthropometry, bioelectrical impedance, dual energy X-ray absorptiometry, or serum indicators of malnutrition) is rarely employed in clinical veterinary medicine. Therefore subjective clinical assessment remains paramount in identification of malnourished animals that require nutritional support as well as those in which nutritional support will help prevent malnutrition. Indicators of malnutrition include weight loss, poor hair coat, muscle wasting, signs of inadequate wound healing, hypoalbuminemia, lymphopenia, and coagulopathy. However, these abnormalities are not specific to malnutrition and do not occur early in the process. In addition, fluid shifts may mask weight loss in critically ill animals. Given these limitations, it is crucial to identify early risk factors that may predispose patients to malnutrition, such as anorexia of greater than 3 days' duration, serious underlying disease (e.g., trauma, sepsis, peritonitis, pancreatitis, gastrointestinal surgery), or significant protein loss (e.g., protracted vomiting, diarrhea, protein-losing nephropathies, draining wounds, or burns).

Nutritional assessment also identifies factors that can affect the nutritional plan, such as the identification of specific electrolyte abnormalities; hyperglycemia, hypertriglyceridemia,

or hyperammonemia; or comorbid illnesses, such as renal or hepatic disease. Such findings require adjustments to be made to the formulation of PN and in some cases prompt changing the nutritional plan. Appropriate laboratory analyses (e.g., serum biochemical profile, serum ammonia, urinalysis) should be performed in all dogs and cats to assess these parameters.

GOALS OF NUTRITIONAL SUPPORT

The goals of nutritional support are to provide for the animal's ongoing nutritional needs, prevent or correct nutritional deficiencies and imbalances, minimize metabolic derangements, and prevent further catabolism of lean body tissues. Restoration of optimal body condition is not necessarily the goal of nutritional support in the acute stages of disease. In severely malnourished dogs and cats, nutritional support should be directed to preservation of lean body tissue and organ function, rather than complete reversal of malnutrition, which is accomplished only when the animal becomes convalescent. The necessity for instituting nutritional support is dictated by individual needs and not by the specific disease. The ultimate goal of nutritional support is to provide the necessary nutrients and calories until the dog or cat voluntarily consumes an adequate amount of food in its own environment.

NUTRITIONAL PLAN

The key to successful nutritional management of a critically ill animal lies in proper diagnosis and treatment of underlying disease. Another crucial factor is selection of the appropriate route for nutritional support. Providing nutrition via a functional digestive system is the preferred route of feeding and so particular care should be taken to determine whether enteral feedings would be tolerated. Even if only small amounts of enteral nutrition would be tolerated, this route of feeding should be pursued and supplemented with PN as necessary to meet nutritional needs. On the basis of the nutritional assessment, the anticipated duration of nutritional support, and appropriate route of delivery (i.e., enteral or parenteral) a nutritional plan is formulated to meet each dog's or cat's nutritional needs.

The first steps in instituting nutritional support include re-establishing proper hydration status, correction of electrolyte or acid-base disturbances, and achieving hemodynamic stability. Commencing nutritional support before these abnormalities are addressed can increase risk of complications and, in some cases, further compromise the animal. Implementation of the nutritional plan should be gradual, with the goal of reaching target level of nutrient delivery in 48 to 72 hours.

CALCULATION OF NUTRITIONAL REQUIREMENTS

Ideally, the provision of nutritional support should provide ample substrates for gluconeogenesis, protein synthesis, and energy necessary to maintain homeostasis. The clinician must ensure that enough calories are being provided to sustain critical physiologic processes, such as immune function, wound repair, and cell division and growth. Therefore calculating the pet's total energy expenditure is necessary. However, as direct measurements of energy expenditure in clinical dogs and cats are still in the developmental phases, the use of mathematical formulas remains the only practical means of estimating energy requirement. The resting energy requirement (RER) is defined as the number of calories required for maintaining homeostasis at rest in a thermoneutral environment while the animal is in a postabsorptive state.[10] Although there are several formulas proposed to calculate the RER, a widely used allometric formula can be applied to both dogs and cats of all weights. For animals that weigh between 2 and 30 kg, there is also a linear formula that provides reasonable estimation of the RER.

$$RER = 70 \times (\text{current body weight in kg})^{0.75}$$

or for animals weighing between 2 and 30 kg:

$$RER = (30 \times \text{current body weight in kg}) + 70$$

Despite the convention of multiplying the RER by an illness factor between 1.0 to 1.5 to account for increases in metabolism associated with different diseases and injuries, less emphasis is now being placed on such subjective and extrapolated factors.[4] The current recommendation is to use more conservative energy estimates, that is, to start with the animal's RER, to avoid overfeeding. Overfeeding can result in metabolic and gastrointestinal complications, hepatic dysfunction, and increased carbon dioxide production.[9]

As the preservation of lean body mass is a primary goal of nutritional support, close monitoring of body weight, fluid distribution, response or tolerance to feedings, and changes in the underlying condition should dictate whether to increase the number of calories provided in the nutritional plan. Typically, if an animal continues to lose weight on nutritional support, the number of calories provided should be increased by 25% and the plan should be reassessed in a few days. Additional adjustments to the nutritional plan might also include the addition or restriction of electrolytes such as magnesium and potassium as dictated by serial biochemical profiles.

NUTRITIONAL SUPPORT

A major advantage of enteral nutrition is superior maintenance of intestinal structure and function, as the presence of nutrients within the intestinal lumen elicits trophic effects that mediate mucosal cell proliferation. It has also been proposed that a lack of enteral nutrition contributes to the impairment of mucosal barrier function, which allows for the translocation of intestinal bacteria or endotoxins leading to sepsis and a systemic inflammatory response.

However, in patients that are unable to tolerate enteral feedings, such as those that are vomiting, regurgitating, or unable to protect their airway, parenteral nutrition should be considered. Inability to tolerate enteral feeding is, in fact, the only major indication for parenteral nutritional support. Although obtaining enteral access in critically ill animals can be difficult, every effort must be made to ensure that a functional gastrointestinal tract is not bypassed. A more extensive review of enteral nutrition is provided elsewhere (see Nasoesophageal, Esophagostomy, and Gastrostomy Tube Placement Techniques).

PARENTERAL NUTRITION

Parenteral nutrition has sometimes been characterized as a technique fraught with complications. In reality, many of the complications attributed to PN in the past might have had more to do with overfeeding or "hyperalimentation," rather than with the route of feeding itself. Although metabolic complications can be associated with PN, these complications are generally mild, have minimal consequences, and rarely require discontinuation of nutritional support. Septic complications associated with PN can be dramatically minimized with careful attention to aseptic technique in the compounding of PN, placement of dedicated PN catheters, and monitoring of the catheter site.

TYPES OF PARENTERAL NUTRITION

Given that the different types of PN can be defined in a number of ways, it may be simpler to categorize the different types of parenteral nutrition in terms of calories provided, that is, when parenteral nutrition is formulated to meet 100% of an animal's energy requirements, it is referred to as *total parenteral nutrition* (TPN). Parenteral nutrition formulated to provide only a portion of the energy requirements, typically 40% to 70%, is termed *partial parenteral nutrition* (PPN). The lower osmolarity of PPN solutions, as compared with TPN solutions, is achieved by diluting the solution (ideally to less than 800 mOsm/L), which decreases the caloric and protein density but makes it suitable for administration via peripheral veins. For this reason, PPN may also be referred to as *peripheral parenteral nutrition*. The lower osmolarity is achieved in part, by utilizing 5% dextrose instead of 50% dextrose in the preparation of PPN and sometimes by the addition of isotonic and sometimes hypotonic crystalloids. As such, PPN is intended for short-term use (less than 5 days) and should be limited to dogs and cats that are not debilitated. Partial parenteral nutrition is also sometimes used as interim nutritional support until TPN can be formulated or it is used when specific contraindications exist to placement of jugular catheters, such as increased intracranial pressure or coagulopathies.

PARENTERAL NUTRITION COMPONENTS

Parenteral nutrition is formulated as a mixture of a carbohydrate source (dextrose), amino acids, and, usually, a fat source (lipid). Carbohydrates in the form of dextrose (typically 5% or 50%), may have benefits beyond acting as a fuel substrate. These potential benefits include stimulation of insulin secretion, reduction of muscle protein catabolism, and inhibition of hepatic glucose output, which may spare muscle proteins from being catabolized for gluconeogenesis. However, the sole administration of dextrose or supplementation of maintenance fluids with dextrose, in most cases, does not amount to adequate nutritional support and should therefore be discouraged. For example, a 5% dextrose infusion provides only 170 kcal per liter of solution and would provide less than 25% of the RER, at maintenance fluid rates. Dextrose infusions are more appropriate for the treatment of hypoglycemia rather than nutritional support.

Crystalline amino acids solutions are an essential component of PN. The importance of supplying amino acids relates to the maintenance of positive nitrogen balance and repletion of lean body tissue, which may be vital in the recovery of critically ill dogs and cats. Supplementation of amino acids may support protein synthesis and spare tissue proteins from being catabolized via gluconeogenesis.[9] The most commonly used amino acid solutions (Travasol, Clintec Nutrition, Deerfield, IL) contain most of the essential amino acids for dogs and cats, with the exception of taurine. However, as PN is typically not used beyond 10 days, the lack of taurine does not become a problem in most circumstances. Amino acid solutions are available in different concentrations from 4% to 10%, but the most commonly used concentration is 8.5%. Amino acid solutions are also available with and without electrolytes. Animals with normal serum electrolytes typically receive amino acid solutions with electrolytes, whereas those with electrolyte disturbances may benefit from amino acid solutions without electrolytes. Special formulations of amino acid solutions containing higher concentrations of the branched-chain amino acids are available at a much greater expense. Although these solutions were originally thought to be useful in management of highly catabolic metabolic diseases or when hepatic encephalopathy was present, studies have not confirmed a clear benefit in overall survival.[12]

Lipid emulsions are the calorically dense component of PN and a source of essential fatty acids. Lipid emulsions are isotonic and are available in 10% to 20% solutions (Intralipid, Clintec Nutrition, Deerfield, IL). These commercially available lipid emulsions are made primarily of soybean and safflower oil and provide predominantly long-chain polyunsaturated fatty acids, including linoleic, oleic, palmitic, and stearic acids. These solutions are emulsified with egg yolk phospholipids and their tonicity is adjusted with glycerol. The emulsified fat particles are comparable in size to chylomicrons and are removed from the circulation via the action of peripheral lipoprotein lipase. A common misconception exists in regard to the use of lipids in cases of pancreatitis. Although hypertriglyceridemia may be risk factor for pancreatitis, infusions of lipids have not been shown to increase pancreatic secretion or worsen pancreatitis and are therefore considered safe.[13] One exception, however, could be when serum triglycerides are increased, which indicates a clear failure of triglyceride clearance. According to the most recent guidelines provided by the American Society of Parenteral and Enteral Nutrition, humans with serum triglycerides exceeding 400 mg/dL should have the lipid proportion in PN markedly reduced or eliminated altogether.[13] Although specific data regarding the maximal safe level of lipid administration in dogs and cats is not available, it would seem prudent to maintain normal serum triglyceride concentrations.

Another concern surrounding the use of lipids in PN are purported immunosuppressive effects via impairment of the reticuloendothelial system, particularly in PN solutions containing a high percentage of lipid.[9] Despite *in vitro* evidence supporting the notion that lipid infusions can also suppress neutrophil and lymphocyte function, studies have not yet correlated lipid use and increased rates of infectious complications.

Daily vitamin recommendations for dogs and cats that receive PN are extrapolated from established oral nutritional requirements.[9] Multivitamin preparations intended for intravenous administration provide a convenient and practical means for vitamin supplementation. It is recommended to add 0.2 ml/kg of a multivitamin preparation (M.V.I.-12 NeoSan Pharmaceuticals Inc., Wilmington, NC) to each PN bag at the time of compounding, up to 10 mL/day. This provides most of the water- and fat-soluble vitamins, except for vitamin K. In certain situations (e.g., longstanding malnutrition, malabsorptive disorders), 0.5 mg/kg of vitamin K can be administered subcutaneously, once weekly. Trace metals (4 Trace Elements, Abbott Laboratories, North Chicago, IL) can also be added to the PN solution at a dose of 0.1 mL/kg (up to 5 mL/day) to provide zinc, manganese, copper, and chromium. Although vitamins are commonly added to PN solutions, trace metals are usually only added when PN is to be administered for greater than 5 days or when food has not been consumed for a prolonged period.

The addition of other parenteral medications to the PN admixture is possible; however, their compatibility must first be verified. Drugs that are known to be compatible and sometimes added to PN include heparin, insulin, potassium chloride, and metoclopramide. Although the addition of insulin to PN is often required in people receiving PN, the hyperglycemia seen in dogs and cats receiving PN does not usually require insulin administration; however, diabetic patients will require adjustments to their insulin regimen. Although there is a described veterinary protocol for the addition of insulin directly to PN, it is often easiest to manage diabetics on PN with subcutaneous injections of insulin.[9] The addition of metoclopramide to PN solutions is often useful in the management of vomiting and ileus, which are commonly encountered in critically ill animals.

PARENTERAL NUTRITION COMPOUNDING

Based on the nutritional assessment and plan, PN can be formulated according to the worksheets found in Boxes 159-1 and 159-2. For TPN (see Table 159-1), the first step is the calculation of the animal's RER. Protein requirements (grams of protein required per day) are then calculated, taking into consideration factors such as excessive protein losses or severe hepatic or renal disease. Although some recommendations provide all energy requirements with only dextrose and lipids, the protocol listed accounts for the energy provided from amino acids in the calculation and subtract it from the daily RER to estimate the total non-protein calories required. The non-protein calories are then usually provided as a 50:50 mixture of lipids and dextrose; however, this ratio can be adjusted in cases of persistent hyperglycemia or hypertriglyceridemia (e.g., a higher proportion of calories would be given from lipid in an animal with hyperglycemia). The calories provided from each component (amino acids, lipids, and dextrose) are then divided by their respective caloric densities and the exact amounts of each component are added to the PN bags in an aseptic fashion. The amount of TPN delivered will often provide less than the daily fluid requirement. Additional fluids can either be added to the PN bag at the time of compounding or be provided as a separate infusion.

For formulation of PPN, Box 159-2 provides a step-by-step protocol in which animals of various sizes can be given 70% of their RER and approximately meet their daily maintenance fluid requirement. In very small animals (≤3 kg), the amount of PPN will exceed the maintenance fluid requirement and increase the risk for fluid overload, so adjustments in volume are necessary. Also, in animals requiring conservative fluid administration (e.g., congestive heart failure), these calculations for PPN may provide more fluid then would be safe. This formulation has been designed so that the proportion of each PN component is dependent on animal weight such that a smaller animal (between 3 and 5 kg) will receive proportionally more calories from lipids, compared to a large dog (greater than 30 kg), which would receive more calories in the form of carbohydrates. This allows the resulting formulation to approximate the daily fluid requirement.

Ideally, compounding of parenteral nutrition should be done aseptically under a laminar flow hood using a semi-automated, closed-system, parenteral nutrition compounder (e.g., Automix compounder, Clintec Nutrition, Deerfield, IL). If an automated compounder is not available, manual compounding

Box • 159-1

Total Parenteral Nutrition (TPN) Calculations

1. Calculate resting energy requirement (RER)
   RER = 70 × (current body weight in kg)$^{0.75}$
   or for animals weighing between 2 and 30 kg:
   RER = (30 × current body weight in kg) + 70 RER = _____kcal/day
2. Protein requirements

	Canine (gm/100 kcal)	Feline (gm/100 kcal)
*Standard	4	6
*Reduced (hepatic/renal disease)	2-3	3-4
*Increased (excessive protein losses)	6	6

   (RER+100) × _____ gm/100 kcal = _____ gm protein required/day
   protein req
3. Volume of nutrient solutions required
   a. 8.5% amino acid solution = 0.085 gm protein/ml
      _____g protein required/day ÷ 0.085 gm/ml = _____ml/day of amino acids
   b. Non-protein calories:
      The calories supplied by protein (4 kcal/gram) are subtracted from the RER to get total non-protein calories needed.
      _____g protein req/day × 4 kcal/gram = _____kcals provided by protein
      RER — kcals provided by protein = _____total non-protein kcal/day required
   c. Non-protein calories are usually provided as a 50:50 mixture of lipid and dextrose
      *20% lipid solution = 2 kcal/ml
      To supply 50% of non-protein calories
      _____lipid kcal required ÷ 2 kcal/ml = ____mls of lipid
      *50% of dextrose solution = 1.7 kcal/ml
      To supply 50% of non-protein calories
      _____dextrose kcal required ÷ 1.7 kcal/ml = ____mls of dextrose
4. Total daily requirements
   _____ mls of 8.5% amino acid solution
   _____ mls of 20% lipid
   _____ mls of 50% dextrose
   _____ total mls of TPN solution to be administered over 24 hr

Note: Using a common 8.5% amino acid solution containing potassium (i.e., Travasol), TPN made according to this worksheet will provide potassium at higher than maintenance levels. Therefore you may not need to supplement potassium in any other fluids your patient is receiving. TPN for animals that are hyperkalemic should be formulated using amino acid solutions without electrolytes. Rates of other IV fluids being concurrently administered should be adjusted accordingly.

Box • 159-2

Partial Parenteral Nutrition (PPN) Calculations

1. Calculate resting energy requirement (RER)
   RER = 70 × (current body weight in kg)$^{0.75}$
   or for animals weighing between 2 and 30 kg:
   RER = (30 × current body weight in kg) + 70 RER = ____kcal/day
2. Calculate the partial energy requirement (PER):
   Plan to supply 70% of the animal's RER with PPN: PER = RER × 0.70 = ____kcal/day
3. Proportion of nutrient requirements according to body weight:
   (Note for animals ≤3 kg, the formulation will exceed maintenance fluid requirements)
   a. Cats and dogs 3 to 5 kg:
      PER × 0.20 = ____kcals/day carbohydrate required
      PER × 0.20 = ____kcals/day protein required
      PER × 0.60 = ____kcals/day lipid required
   b. Cats and dogs 6 to 10 kg:
      PER × 0.25 = ____kcals/day carbohydrate required
      PER × 0.25 = ____kcals/day protein required
      PER × 0.50 = ____kcals/day lipid required
   c. Dogs 11 to 30 kg:
      PER × 0.33 = ____kcals/day carbohydrate required
      PER × 0.33 = ____kcals/day protein required
      PER × 0.33 = ____kcals/day lipids required
   d. Dogs >30 kg:
      PER × 0.50 = ____kcals/day carbohydrate required
      PER × 0.25 = ____kcals/day protein required
      PER × 0.25 = ____kcals/day lipid required
4. Volumes of nutrient solutions required:
   a. 5% dextrose solution = 0.17 kcals/ml
      ____kcals carbohydrate required/day ÷ 0.17 kcals/ml = ____ ml/day dextrose
   b. 8.5% amino acid solution = 0.34 kcals/ml
      ____kcals protein required/day ÷ 0.34 kcals/ml = ____ ml/day amino acids
   c. 20% lipid solution = 2 kcal/ml
      ____kcals lipid required/day ÷ 2 kcals/ml = ____ ml/day lipid
      = ____ total ml of PPN to be administered over 24 hrs

Note: This formulation provides approximately a maintenance fluid rate. Commonly used 8.5% amino acid solutions (i.e., Travasol) with electrolytes contain potassium. For animals ≤35 kg, the PPN solution made according to this worksheet will provide approximately maintenance levels of potassium. For animals >35 kg, the potassium contained in the PPN solution will be lower than maintenance levels. Rates of other IV fluids being concurrently administered should be adjusted accordingly.

can be done in a clean, low-traffic area with strict adherence to aseptic technique using a 3-in-1 bag (All-In-One EVA container, Clintec Nutrition, Deerfield, IL). Given these ideal conditions, it is often easier and more cost effective to have a local human hospital or a human home healthcare company compound parenteral nutrition solutions. Alternatively, commercial ready-to-use preparations of glucose or glycerol and amino acids are available for intravenous (peripheral) use (Table 159-1). Although these ready-to-use preparations are convenient, they provide only 30% to 50% of caloric requirements when administered at maintenance fluid rates and as a result should only be used for interim nutritional support or to supplement low-dose enteral feedings.

PARENTERAL NUTRITION ADMINISTRATION

The administration of any PN requires a dedicated catheter used solely for PN administration and that is placed using aseptic technique. In most cases, this will require placement of

Table • 159-1

Commercially Available Alternatives for Partial Parenteral Nutrition (PPN)

PRODUCT NAME	FEATURES	MANUFACTURER
Clinimix	2.75% amino acid 5% dextrose	Clintec Nutrition, Deerfield, IL
Quickmix	2.75% amino acid 5% dextrose	Clintec Nutrition, Deerfield, IL
ProcalAmine	3% amino acids 3% glycerol	McGraw Inc., Irvine, CA

Note: These solutions only provide 30% to 50% of resting energy requirements when administered at maintenance fluid rates. Therefore these should only be used as an interim form of nutritional support or to supplement low-dose enteral nutrition.

additional catheters because PN should not be administered through existing catheters that were placed for reasons other than PN. Long catheters composed of silicone, polyurethane, or tetrafluroethylene are recommended for use with any type of PN to reduce the risk of thrombophlebitis.[3-4] Multilumen catheters are often recommended for TPN because they can remain in place for long periods and can also be used for blood sampling and administration of additional fluids and intravenous medications without the need for separate catheters placed at other sites.[5,11]

Although placement of multi-lumen catheters does require more technical skills than conventional jugular catheters, they can be valuable in treatment of any critically ill pet. The high osmolarity of TPN solutions (often 1200 mOsm/L) require its administration through a central venous (jugular) catheter, whereas PPN solutions can be administered through either a jugular catheter or catheters placed in peripheral veins. The concern with administering fluids high in osmolarity is that it may increase the incidence of thrombophlebitis, although this has not been consistently demonstrated in veterinary medicine.

Because of the various metabolic derangements associated with critical illness, TPN should be instituted gradually over 48 hours. At the hospital where the author practices, TPN is started typically at 50% of the RER on the first day and then increased to the targeted amount by the second day. In most cases, PPN can be started without gradual increase. It is also important to adjust the rates of other fluids being concurrently administered. For both TPN and PPN, the animal's catheter and infusion lines must be handled aseptically at all times to reduce the risk of PN-related infections.

Parenteral nutrition should be administered as continuous rate infusions over 24 hours via fluid infusion pumps. Inadvertent delivery of massive amounts of PN can result if administration is not properly regulated. Cyclic administration of PN (i.e., alternating PN with other parenteral fluids every 12 hr) has also been described. However, this practice is not recommended as it circumvents maintenance of a closed-system for PN administration and can increase the rate of complications. Once a bag of PN is set up for administration, it should not be disconnected even for walks or diagnostic procedures. The drip regulator is decreased to a slow drip and accompanies the pet throughout the hospital. Administration of PN through an in-line filter (Air eliminating filter, Clintec Nutrition Division, Deerfield, IL) is also recommended and is attached at the time of set up. This set-up process is performed daily with each new bag of PN. Each bag should only hold one day's worth of PN and the accompanying fluid administration sets and in-line filter are changed at the same time using aseptic technique. Discontinuation of PN should be done when the animal resumes consuming an adequate amount of calories of at least 50% of RER. Whereas TPN should be gradually discontinued over a 6- to 12-hour period, PPN can be discontinued abruptly.

COMPLICATIONS

As with any therapy for critically ill animals, complications can occur. Complications associated with PN can include mechanical complications of the catheter and lines, thrombophlebitis, metabolic abnormalities, and sepsis. Mechanical complications such as inadvertent catheter removal, catheter occlusion, and line disconnection or breakage are probably not inherently related to PN and are likely no more common than in any dog or cat with an intravenous catheter. Metabolic complications are much more likely to be related to PN and include hyperglycemia, hypertriglyceridemia, hyperbilirbinemia, increased alkaline phosphatase activity, azotemia, electrolyte shifts, and hyperammonemia.[2,5,11] The more commonly encountered complications, namely hyperglycemia and hypertriglyceridemia, are for the most part transient and can be effectively managed without serious consequences. Decreasing the rate of infusion for 12 to 24 hours is often effective; although in some instances, re-formulation of PN is required. Animals with biochemical changes subsequent to initiation of PN should have more frequent evaluation of laboratory parameters.

Septic complications, including catheter-site infections with and without systemic sepsis have also been reported in dogs and cats receiving PN but are uncommon and range from 3% to 12% in dogs and cats that receive PN.[5,11] Septic complications can be minimized by strict adherence to established protocols and careful attention to early signs of problems relating to catheter care. Any catheter suspected of causing fever, white cell count elevations, or other sign compatible with infection should be removed and cultured.

One of the proposed advantages of PPN over TPN is lower risk of complications. This is supported by a recent study that documents lower rates of complications in dogs and cats receiving PPN, compared with previously reported complication rates associated with TPN in dogs.[5,11] Although direct comparisons between the two patient populations cannot be made, there were approximately 0.17 complications per day of PPN administration versus 0.53 complications per day reported with TPN administration in dogs.[5,11] Reasons for these differences could be attributed to differences in severity of illness between these animal populations, although there is a potential that hypocaloric nutritional support may actually confer some benefits in certain populations, including lower complication rates.[15]

MONITORING

Given the potential for complications, monitoring of dogs and cats receiving PN is a vital part of nutritional support. This monitoring is similar to that already in place for critically ill pets. Careful monitoring of the catheter site is recommended to detect problems early (e.g., signs of inflammation or malposition) and should be done on a daily basis. The catheter should be evaluated for patency and the bandage should be changed daily. At a minimum, body weight, body temperature, respiratory rate, catheter site, and serum glucose should be evaluated daily. All blood tubes should be inspected for visible lipemia. Monitoring of other parameters (e.g., electrolytes, complete blood count, biochemical profile) may also be indicated. Persistent hyperglycemia, hypertriglyceridemia, or signs of encephalopathy should prompt re-evaluation and may necessitate decreasing rate of infusion or re-formulation of parenteral nutrition and serial evaluation of blood work.

SUMMARY

With the growing recognition that nutritional support is an integral part of the therapeutic regimen for many critically ill pets, it is becoming increasingly important for veterinarians to be able to incorporate parenteral nutritional support in their practice or to refer these pets to facilities capable of providing such therapy when necessary. Proper identification of dogs and cats most likely to benefit from PN and the ability to formulate, administer, and monitor PN are key factors in ensuring successful incorporation of parenteral nutritional support in their care.

CHAPTER 160

Dietary and Medical Considerations in Hyperlipidemia

Denise A. Elliott

Hyperlipidemia is a consequence of elevated plasma concentrations of triglyceride and/or cholesterol and is due to a disturbance in plasma lipoprotein metabolism.[1] In the fasted state hyperlipidemia is an abnormal finding that represents either accelerated production or delayed degradation of lipoproteins. The lipoproteins function to transport insoluble triglyceride and cholesterol through the blood. Lipoproteins consist of a triglyceride and cholesteryl ester core surrounded by a surface layer of cholesterol, phospholipid, and apolipoproteins. The apolipoproteins (A, B, C, E) are responsible for the structure of the lipoprotein particle, for binding of the particle to cell surface receptors, and activation of enzymes.[1] There are four major classes of lipoproteins that differ in their lipid and apoprotein content and their physicochemical characteristics. These variabilities include size, density, and electrophoretic mobility.

Lipoproteins are categorized according to their buoyant density upon ultracentrifugation into the chylomicron, very–low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and the high-density lipoprotein (HDL). The classification system is arbitrary and it should be appreciated that there is significant structural and functional heterogeneity within each category. In addition, the system is dynamic; one class produces another during its metabolism (Figure 160-1). The chylomicron and VLDL are involved primarily in triglyceride metabolism, whereas HDL and LDL are involved primarily in cholesterol metabolism.

PATHOPHYSIOLOGY

After digestion and absorption, cholesterol and triglyceride are packaged into chylomicron particles by enterocytes. Chylomicrons are secreted into mesenteric lymph, through which they ultimately reach the systemic circulation. Here they receive Apo E and Apo C-II from HDL. In adipose and muscle tissues, endothelial lipoprotein lipase is activated by

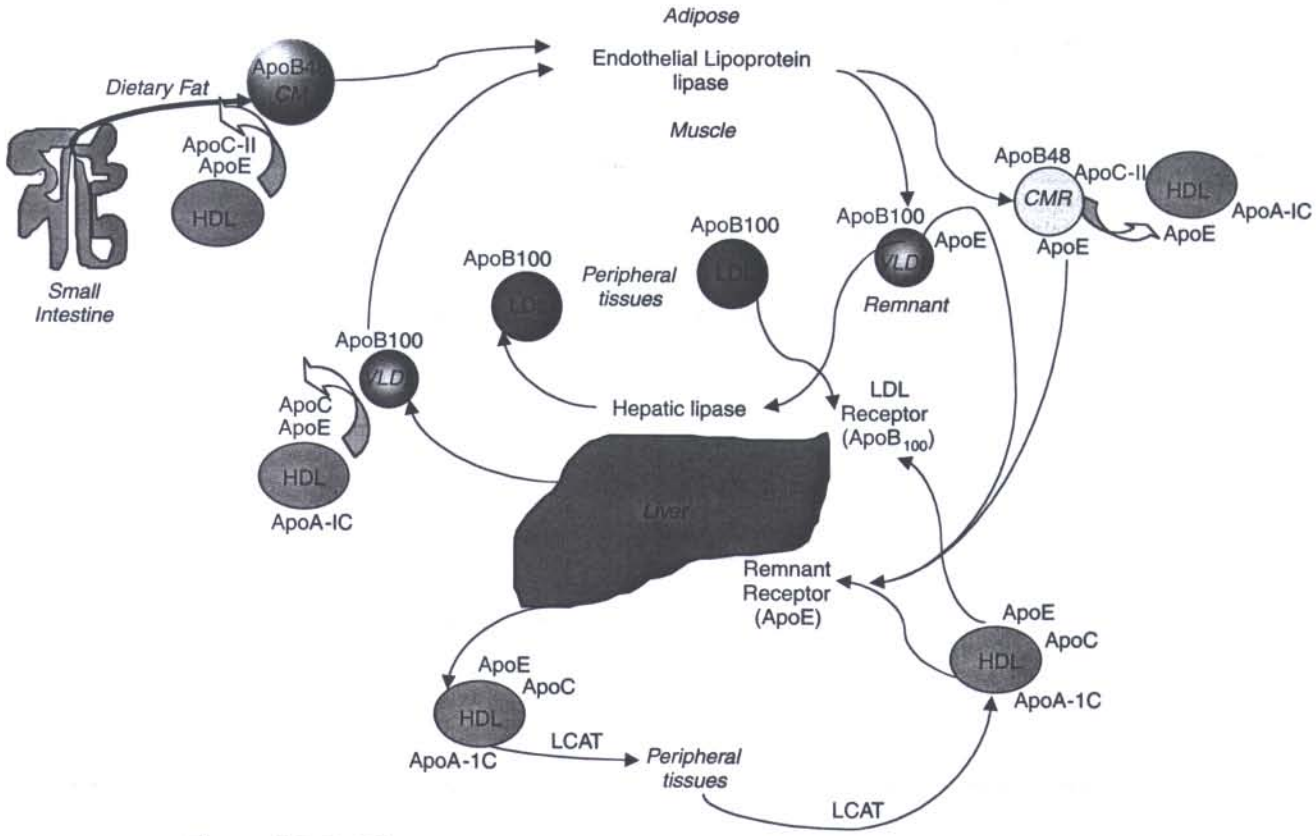

Figure 160-1 Schematic representation of lipid metabolism. *CM*, Chylomicron; *CMR*, chylomicron remnant; *VLDL*, very low-density lipoprotein; *LDL*, low-density lipoprotein; *HDL*, high-density lipoprotein; *LCAT*, lecithin:cholesterol acyl transferase.

apoprotein C-II and hydrolyzes the triglyceride core of the chylomicron to free fatty acids and glycerol. The free fatty acids diffuse into adjacent tissues and are either resynthesized into triglyceride and stored (adipocyte) or used for energy (myocyte). Lipoprotein lipase activity is influenced by factors such as heparin, insulin, glucagon, and thyroid hormone. Depletion of the triglyceride component of the chylomicron alters the surface so that the chylomicron is converted into a chylomicron remnant. The remnant particle transfers phospholipid and Apo C-II back to the HDL particle, prior to being recognized and removed from the circulation by specific Apo-E hepatic remnant receptors. Within the hepatocyte, the contents of the chylomicron remnant are degraded and utilized. Chylomicrons are present in plasma 30 minutes to 2 hours after a fat-containing meal and hydrolysis is normally complete within 6 to 10 hours after a meal.

Intrahepatic free fatty acids may originate from residual dietary triglyceride present in chylomicron remnant particles, from endogenous production secondary to surplus dietary carbohydrate, and from excessive endogenous mobilization. Intracellular hormone sensitive lipase is responsible for hydrolysis of stored adipocyte triglyceride to release free fatty acids and glycerol. Hormone sensitive lipase can be activated by epinephrine, norepinephrine, ACTH, corticosteroids, growth hormone, thyroid hormone, and insulin deficiency. Excess free fatty acids that are not directly oxidized for energy are transformed by the hepatocyte into triglyceride, packaged into VLDL particles, and secreted into blood. Analogous to chylomicron metabolism, the VLDL particle acquires ApoC-II and ApoE from the VLDL particle. Endothelial lipoprotein lipase then removes and hydrolyzes the triglyceride portion of the VLDL into free fatty acids and glycerol. In addition, an endothelial hepatic lipase will also hydrolyze the triglyceride portion of the VLDL. Removal of the triglyceride core converts the VLDL to a LDL particle. The LDL particle is a cholesterol- and phospholipid-rich entity that functions to transport cholesterol to tissues where it may be used for membrane synthesis or steroid hormone production. Ultimately, the LDL particle binds to the LDL receptor that recognizes $ApoB_{100}$, and is removed by the liver.

The liver also secretes nascent HDL particles into the circulation. These particles consist of a phospholipid bilayer, unesterified cholesterol, Apo C, Apo E, and Apo-A-I. The HDL acts as a reservoir of Apo C and Apo E and transfers these apolipoproteins to chylomicron and VLDL particles. Plasma lecithin:cholesterol acyl transferase (LCAT), activated by Apo-A-I, esterifies cholesterol to hydophobic cholesteryl ester, which moves from the surface to the inner core of the HDL. A concentration gradient is thus produced such that excess tissue cholesterol is transferred to the HDL particle. HDLs scavenge excess unesterified cholesterol from cells and other lipoproteins and return it to the liver for excretion into bile. This process is often referred to as *reverse cholesterol transport*. In humans, a second enzyme (cholesteryl ester transfer protein; CETP) can function to transfer HDL cholesteryl esters to chylomicrons, VLDL and LDL particles, in exchange for triglyceride. However, dogs do not appear to have CETP. Rather, the HDL particles are removed by the liver via Apo E binding LDL and remnant-receptors.[2] It is not yet apparent if the cat has CETP.

Hypertriglyceridemia can develop secondary to increased chylomicron production (excessive dietary intake of lipid), ineffective clearance of the chylomicron particle, increased VLDL production (excessive dietary intake of lipids and/or carbohydrate, excessive endogenous production, or mobilization of lipids), and ineffective clearance of the VLDL particle. Likewise, hypercholesterolemia can arise from increased production of the LDL precursor (VLDL), or reduced clearance of the LDL or HDL particle.

CLASSIFICATION

Post-prandial hyperlipidemia is the most common cause of hyperlipidemia in the dog and cat. This is a normal physiologic manifestation caused by the production of triglyceride-rich chylomicrons and usually resolves within 2 to 10 hours. Pathologic abnormalities in plasma lipids and lipoproteins may be of genetic or familial origin (primary) or arise as a consequence of disease (secondary). Primary hypertriglyceridemias include idiopathic hyperlipidemias of miniature Schnauzers and hyperchylomicronemia of cats. Idiopathic hyperlipidemia of miniature Schnauzers is characterized by excessive VLDL particles with or without concurrent chylomicronemia, and mild hypercholesterolemia.[3] The exact mechanism and genetics have not been fully elucidated. Feline familial hyperlipidemia is characterized as a fasting chylomicronemia with a slight increase in VLDL and is due to production of an inactive lipoprotein lipase.[4] Idiopathic hyperchylomicronemia has also been observed in dogs and is characterized by hypertriglyceridemia, hyperchylomicronemia, and normal serum cholesterol concentrations. Idiopathic hypercholesterolemia due to an increase in LDL has been reported in Doberman Pinschers and Rottweilers.

Diseases associated with secondary hyperlipidemia include endocrine disorders (hypothyroidism, diabetes mellitus, hyperadrenocorticism), nephrotic syndrome, cholestasis, and drug-induced (glucocorticoids, megastrol acetate).[5] Hypothyroidism is the most common cause of hypercholesterolemia in the dog. It is attributed to both a decrease in lipid synthesis and degradation (lipid degradation is more severely affected). Decreased lipoprotein lipase activity contributes to the impaired removal of triglyceride-rich lipoproteins. In addition, thyroid hormone deficiency reduces the biliary excretion of cholesterol. The resultant increase in intrahepatic cholesterol down-regulates the hepatic LDL receptor, increasing the level of circulating LDL and HDL. Insulin deficiency reduces the production of lipoprotein lipase, with subsequent decreased clearance of triglyceride-rich lipoproteins. Furthermore, hormone sensitive lipase is activated, which causes the release of large quantities of free fatty acids into the blood, which are ultimately converted by the liver into triglycerides, packaged into VLDL particles, and secreted back into the circulation. Therefore hypertriglyceridemia seen with diabetes mellitus is attributed to both a reduction of lipoprotein lipase and increased production and decreased clearance of VLDL particles. Insulin deficiency increases the synthesis of cholesterol in the liver. The increased intrahepatic cholesterol concentration down-regulates the hepatocyte LDL receptor and consequently reduces the clearance of circulating LDL and HDL particles. The mechanism of hypertriglyceridemia associated with hyperadrenocorticism is probably due to stimulation of hormone-sensitive lipase with release of free fatty acids into the circulation. Similarly to diabetes mellitus, excess free fatty acids are converted into VLDL particles. In addition, glucocorticoids inhibit lipoprotein lipase activity, thereby reducing the clearance of triglyceride-rich lipoproteins.

CLINICAL FEATURES

Waxing and waning vomiting, diarrhea and/or abdominal discomfort are the most common clinical presentations associated with hypertriglyceridemia.[6] Severe hypertriglyceridemia (>1000 mg/dL) has been associated with pancreatitis, lipemia retinalis, seizures, cutaneous xanthomas, peripheral nerve paralysis, and behavioral changes. Cutaneous xanthomas, which represent lipid-laden macrophages and foam cells, are the most common manifestation of hypertriglyceridemia in

the cat. Severe hypercholesterolemia has been associated arcus lipoides corneae, lipemia retinalis, and atherosclerosis.

DIAGNOSIS

Lipemic serum suggests that the animal has hypertriglyceridemia. Lactescence refers to increases of triglyceride sufficient (typically >1000 mg/dL) to cause serum or plasma samples to become milk-like in appearance and opaque. Conversely, patients with pure hypercholesterolemia do not exhibit lipemic or lactescent serum as LDL and HDL particles are too small to refract light. Blood samples to confirm hypertriglyceridemia should be obtained after a 12- to 18-hour fast. A serum sample rather than whole blood or plasma should be submitted for assessment. The sample can be refrigerated or frozen for several days without affecting the test. During assessment of the sample for hypertriglyceridemia, the laboratory should not clear the sample prior to determination of the triglyceride concentration. Clearing lipemic samples by centrifugation removes chylomicrons, which will artificially lower the triglyceride concentration.

The chylomicron test, which requires refrigeration of a sample for 12 hours, can be helpful to delineate if the lipemia is predominantly a chylomicron or VLDL defect.[6] The chylomicrons are least dense and will float to form an opaque cream layer over a clear infranatant of serum. If the hypertriglyceridemia is due to excess VLDLs, the plasma sample will remain turbid. Formation of a cream layer over a cloudy serum layer suggests both excess chylomicrons and VLDL particles.

Lipoprotein electrophoresis can be utilized to distinguish the lipoproteins and ultracentrifugation can provide a quantitative measurement of each lipoprotein class.[7] However, both of these procedures are time consuming and not routinely available. The activity of lipoprotein lipase can be assessed by the heparin release test. Serum samples for the determination of triglyceride (and if possible, lipoprotein) concentrations are obtained prior to and 15 minutes after the intravenous administration of heparin (90 IU/kg BW dog; 40 IU/kg BW cat). Heparin causes the release of lipoprotein lipase from the endothelium and stimulates the hydrolysis of triglycerides. A defect in lipoprotein lipase is suspected if there is no difference between the pre- and post-serum triglyceride concentrations.

MANAGEMENT

Prior to recommending therapy, every attempt should be taken to determine if the hyperlipidemia is primary or secondary, as lipemia secondary to an underlying disorder will typically resolve or improve with correction of the metabolic disturbance. Therefore each dog or cat requires a full history, physical examination, complete blood count, serum biochemistry panel, serum lipase, serum thyroxine concentration, and urinalysis. Additional diagnostic tests such as bile acids, abdominal ultrasound, and evaluation of the adrenocorticotropic hormone axis may be required. A recommendation to treat hyperlipidemia involves a life-long commitment by the owner and must therefore not be undertaken lightly. In general, severe hypertriglyceridemia (>500 mg/dL) mandates treatment. In this circumstance catabolic mechanisms can be assumed to be overwhelmed and the triglyceride level is sensitive to small increases from the intestine or liver. The triglyceride levels must be decreased to prevent complications including pancreatitis. In other situations, the recommendations will be influenced by additional variables, including the underlying disease process. A realistic goal of therapy is to reduce the triglyceride concentrations to less than 400 mg/dL.

Chylomicrons are produced from dietary fat, hence restriction of dietary fat is the cornerstone of therapy for hypertriglyceridemia. The dietary history should be reviewed and the diet altered to one that contains less than 20% fat on a metabolic energy basis for dogs, and less than 25% fat on a ME basis for cats (Table 160-1). Treats should be restricted to 5% of the daily caloric intake and changed to low-fat commercial varieties. Carrots or brown rice crackers are useful alternatives. In addition to providing a low-fat diet, the absolute caloric intake should be evaluated. If the pet is overweight, caloric restriction is indicated and beneficial as it decreases the production of VLDL from excess dietary energy. The triglyceride concentration should be reevaluated after 4 weeks of feeding a low-fat diet. If the reduction in triglyceride concentration is less than ideal, the history should be reevaluated to ensure that there are no extra fat calories from treats, no access to other pet foods, and no additional family members or neighbors who are inadvertently providing the patient with fat. Unfortunately, inappropriate initial dietary selection is the most likely reason for failure to respond to nutritional therapy. A commercial diet should not be selected because the manufacturer recommends the diet for the management of hyperlipidemia. Rather, the diet should be selected because the dietary fat content is less than 20% on a metabolic energy basis. In addition, care should be given to the form of the diet as the fat content of canned and dry version of the diet may differ significantly (see Table 160-1). The medical record should also be reviewed to ensure the exclusion of underlying disorders. If commercial products are not able to control hypertriglyceridemia, then a complete and balanced ultra–low-fat (10% to 12% ME), home-prepared diet can be specifically formulated by a veterinary clinical nutritionist.

Diets rich in omega-3 fatty acids have been suggested to improve hypertriglyceridemia in humans by decreasing the production of VLDL particles. In addition, fish oils are poor substrates for triglyceride synthesizing enzymes and lead to the formation of triglyceride poor VLDL particles. Menhaden fish oil (200 mg/kg BW, dog) has been recommended for use in dogs.[6]

Treatment with drugs, all of which have toxicity, should be undertaken with particular care. In general, drugs should not be used when the serum triglyceride concentration is less than 500 mg/dL. Several classes of drugs are available for humans[8]; however, there are few reports of their use in cats and dogs. Until further studies evaluate the dose, effect, and toxicity, drug therapy is indicated only in those animals that have clinical signs associated with severe elevations in triglyceride that cannot be ameliorated by dietary therapy.

Niacin (100 mg/day, dog) reduces serum triglyceride concentrations by reduction of free fatty acid release from adipocytes and by reduction of the production of VLDL particles. Adverse effects are frequent and include vomiting, diarrhea, erythema, pruritus, and abnormalities in liver function tests. Fibric acid derivatives (clofibrate, bezafibrate, gemfibrozil, ciprofibrate, fenofibrate) lower triglyceride concentrations by stimulating lipoprotein lipase activity, in addition to reducing the free fatty acid concentration, which decreases the substrate for VLDL synthesis. In humans, the fibrates generally lower serum triglyceride concentrations by 20% to 40%. Gemfibrizol has been used in the dog (200 mg/day) and cat (10 mg/kg BW q12hr). Reported adverse effects include abdominal pain, vomiting, diarrhea, and abnormal liver function tests. The statins (lovastatin, simvastatin, pravastatin, fluvastatin, cerivastatin, atorvastatin) are HMG-CoA reductase inhibitors that primarily suppress cholesterol metabolism.

Table • **160-1**

Key Nutrients* in Diets Recommended by Selected Manufacturers for Hypertriglyceridemia

CANINE	TYPE	FAT g/1000 kcal (%ME)	PROTEIN g/1000 kcal (%ME)	ME kcal
WALTHAM Canine Veterinary Diet Low Fat	Dry	21 (18%)	66 (24%)	274/8 oz
WALTHAM Canine Veterinary Diet Low Fat	Can	20 (16%)	93 (31%)	377/13.6 oz
Purina Veterinary Diets EN GASTROENTERIC	Dry	28 (26%)	62 (23%)	397/8 oz
Purina Veterinary Diets EN GASTROENTERIC	Can	34 (31%)	76 (25%)	424/12.5 oz
Purina Veterinary Diets OM OVERWEIGHT MANAGEMENT	Dry	22 (16%)	104 (37%)	276/8 oz
Purina Veterinary Diets OM OVERWEIGHT MANAGEMENT	Can	34 (28%)	178 (55%)	189/12.5 oz
Purina Veterinary Diets HA HYPOALLERGENIC	Dry	26 (24%)	53 (19%)	302/8 oz
Hill's Prescription Diet Canine w/d	Dry	27 (24%)	58 (21%)	226/8 oz
Hill's Prescription Diet Canine w/d	Can	38 (31%)	53 (18%)	372/14.75 oz
Hill's Prescription Diet Canine r/d	Dry	29 (25%)	84 (30%)	205/8 oz
Hill's Prescription Diet Canine r/d	Can	28 (24%)	85 (30%)	292/14.25 oz
Eukanuba Veterinary Diets Nutritional Weight Loss Formula Restricted-Calorie	Dry	17 (15%)	63 (18%)	238/8 oz
FELINE				
WALTHAM Feline Veterinary Diet Calorie Control	Dry	28 (18%)	128 (50%)	208/8 oz
WALTHAM Feline Veterinary Diet Selected Protein with Rice and Duck	Dry	38 (25%)	99 (38%)	258/8 oz
Purina Veterinary Diets OM Overweight Management	Dry	25 (20%)	112 (42%)	326/8 oz
Purina Veterinary Diets OM Overweight Management	Can	37 (22%)	113 (45%)	150/5.5 oz
Hills Prescription Diet Feline w/d	Dry	28 (24%)	110 (39%)	281/8 oz
Hills Prescription Diet Feline w/d	Can	44 (38%)	110 (40%)	148/5.5 oz
Hills Prescription Diet Feline r/d	Dry	29 (25%)	114 (41%)	263/8 oz
Hills Prescription Diet Feline r/d	Can	28 (24%)	114 (40%)	116/5.5 oz
Eukanuba Veterinary Diets Nutritional Weight Loss Formula Restricted-Calorie	Dry	26 (23%)	92 (34%)	271/8 oz

*Information obtained from manufacturers' published information.

As a consequence of lower intracellular cholesterol concentrations, the hepatic LDL receptor is up-regulated to increase the removal and clearance of LDL (VLDL remnant particles) from the circulation. In addition, the statins decrease hepatic production of VLDL. In humans, the statins can lower triglyceride by 10% to 15%. Adverse effects include lethargy, diarrhea, muscle pain, and hepatotoxicity.

Unlike in humans, hypercholesterolemia rarely poses a health risk to dogs or cats. Specific therapy is only indicated if a prolonged marked increase in the serum cholesterol (>800 mg/dL) is documented because it may be associated with the development of atherosclerosis. Nutritional therapy with low fat diets is the initial treatment of choice for severe hypercholesterolemia (see Table 160-1). The addition of soluble fiber to the diet may also help to reduce cholesterol by as much as 10%. Soluble fiber interferes with the enteric reabsorption of bile acids. Consequently, the liver uses cholesterol to increase the synthesis of bile acids.

Pharmacologic agents that can be considered for the management of severe hypercholesterolemia include bile acid sequestrates, HMG-CoA reductase inhibitors, and Probucol. Bile acid sequestrates are ion exchange resins that interrupt the enterohepatic circulation of bile acids. Decreased reabsorption of bile acids stimulates the liver to synthesize bile acids and therefore uses intrahepatic cholesterol. Depletion of intrahepatic cholesterol stores stimulates the hepatic LDL receptor to increase the removal of LDL and HDL particles from the circulation. Cholestyramine (1 to 2 g PO BID) is effective at lowering cholesterol. However, its use has been associated with constipation, it interferes with the absorption of several oral medications, and it may increase hepatic VLDL synthesis with an increase triglyceride concentration. HMG-CoA reductase is the rate-limiting enzyme for cholesterol synthesis. The HMG-CoA reductase inhibitors are the most potent cholesterol lowering agents and, in humans, may reduce cholesterol concentrations by 20% to 40%. Lovastatin, 10 to 20 mg PO every 24 hours, may be tried in dogs with persistent severe idiopathic hypercholesterolemia that does not respond to diet alone. Potential adverse effects include lethargy, diarrhea, muscle pain, and hepatotoxicity. Lovastatin should not be administered to dogs with hepatic disease. Probucol is a cholesterol-lowering agent whose mechanism of action is not completely clear. Probucol is not widely recommended for the management of hypercholesterolemia as its effect on lowering cholesterol concentration is variable and it has been associated with the development of arrhythmias.

CHAPTER 161

The Principles and Implementation of Enteral Nutrition

Stanley L. Marks

The documented benefits of enteral nutritional support of hospitalized human patients and experimental animal models include maintenance of intestinal structure and function, decreased mucosal permeability to bacteria and endotoxins, and preservation of secretory immunoglobulin A concentrations in biliary tract secretions.[1,2] Despite these benefits, veterinarians may fail to respond to the nutritional needs of sick animals, perhaps because the translation of research findings into practical applications is difficult. In addition, the nutritional needs of sick animals may be neglected due to the intense focus on life-threatening medical and surgical problems. The goal of nutritional support is to provide a formula of fuels and nutrients in proportions that can be utilized by animals with maximal efficiency. Choosing the proper enteral access technique requires knowledge of the limitations and benefits of the techniques available for obtaining enteral access. The reader is encouraged to read the section on Nasoesophageal, Esophagostomy, and Gastrostomy Tube Placement Techniques for a thorough review of the techniques and complications associated with placement of these devices.

RATIONALE FOR ENTERAL NUTRITIONAL SUPPORT

Enteral feeding is indicated for animals unable to ingest adequate amounts of calories but that have sufficient gastrointestinal function to allow digestion and absorption of feeding solutions delivered into the gastrointestinal tract via an enteral feeding device. The rationale for prescribing enteral nutrition rather than parenteral nutrition (PN) is based on the superior maintenance of intestinal structure and function, safety of administration, and reduced cost of enteral alimentation. The average daily cost of TPN for maintaining the caloric requirements of a 20-kg dog at the University of California, Davis, Veterinary Medical Teaching Hospital, is approximately seven times greater (excluding catheter costs) than the cost of a commercial liquid enteral formula and a commercial canned diet. The most important stimulus for mucosal cell proliferation is the direct presence of nutrients in the intestinal lumen. Bowel rest due to starvation or administration of TPN leads to villous atrophy[3], increased intestinal permeability, and a reduction in intestinal disaccharidase activities.[4] Prolonged fasting in the stressed, critically ill animal can lead to intestinal barrier failure and increased permeability to bacteria and endotoxins.

PATIENT SELECTION FOR NUTRITIONAL SUPPORT

Efforts to assess nutritional status and attempts to decide whether nutritional support is required on the basis of a single biochemical measurement or body weight determination are simplistic and of limited value. Objective methods of assessing nutritional status such as body composition measurement (anthropometry, impedance measurements, dual energy X-ray absorptiometry) are still in their infancy in veterinary medicine, with the result that a subjective global assessment of an animals nutritional status needs to be performed. This technique is based on easily collected historical information (changes in oral intake, degree of weight loss, presence of vomiting or diarrhea) and changes found on physical examination (muscle wasting, body condition, and presence of edema or ascites).

Although body weight is routinely determined in sick animals, it is important to appreciate its limitations. The appearance of the animal cannot be equated with its state of nourishment because body weight does not differentiate between fat, lean tissue, and extracellular water. The animal's serum albumin concentration and total lymphocyte count are insensitive determinants of nutritional status because of the large number of disease processes that influence these parameters unrelated to the effects of malnutrition. Nutritional support should be considered for animals that demonstrate recent weight loss that exceeds 10% of optimal body weight or for those whose oral intake has been or will be interrupted for more than 5 days. Animals with increased nutrient losses from chronic diarrhea or vomiting, wounds, renal disease, or burns should also be considered for nutritional support.

CALCULATION OF NUTRITIONAL REQUIREMENTS

Nutritional support provides substrates for gluconeogenesis and protein synthesis and provides the energy needed to meet the additional demands of host defense, wound repair, and cell division and growth. An estimate of an animal's nutrient requirements is needed to determine the minimum amount of food necessary to sustain critical physiologic processes (Box 161-1). The resting energy requirement (RER) is the animal's energy requirement at rest in a thermoneutral environment and in a postabsorptive state. A linear formula can be applied to determine the RER of dogs and cats weighing at least 2 kg, but no more than 15 kg. Alternatively, an allometric formula can be applied to dogs and cats of all weights.

$$\text{Linear formula: RER (kcal/day)} = (30 \times BW_{kg}) + 70$$

$$\text{Allometric formula: RER (kcal/day)} = 70\ (BW_{kg}^{0.75})$$

Accurate, direct measurements of energy expenditure in sick dogs and cats are not available. Despite the paucity of data on energy requirements of sick animals, veterinary nutritionists have recognized that the caloric requirements of critically ill animals are less than normal maintenance amounts (MER), but greater than RER. Hospitalized animals should be fed at their calculated RER initially, although their actual energy requirement is likely to change over the course of the disease process through recovery. Use of "fudge factors" extrapolated from the human literature to calculate the energy requirements

Box • 161-1

Enteral Feeding Worksheet for Dogs and Cats

1. Calculate resting energy requirement (RER):
   Body weight 2 to 45 kg: RER (kcal) = 30 Wt_{kg} + 70
   Body weight <2 or >45 kg: RER = 70 ($Wt_{kg}^{0.75}$)
   Body weight = _____kg
   RER = _____kcal
2. Calculate illness energy requirement (IER)*
   Illness factor = 1.2 to 1.4 for dogs
   Illness factor = 1.1 to 1.2 for cats
   IER = RER × illness factor
   IER = _____kcal
3. Calculate amount of diet to feed:
   Daily volume to feed: IER ÷ energy density (kcal/mL)
   Daily volume = _____mL
4. Evaluate responses and modify as needed:
   Weight changes often reflect fluid dynamics in the early period after injury. Caloric requirement may need to be increased or decreased depending on animal's metabolic rate and response to nutritional support.

Modified from Marks SL: The principles and practical application of enteral nutrition, *Vet Clin North Am Small Anim Pract* 28:677, 1998.

*Animals should be fed their RER initially, and have their body weights, physical examination findings, and ongoing losses carefully evaluated before gradually increasing their caloric intake based on the IER formula.

of critically ill animals is discouraged, particularly in the early phase of nutritional support. Close observation of changes in body weight, physical examination findings (decreased subcutaneous fat stores, muscle wasting, and presence of edema or ascites), and ongoing losses (diarrhea, vomiting, exudative wounds) will help determine whether to increase or decrease the patients caloric intake towards the illness energy requirement (IER) or RER, respectively. The term *illness energy requirement* (IER) is used to determine caloric requirements of critically ill animals and can be determined from these formulas:

$$\text{Canine IER (kcal/day)} = 1.2 - 1.4 \times \text{RER}$$

$$\text{Feline IER (kcal/day)} = 1.1\text{–}1.2 \times \text{RER}$$

DIET SELECTION

The type of formula to feed the patient depends on the selected route of feeding, the functional status of the gastrointestinal tract, and the animal's nutrient requirements. Other factors, such as cost, availability, and ease of use may also be important. Animals fed via nasoesophageal or jejunostomy feeding tubes are limited to receiving liquid enteral formulas that have a caloric density of approximately 1 kcal per ml. When selecting a liquid formula for feeding, veterinary professionals should pay particular attention to the amount of protein in the formula, the type of protein (intact proteins, peptides, and amino acids), and the quality of the protein. Whole egg has the highest biologic value, followed by cow milk, lactalbumin, beef, soy, and casein. Most human liquid formulas contain less than 20% protein calories, precluding their use for the long-term (longer than 2 weeks) feeding of cats. The lower-protein formulas should be supplemented with protein modules such as Promod (Ross Laboratories, Columbus, OH), Casec (Mead-Johnson, Evansville, IN) or Promagic (Animal Nutrition Laboratories, Burlington, NJ) at 15 to 30 g casein or whey powder per 8 fl oz can. Almost all human liquid enteral formulas lack taurine, an essential amino acid in cats, which necessitates its supplementation (250 mg taurine per 8 fl oz can) in this species. High-protein commercial human liquid formulations contain between 21% to 30% protein calories and include Impact (Sandoz Nutrition, Minneapolis, MN), Immun-Aid (McGaw, Inc., Irvine, CA), Alitraq (Ross Laboratories, Columbus, OH), Promote (Ross Laboratories, Columbus, OH), and Traumacal (Mead-Johnson, Evansville, IN).

Polymeric solutions contain macronutrients in the form of isolates of intact protein (casein, lactalbumin, whey, egg white), triglycerides, and carbohydrate polymers. The carbohydrates are usually glucose polymers in the form of starch and its hydrolysates and the fats are of vegetable origin. The osmolality varies between 300 and 450 mOsm/kg in solutions with a caloric density of 1 kcal/ml; however, the osmolality may reach 650 mOsm/kg in solutions with a greater caloric density. Monomeric solutions contain protein as peptides or amino acids, fat as long-chain triglycerides (LCT), or a mixture of LCT and medium-chain triglycerides (MCT), and carbohydrates as partially hydrolyzed starch maltodextrins and glucose oligosaccharides. These solutions require less digestion and their absorption is more efficient than regular foods or polymeric solutions; however, the partially digested macronutrients contribute to the higher osmolality, which is between 400 and 700 mOsm/kg.

Commercial blenderized pet food diets are recommended for feeding via pharyngostomy, esophagostomy, or gastrostomy tubes. In select cases, the feeding of a liquid enteral formulation may be indicated (nasoesophageal or jejunostomy tube feeding). There are a number of complete and balanced veterinary enteral formulations (Table 161-1) that contain adequate amounts of protein, taurine, and micronutrients, which precludes the need for supplementation in most situations. Feeding should be delayed for 24 hours after placement of a gastrostomy tube, to allow return of gastric motility and allow formation of a fibrin seal. In contrast, feeding can be instituted immediately after esophagostomy tube placement, once the animal has fully recovered from anesthesia. Diet can be administered as bolus feedings or continuous infusion when a gastrostomy tube is used for feeding. Improved weight gain and decreased gastroesophageal reflux have been reported in human patients given continuous feedings[5], although similar studies are lacking in the veterinary literature. If continuous feeding is employed, it should be interrupted every 8 hours to determine the residual volume by application of suction to the feeding tube. If the residual volume is more than twice the volume infused in 1 hour, feeding should be discontinued for 2 hours, and the rate of infusion decreased by 25% to prevent vomiting. Treatment with metoclopramide (1 to 2 mg/kg/24 hour as a continuous infusion) may be used to enhance gastric emptying and prevent vomiting.[6]

With bolus feeding, the required daily volume of food should be divided into four to six feeds. Dogs and cats are usually fed approximately 25% of their caloric requirement on the first day of feeding, with a gradual increase of 25% of the caloric requirement per day. Most animals are able to reach their energy requirement by the fourth or fifth day of feeding. The food should be warmed to room temperature and fed slowly through the tube to prevent vomiting. Flushing of the tube with 15 to 20 mL of lukewarm water helps prevent clogging. Before each feeding, aspirate the tube with an empty syringe to check for residual food left in the stomach from the previous feeding. If more than half of the last feeding is

Table • **161-1**

Macronutrient Composition of Selected Veterinary Liquid Enteral Formulations

PRODUCT	PROTEIN TYPE	CALORIC DENSITY (kcal/ml)	NUTRIENTS (% OF TOTAL kcal)			FORMULA CHARACTERISTICS
			PROTEIN	FAT	CARBOHYDRATE	
Prescription diet Canine & Feline a/d *(Hill's)*	Liver Chicken Corn flour Casein	1.3	34	55	4	Isotonic, lactose free, fiber 1.3% DM, adequate taurine, fatty acid ratio (n6:n3 = 2.2:1)
Eukanuba Maximum-Calorie Canine & Feline *(Iams)*	Chicken Chicken by-product meal	2.1	29	66	5	Isotonic, lactose free, fiber 1.6% DM, adequate taurine, fatty acid ratio (n6:n3 = 8.3:11)
CliniCare Canine *(Abbott)*	80% casein 20% whey	1.0	20	55	25	Isotonic (230 mOsm/kg), lactose free, fiber free, fatty acid ratio (n6:n3 = 6.4:1)
Clinicare Feline *(Abbott)*	60% casein 40% whey	1.0	30	45	25	Isotonic (235 mOsm/kg), lactose free, fiber free, adequate taurine, fatty acid ratio (n6:n3 = 6.4:1)
Clinicare RF Specialized Feline *(Abbott)*	80% casein 20% whey	1.0	22	57	21	Isotonic (165 mOsm/kg), lactose free, fiber free, adequate taurine, fatty acid ratio (n6:n3 = 6.4:1)

Modified from Marks SL: The principles and practical application of enteral nutrition, *Vet Clin North Am Small Anim Pract* 28:677, 1998.

removed from the stomach, the feeding should be skipped and residual volume rechecked at the next feeding.

Jejunal feeding can be started within 6 hours of tube placement if peristalsis is present. Continuous feeding should be used with jejunostomy feeding to avoid abdominal cramping and diarrhea associated with bolus feeding via this route. Continuous infusion is recommended at an initial flow rate of 1 ml/kg/hr and increased gradually over 48 hours until the total daily volume can be given over a 12- to 18-hour period.[7]

SECTION VIII

Infectious Disease

CHAPTER 162

Serology

Michael R. Lappin

Serology is the study of antigen-antibody reactions in vitro. Immunoassays for use with serum, blood, or plasma can be developed to detect antigens, antibodies, or antigen-antibody complexes; some assays are only qualitative, and others are quantitative. Some assays have been adapted to detect antigen-antibody reactions in other body fluids as well. This chapter discusses the use of immunoassays in the diagnosis of infectious diseases. Commonly used terms and their definitions are listed in Table 162-1. A discussion of serologic tests used in the diagnosis of immune-mediated diseases is presented in Chapters 277 and 278.

Complement fixation, hemagglutination inhibition, serum neutralization, agglutination assays, agar gel immunodiffusion, indirect fluorescent antibody assay (IFA), enzyme-linked immunosorbent assay (ELISA), and Western blot immunoassay are commonly used methodologies. It is beyond the scope of this chapter to discuss the intricacies of each assay; the reader is directed to other chapters and publications for further information on the development, validation, and techniques for the different assays.[1-5] It is impossible to make generic statements concerning the sensitivity, specificity, predictive values, and precision of different immunoassays in general or to compare the results of one type of assay with those of another. When new immunoassays are made available, the veterinary health care worker should critically evaluate the published results of the assay prior to use.

In serologic test results, the *analytic sensitivity* defines the minimum detectable amount of the substance in question that can accurately be measured; the *analytic specificity* defines whether the substance detected cross-reacts with other substances. The *diagnostic sensitivity* is the proportion of positive test results from known infected animals; the *diagnostic specificity* is the proportion of negative test results from known uninfected animals. The *predictive value of a positive test* is the probability that a test-positive animal is diseased; the *predictive value of a negative test* is the probability that a test-negative animal is normal. The lower the prevalence of disease, the lower the predictive value of a positive test result. Disease prevalence has little effect on negative predictive values.

The following is a brief discussion of the interpretation of test results for antibody and antigen assays used with blood, serum, plasma, or other body fluids by small animal veterinary health care workers.

ANTIBODY DETECTION

Once exposed to foreign antigens, the immune system generates serum antibodies (humoral immune response). Complement fixation, hemagglutination inhibition, serum neutralization, agglutination assays, agar gel immunodiffusion, IFA, ELISA, and Western blot immunoassay are commonly used to detect serum antibodies against infectious agents. Complement fixation, hemagglutination inhibition, serum neutralization, and agglutination assays generally detect all antibody classes in a serum sample. Specific antibodies for which assays are most commonly performed include immunoglobulin M (IgM), immunoglobulin G (IgG), immunoglobulin A (IgA), and immunoglobulin E (IgE). ELISA, Western blot immunoassay, and IFA are the assay types that are usually adapted to detect specific IgM, IgG, or IgA responses. Western blot immunoassays have the potential advantage of allowing the determination of the different antigens recognized by the humoral immune responses (Figure 162-1). Comparison of IgM, IgA, and IgG antibody responses against an infectious agent can be used to attempt to prove recent or active infection. In general, immunoglobulin M (IgM) is the first antibody produced after antigenic exposure.[6] Antibody class shift to IgG occurs in days to weeks. Serum IgA responses often mirror those of IgG (Figure 162-2).

The timing of antibody testing is important. In general, serum antibody tests in puppies and kittens cannot be interpreted as specific responses until at least 8 to 12 weeks of age because of the presence of antibodies from the dam, which are passed to the puppy or kitten in colostrum. Most infectious agents can induce disease within 3 to 10 days of initial exposure; with many assays, serum IgG antibodies usually are not detected until at least 2 to 3 weeks after initial exposure. Examples include *Ehrlichia canis*,[7] feline immunodeficiency virus,[8] and *Rickettsia rickettsii*.[9] For these reasons, falsely negative serum antibody test results during acute disease are probably common in small animal practice. If specific serum antibody testing is negative initially in an animal with acute disease, repeat antibody testing should be performed in 2 to 3 weeks to assess for seroconversion. Documentation of increasing antibody titers is consistent with recent or active infection. Because of a slight potential for interassay variation, it is preferable to assess both the acute and convalescent sera in the same assay on the same day.

Many of the infectious agents encountered in small animal practice infect a large percentage of the population, resulting in serum antibody production, but they induce disease only in a small number of animals in the infected group. Notable examples include coronaviruses, *Bartonella henselae*, *Toxoplasma gondii*, and *Borrelia burgdorferi*.[6,8,10,11] For these examples, even though assays with good sensitivity and specificity for the detection of serum antibodies are available, the predictive value of a positive test result for the presence of disease is extremely low because antibodies are commonly detected in nondiseased animals. The diagnostic utility of some serologic tests is also limited by the presence of antibodies induced by vaccination. Examples include feline coronaviruses, some *B. burgdorferi* assays, feline herpesvirus-1 (FHV-1), feline immunodeficiency virus, parvoviruses, calicivirus, and canine distemper virus.

Positive results in serum antibody tests should always be interpreted only as evidence of present or prior infection by the agent in question. Recent or active infection is suggested by the presence of IgM, an increasing antibody titer over 2 to 3 weeks, or seroconversion (negative antibody result on the first test, positive antibody result on convalescent testing). Documentation of increasing antibody titers may suggest

Table • 162-1

Terms Commonly Used in Serologic Tests

TERM	DEFINITION
Affinity	The intrinsic attractiveness of one substance for another (e.g., antibody for antigen)
AGID	Agar gel immunodiffusion; an immunoassay in which the immunochemical reaction between antigen and antibody occurs in agar
Analyte	The antigen or antibody to be measured
Antibody binding site	The site of the variable region of antibodies that binds to the antigen epitope
Antigen	A substance specifically recognized by the immune system (e.g., antibody in immunoassays)
Antiglobulin	An antibody that detects another antibody
Avidity	The property of a molecular dissociation that inhibits disassociation; usually the combination of affinity and the interaction of reagents with the solid phase
Blocking	A protein or detergent used to block nonspecific reactions between reagents of an enzyme-linked immunosorbent assay (ELISA) or between reagents and the solid phase
Capture antibody	An immobilized antibody used to capture the antigen of interest from the sample
Competitive ELISA	An ELISA in which detection of the analyte is based on its ability to quantitatively inhibit the binding of a known amount of a standard analyte to a limiting amount of antibody
Conjugate	A covalent complex of two biomolecules; in ELISA, the conjugate is an antibody or antigen bound to enzyme
Direct ELISA	An ELISA in which the primary antigen-antibody interaction is measured directly because the enzyme is directly labeled to one or the other
Epitope	The portion of a biomolecule (antigen) that is specifically recognized by the antibody binding site; also called an *antigenic determinant*
HI	Hemagglutination inhibition
IFA	Immunofluorescent antibody assay; an immunoassay in which the primary antigen-antibody reaction is detected by a fluorescein-labeled secondary antibody
Immunoblot	An immunoassay in which the immunochemical reaction between antigen and antibody occurs on a blotting membrane
Indirect ELISA	An ELISA in which the primary antigen-antibody reaction is detected using an enzyme-labeled antiglobulin
LA	Latex agglutination
Nitrocellulose	The membrane most commonly used for immunoblot
Nonspecific binding	Binding of the conjugate in a nonimmune/nonspecific fashion, possibly resulting in a high signal and false-positive reactions
Precision	Agreement of replicate measurements within an assay or between assays; a measure of reproducibility
Reporter substance	A biomolecule that generates a signal as an indication of its presence; in ELISA, the substrate often is the reporter substance
Sandwich ELISA	A type of ELISA in which the analyte is captured by one antibody and detected by another, enzyme-linked antibody
SN	Serum neutralization
Titer	The reciprocal of the highest dilution of sample giving a predefined positive reaction in an immunoassay
Western blot (immunoassay)	A method by which molecules are electrophoretically separated on a gel, transferred to a blotting membrane, and then detected by antibodies or special stains

recent exposure to an antigen. However, the interval between the first positive result and maximal antibody titers can be very short. For example, some cats experimentally inoculated with *T. gondii* progress from the first detectable titer to the maximal titer within 1 to 2 weeks.[6]

Detection of recent infection based on antibody testing does not always prove disease caused by the agent in question. This is especially true in affected animals with a subclinical infection. *B. burgdorferi*, *T. gondii*, and *B. henselae* are common examples of this. Conversely, failure to document recent or active infection based on serologic testing does not exclude a diagnosis of clinical disease. For example, many dogs with ehrlichiosis and dogs or cats with systemic fungal infections develop clinical signs of disease after serum antibody titers have reached their plateau.

Individual animals vary in the humoral responses against specific antigens. Some animals are high responders and produce large concentrations of specific antibody, whereas others do not. Thus the magnitude of an antibody titer does not definitely document that an antigenic exposure was recent, active, or associated with clinical disease. This is particularly true for the IgG class of antibody and for agents resulting in persistent infections. For example, many healthy cats experimentally inoculated with *T. gondii* have had IgG antibody titers greater than 1:10,000 even 6 years after the last inoculation.[6] Because no antibody test by itself can prove the presence of disease, clinical diagnosis of an infectious disease usually includes the following factors:

- Clinical signs referable to the agent
- Serologic evidence of exposure to the agent

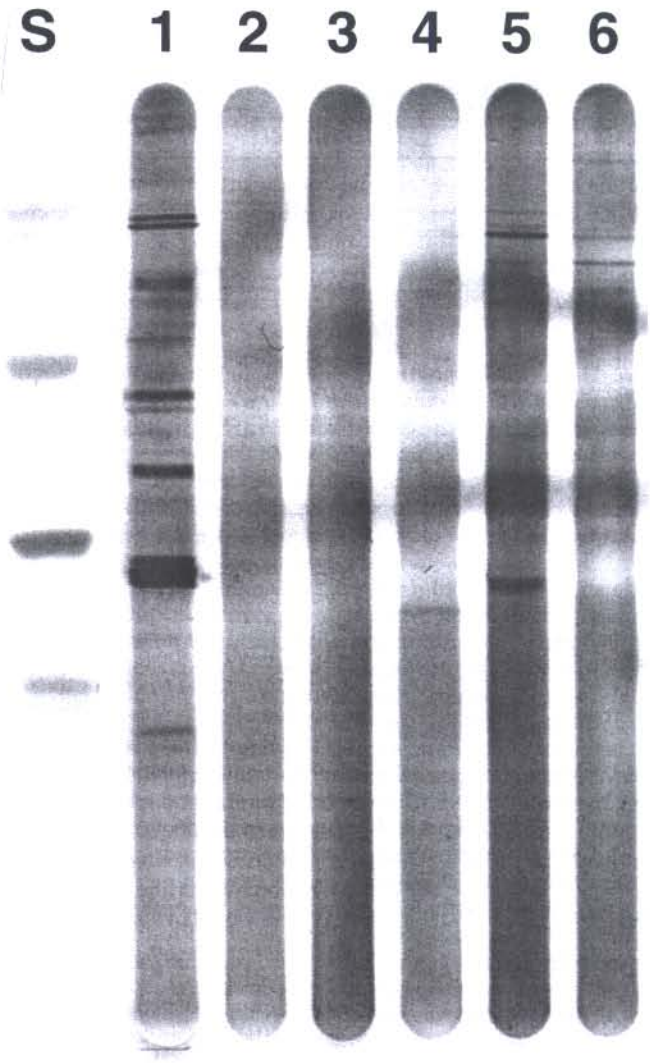

Figure 162-1 Example of a Western blot immunoassay. The bands that have developed in the suspect serum lanes are consistent with an antigen-antibody reaction. Comparison to the molecular mass standards allows determination of the approximate size of the antigen inducing the immune response.

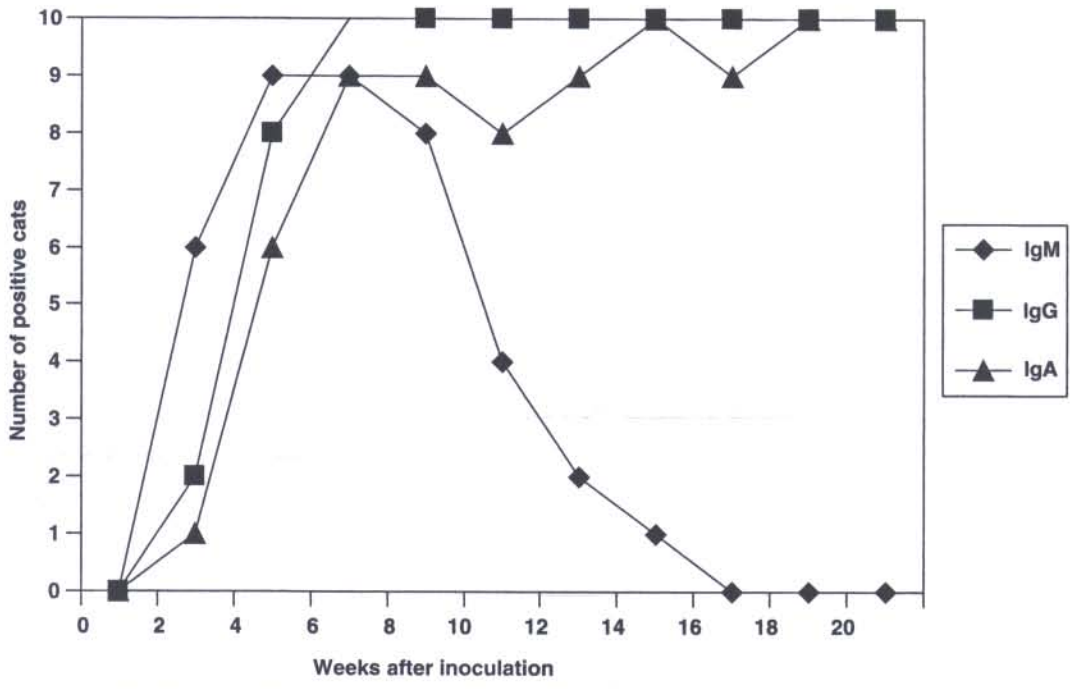

Figure 162-2 Graphic representation of IgM, IgG, and IgA immune responses characteristic for cats after antigenic exposure in week 0.

- Exclusion of other causes of the clinical syndrome
- Demonstration of the agent or of response to treatment

ANTIGEN DETECTION

Immunoassays can be used to measure any substance against which an antibody can be generated. Examples include antigens of infectious agents, cell-associated antigens (including tumors), receptors, hormones, and drugs. Positive results in immunoassays that detect the presence of antigens of an infectious disease agent document that the animal is currently infected. The presence of antibodies denotes current or previous infection.

Immunoassays are commercially available for the detection of *Dirofilaria immitis*,[12] feline leukemia virus (FeLV),[13] and *Cryptococcus neoformans*[14] antigens in serum, plasma, or blood. The performance of specific assays may vary with the different fluids; in general, serum gives the most consistent results. For the most part, the sensitivities and specificities of the infectious disease antigen assays are good. *D. immitis* antigen test results can be negative in some animals with low worm burdens or single sex infections; this is particularly true for cats.[12] Feline leukemia virus antigen test results can be negative in cats with localized or sequestered infection (latent). Serum- or plasma-based feline leukemia virus antigen tests can also yield transiently positive results in cats that are limiting infection; the results for healthy, ELISA-positive cats should always be confirmed by repeat ELISA testing or by IFA testing.[14] Because clinically normal animals can be antigen positive by ELISA, the positive predictive value for disease is not 100%, particularly if the prevalence of disease is low. Positive feline leukemia antigen test results also do not prove immunodeficiency. In dogs and cats with localized cryptococcosis, serum antigen test results can be negative.

Body Fluids

Some infectious agents induce disease of the eyes and central nervous system (CNS). Documentation of agent-specific antibodies in aqueous humor, vitreous humor, or cerebrospinal fluid (CSF) can be used to prove the involvement of these tissues. Quantification of ocular and CSF antibodies is difficult to interpret if serum antibodies and inflammatory disease are present, because serum antibodies leak into ocular fluids and CSF in the presence of inflammation. Detection of local production of antibodies in the eye or CNS has been used to aid the diagnosis of canine distemper virus infection (see Chapter 169) and feline toxoplasmosis (see Chapter 169). The following ratio is a method of proving local antibody production by the eye or CNS:

$$\frac{\text{Aqueous humor or CSF specific antibody}}{\text{Serum specific antibody}} \times \frac{\text{Serum total antibody}}{\text{Aqueous humor or CSF total antibody}}$$

A ratio greater than 1 suggests that the antibody in the aqueous humor or CSF was produced locally. This formula has been used extensively in the evaluation of cats with uveitis. Approximately 60% of cats with uveitis in the United States have *T. gondii*–specific IgM, IgA, or IgG values greater than 1.[6,15] This technique also was used to help prove that FHV-1[16] and *B. henselae*[17] are causes of uveitis in cats.

Feline leukemia virus antigen can be detected in saliva, tears, and cells from the bone marrow or direct blood smear.[13] The sensitivity and specificity of FeLV tests using tears and saliva are less than for those using serum. Detection of FeLV antigen in cells by fluorescent antibody testing generally denotes persistent infection. *T. gondii* antigens have been detected in aqueous humor and CSF, but their presence does not correlate with the presence of disease.[6] The *C. neoformans* latex agglutination procedure for detection of antigen can also be performed on aqueous humor, vitreous humor, and cerebrospinal fluid.

Immunoassays are available for th · detection of parvovirus, *Cryptosporidium parvum*, and *Giard .ı spp.* in feces. The commercially available parvovirus assay was titrated for use with canine feces and canine parvovirus, but generally it can detect panleukopenia antigen in the feces of infected cats as well. Sensitivity appears to be good with parvovirus fecal antigen tests, but positive test results are not specific for natural exposure because modified live parvovirus vaccines are shed into feces, giving transiently positive results (see Chapter 169). The currently available assays for the detection of *C. parvum* and *Giardia spp.* in feces were titrated for human isolates and feces. Minimal sensitivity and specificity results are available for these assays when they are used with feces from small animals (see Chapter 168). If these assays are used, the results should be interpreted with results from fecal examination techniques for oocysts *(Cryptosporidium)* or cysts *(Giardia)*.

CHAPTER 163

Canine Vaccination

Richard B. Ford

The recent publication of the *2003 Canine Vaccine Guidelines and Recommendations*[1] is the first such effort intended to provide a unified consensus reference on canine vaccination for the veterinary profession.

As published, the *Guidelines* address 15 types of canine vaccine licensed for use in the United States and provide critical information pertinent to the development and implementation of vaccination protocols for dogs. The *Guidelines* are *not* intended to represent vaccination *standards* for dogs nor do they define a uniform vaccination protocol for use in clinical practice. As new information is gained and as new vaccines are licensed for use in dogs, these *Guidelines* will be updated.

The context of the *2005 Canine Vaccine Guidelines* centers on vaccine selection and frequency of use. Additional supportive information includes an overview of immunology as it pertains to vaccination, the role of serologic testing in determination of the need to administer booster vaccines to individual patients, vaccine adverse events, and pertinent legal and liability issues related to administering vaccines. The Canine Vaccine Guidelines outlined by the Task Force are summarized in Table 163-1. The reader is encouraged to consult the full text of the Guidelines for further information on individual vaccine types and supporting literature.[2]

VACCINE SELECTION

Vaccination guidelines published for cats as well as dogs have endorsed terms (*core* and *noncore*) that categorize vaccine types (not individual products) using criteria such as health risk associated with infection, disease incidence and severity, and vaccine efficacy. *Core* vaccines are generally defined as those vaccines that should be administered to *every* dog (and every cat) that is 6 months of age or younger or is not known to have received prior vaccination. These vaccines are deemed particularly important because the infections they prevent are associated with significant morbidity and mortality, are widely distributed, or are zoonotic. The Canine Vaccine Task Force has designated vaccines against canine distemper, canine parvovirus, canine adenovirus-2, and rabies virus as *core*.

Vaccines defined as *noncore* (or "optional") are those that should be administered only after consideration of the risk an individual dog has for exposure to a defined infectious agent. Factors such as geographic distribution of the disease (e.g., Lyme borreliosis), age of the patient (puppy versus adult), and lifestyle (strict indoor versus free-roaming) are considered in the decision to administer, or not administer, noncore vaccines. Vaccines placed in this category are recommended when it is the objective to protect individual dogs against less common, or less severe, infections that are either self-limiting or amenable to treatment. The Canine Vaccine Task Force has designated vaccines against measles (distemper-measles), canine parainfluenza, *Leptospirosis* spp., *Bordetella bronchiseptica*, and *Borrelia burgdorferi* as *noncore*.

Additionally, the Task Force has designated vaccines against *Giardia* spp., canine coronavirus, and canine adenovirus-1 (canine hepatitis) as "not generally recommended." The basis for such designation is based on information discussed in detail within the context of the *Guidelines*. Reasons for placing a particular vaccine in this category have been based on one or more of the following: the disease a vaccine is intended to prevent is either of little or no clinical significance (e.g., coronavirus), the vaccine is known to be associated with potentially serious adverse events (e.g., adenovirus-1), or the vaccine does not prevent infection (e.g., *Giardia* spp.).

The Canine Vaccine Task Force acknowledges the fact that all veterinarians may not agree with which vaccines belong in which category. For that reason, the *Canine Guidelines* have been written to support individual clinicians and practices in designation of which vaccines should be given to all dogs presented to the practice and which vaccines are administered only on the basis of a defined health risk assessment. Veterinarians are therefore encouraged to designate, for the individual practice, which vaccines should be *core* and which *noncore*. The decision to administer, or *not* to administer, a vaccine categorized as *noncore* rests with the individual clinician after interviewing the pet owner and assessing reasonable risk for exposure. For example, the Canine Vaccine Task Force designated canine adenovirus-2 vaccine as *core* and the canine parainfluenza vaccine as *noncore*. However, the majority of parainfluenza vaccine products on the market today are combined with canine adenovirus-2. It is therefore quite reasonable for an individual practice to designate *both* canine adenovirus-2 and parainfluenza vaccines as *core* when developing a vaccine protocol.

FREQUENCY OF VACCINE USE

Among the most significant recommendations made by the Canine Vaccine Task Force is that, despite traditional recommendations, certain vaccines, when administered to adult dogs as a booster vaccination, may be administered at intervals of 3 years without degradation of protection or increased risk if exposed to the virulent agent. In fact, limited studies involving most core vaccines support a minimum duration of immunity (DOI) of 5 to 7 years. Recommendations pertaining to *initial* vaccination intervals for puppies and adult dogs (not previously vaccinated) remain unchanged.

Current information on DOI, as presented in the full text of the *Guidelines*, supports the recommendation for 3-year booster vaccination intervals for the following vaccines: canine distemper (modified-live and recombinant), parvovirus (modified-live), canine adenovirus-2 (modified-live), and parainfluenza virus.

Obviously the actual DOI for any vaccine is influenced by such factors as the vaccine manufacturing process, route of administration, concentration of antigen in the product, product handing, health status of the patient at time of vaccination, and genetic variances in an individual animal's ability to response to a vaccine.

Text continued on p. 611.

Table • **163-1**

Canine Vaccine Recommendations—2005

VACCINE	PRIMARY VACCINATION (PUPPY) ≤16 WEEKS	PRIMARY VACCINATION (ADULT) >16 WEEKS	REVACCINATION (BOOSTER) RECOMMENDATIONS	COMMENTS
Canine Distemper Virus (MLV)	Administer one dose at 6-8 weeks, then 9-11 weeks, then 12-14 weeks of age	1 dose is protective	First booster is administered 1 year following the last dose of the initial (puppy) series. **Additional boosters are administered every 3 years thereafter.**	***Highly Recommended:*** Despite manufacturer's annual booster recommendations, studies have shown that adult dogs challenged 7 years (Rockborn Strain) and 5 years (Onderstepoort Strain) following MLV vaccination were protected. A booster vaccination interval of every 3 years among adult dogs in protective.
CORE				
rCanine Distemper Virus (**r**CDV) (recombinant vaccine)	Administer one dose at 6-8 weeks, then 9-11 weeks, then 12-14 weeks of age	2 doses, 2-4 weeks apart	Booster annually -or- **Booster may be administered (see comments section) every 3 years.**	***Recommended:*** May be used interchangeably or as an alternative to the MLV-CDV vaccine. Does not provide "sterile" immunity and may take longer to protect immunologically naïve dogs. Minimum demonstrated. Duration of Immunity (DOI) for **r**CDV is >2 years. Does not routinely provide sterile immunity and may take longer to protect immunologically naïve dogs. The vaccine is not recommended where the threat of exposure to CDV may be significant (e.g., shelters; pet stores). NOTE: A vaccination program that includes MLV-CDV vaccine for the initial vaccination followed by booster vaccination with **r**CDV would provide excellent protection; revaccination with **r**CDV every 3 years would then be reasonable.
CORE VACCINE (alternative to MLV CDV)				
Distemper-Measles Virus (MLV) **Administer by the INTRA-MUSCULAR route only**	One dose between 4 and 12 weeks of age...**only**. (Follow with one dose of MLV-CDV -or- 2 doses of **r**CDV vaccine after 12 weeks of age)	Not recommended for use in dogs over 12 weeks of age	Booster vaccination is **NOT** recommended.	**Optional. *Not Recommended for Routine Use.*** Intended to provide *temporary* protection in young dogs only. Indicated for use in households/kennels where distemper is a recognized problem. *Do not administer to female dogs over 12 weeks of age.*

Continued

Table • 163-1

Canine Vaccine Recommendations—2005—cont'd

VACCINE	PRIMARY VACCINATION (PUPPY) ≤16 WEEKS	PRIMARY VACCINATION (ADULT) >16 WEEKS	REVACCINATION (BOOSTER) RECOMMENDATIONS	COMMENTS
				Not recommended for use in ANY dog over 12 weeks of age. NOTE: If used in adults, the vaccine may result in maternal measles virus antibody that would be passed to offspring. This maternal antibody would interfere with subsequent vaccination against distemper. This vaccine will not immunize dogs if given by the subcutaneous route.
NONCORE				
Canine Parvovirus (MLV)	Administer one dose at 6-8 weeks, then 9-11 weeks, then 12-14 weeks of age	1 dose (however, recommending 2 doses, 3-4 weeks apart is acceptable)	First booster is administered 1 year following the last dose of the initial (puppy) series. **Additional boosters are administered every 3 years thereafter.**	***Highly Recommended:*** Although annual boosters are recommended by vaccine manufacturers, studies have shown protection against challenge up to 7 years post-vaccination with MLV vaccine.
CORE				
Canine Parvovirus (killed)	Administer one dose at 2, 3 and 4 months of age	2 doses, 3-4 weeks apart	Annual NOTE: Studies are not currently available demonstrating an extended DOI for killed CPV products. NOTE: Puppies completing the initial series with an MLV CPV vaccine and revaccinated 1 year later with an MLV CPV vaccine could be vaccinated every 3 year thereafter with the KILLED virus vaccine.	***Recommended:*** A suitable to the MLV alternative canine parvovirus vaccine in a LOW-risk environment, ALTHOUGH most practices routinely use the MLV vaccine. NOTE: Killed parvovirus products are susceptible to maternal antibody interference in puppies as old as 16 to 18 weeks of age. NOTE: Studies have shown protection against challenge 16 months post-vaccination in dogs only vaccinated with killed vaccine.
NON-CORE an alternative to the MLV vaccine				
Canine Adenovirus-1 (CAV-1) (MLV and killed)	Administer one dose at 6-8 weeks, then 9-11 weeks, then 12-14 weeks of age	2 doses, 2-4 weeks apart (Killed vaccine) 1 dose (MLV vaccine)	Annual (manufacturer recommendation)	***Not Recommended.*** Infectious Canine Hepatitis is uncommon in the U.S. Considering the low (to absent) prevalence, the risk of "hepatitis Blue-Eye" reactions, and the fact that CAV-2 will cross-protect against CAV-1, use of vaccines containing CAV-1 are *not* recommended.
NOT RECOMMENDED				***Caution:*** **At least 9 OTC vaccines (available to pet owners without a prescription)**

Continued

Table • 163-1

Canine Vaccine Recommendations—2005—cont'd

VACCINE	PRIMARY VACCINATION (PUPPY) ≤16 WEEKS	PRIMARY VACCINATION (ADULT) >16 WEEKS	REVACCINATION (BOOSTER) RECOMMENDATIONS	COMMENTS
				are currently on the market. Three of those vaccines contain a combination of BOTH CAV-1 and CAV-2!
Canine Adenovirus-2 (CAV-2) (MLV-parenteral or topical) (Killed)	Administer one dose at 6-8 weeks, then 9-11 weeks, then 12-14 weeks of age	2 doses, 2-4 weeks apart (Killed vaccine) 1 dose (MLV vaccine)	First booster is administered 1 year following the last dose of the initial (puppy) series. **Additional boosters are administered every 3 years thereafter.**	***Highly Recommended.*** Demonstrated cross protection against canine hepatitis (CAV-1) and CAV-2, one of the agents known to be associated with infectious tracheobronchitis (ITB). Usually combined with CDV and CAV vaccine. *Currently this product is not available as a monovalent vaccine.* Adult dogs challenged 7 years following CAV-2 MLV vaccination were found to be protected against the more virulent CAV-1.
CORE				
Parainfluenza Virus (CpiV) (MLV-parenteral or topical)	Administer one dose at 6-8 weeks, then 9-11 weeks, then 12-14 weeks of age	1 dose is adequate (However, recommending 2 doses, 3-4 weeks apart is acceptable.)	*Parenteral:* First booster is administered 1 year following the last dose of the initial (puppy) series. **Additional boosters are administered every 3 years thereafter.** *Intranasal:* Available only in combination with those *Bordetella bronchiseptica* indicated for intranasal administration. **Unpublished data suggests the DOI may persist beyond 1 year.**	***Recommended.*** Usually combined with CDV and CAV vaccine. Currently this product is not available as a monovalent vaccine. Parenterally administered vaccine is less effective than topically (intranasal) administered vaccine. DOI by challenge has been shown to be at least 1 year (unpublished) for topical vaccine. Parenteral CPiV vaccine is available in combination with CDV, CPV, and CAV-2 vaccines. Intranasal CPiV vaccine is available In combination with *B. bronchiseptica* and CAV-2 vaccines.
NONCORE				
Bordetella bronchiseptica (killed bacterin)-Parenteral	Administer one dose at 6-8 weeks, then 10-12 weeks of age	2 doses, 2-4 weeks apart	Annual	***Optional.*** Recent studies suggest the parenteral *B. bronchiseptica* vaccine may be more efficacious than the topical vaccine when administering boosters to adult dogs. The DOI is believed to be less than 1 year.

Continued

Table • 163-1

Canine Vaccine Recommendations—2005—cont'd

VACCINE	PRIMARY VACCINATION (PUPPY) ≤16 WEEKS	PRIMARY VACCINATION (ADULT) >16 WEEKS	REVACCINATION (BOOSTER) RECOMMENDATIONS	COMMENTS
				There is no clear advantage in administration of the parenteral and the topical *B. bronchiseptica* simultaneously.
NONCORE				
Bordetella bronchiseptica (live avirulent bacterin) + Parainfluenza Virus (MLV)	Administer a single dose as early as a 3 WEEKS OF AGE. (See product literature for age recommendations.)	Not stipulated, although a single dose is recommended.	Annual ... if *not* vaccinated within the last 6 months, a booster is recommended 1 wk prior to known exposure (e.g., boarding, showing)	***Optional-Recommended*** for dogs housed in kennels, shelters, pounds; prior to boarding in kennels. Transient (3-10 days) coughing, sneezing, or nasal discharge occurs in a small percentage of vaccinates. Antimicrobial therapy may be indicated (Rx Doxycycline, 5-7 days) to manage post-vaccination upper respiratory signs (persistent cough and nasal discharge). DOI is believed to be approx. 10 months for *B.bronchiseptica.*
TOPICAL (intranasal) USE ONLY	If topical vaccine is administered prior to 5-6 weeks of age, it should be administered again after 6 weeks of age and at least 2 weeks following the last dose.			NOTE: Topically administered vaccines for canine infectious tracheobronchitis may provide a superior local immune response compared to parenterally administered vaccines.
NONCORE				
Bordetella bronchiseptica (live avirulent bacterin) + Parainfluenza Virus (MLV) + Canine Adenovirus-2 (MLV)	Administer a single dose at ≥8 weeks of age. Some manufacturers may recommend administration as early as 3 to 4 weeks of age. This is recommended only when extremely high risk of exposure is likely.	A single dose is recommended.	Annual ... if *not* vaccinated within the last 6 months, a booster is recommended 1 wk prior to known exposure (e.g., boarding, showing)	***Recommended*** for dogs considered to be at risk of exposure to any of the pathogens listed. NOTE: Topically administered vaccines for canine infectious tracheobronchitis may provide a superior local immune response compared to parenterally administered vaccines. DOI as noted above for individual vaccines.
TOPICAL (intranasal) USE ONLY				
OPTIONAL				
Borrelia burgdorferi; **r**Lyme borreliosis (recombinant) Outer Surface Protein A (OspA)	Initial dose may be given at 9 weeks of age and a required second dose 2-4 weeks later. Optimal age for the initial dose is ≥3 months with a second dose 2-4 weeks later.	2 doses, 2-4 weeks apart	Annual (The Task Force has recommended that, depending on geographic location, the vaccine be administered prior to the start of the tick season.)	***Optimal. NOTE:*** Lyme disease has limited regional prevalence; therefore recommendation for use is limited to dogs known to have a high risk of exposure.

Continued

Table • 163-1

Canine Vaccine Recommendations—2005—cont'd

VACCINE	PRIMARY VACCINATION (PUPPY) ≤16 WEEKS	PRIMARY VACCINATION (ADULT) >16 WEEKS	REVACCINATION (BOOSTER) RECOMMENDATIONS	COMMENTS
NONCORE				The minimum DOI for the recombinant vaccine is 1 year based on challenge.
Borrelia burgdorferi; Lyme borreliosis (killed whole bacterin)	Initial dose may be given at 9 weeks of age and a required second dose 2-4 weeks later. Optimal age for the initial dose is ≥3 months with a second dose 2-4 weeks later.	2 doses, 2-4 weeks apart	Annual (The Task Force has recommended that, depending on geographic location, the vaccine be administered prior to the start of the tick season.)	***Optional.*** Lyme disease has limited regional prevalence. Recommendation for use is limited to dogs with a known high risk of exposure, preferably dogs living in the Northeastern U.S. and the upper Midwest (Wisconsin, Michigan) or perhaps those traveling to endemic areas when the risk of tick exposure is considered to be high. Minimum DOI based on challenge studies is 1 year.
NONCORE				
Canine coronavirus (killed and MLV)	Administer one dose every 2-4 weeks of age until 12 weeks of age (MLV and killed). The *killed* vaccine may be administered as early as 6 weeks of age followed by an additional dose every 2-3 weeks with the final dose at 12 weeks of age.	1 dose (if using MLV) 2 doses, 2-3 wks apart (if using killed) (The Task Force does not recommend the use of CCV vaccine in adult dogs since neither need nor benefit has been demonstrated in challenge studies.)	Annual (manufacturer recommendation) Neither product is recommended until clinical benefit demonstrated over combined vaccines (e.g., CPV and CDV only) that do not contain CCV antigen.	Prevalence of clinical cases of confirmed canine coronavirus infection does not justify routine inoculation of all dogs. Clinical infections are most likely to occur in puppies less than 6 weeks of age. Clinical signs are mild or not apparent and typically resolve spontaneously. It is recommended that animal shelters NOT utilize CCV vaccine in routine vaccination programs due to additional costs incurred by doing so and the lack of defined benefit. Experience has shown no additional increase in infectious enteritis among adults or puppies subsequent to discontinuing CCV vaccine. The DOI for CCV vaccine can not be determined since control dogs that are challenged do not become ill.
NOT GENERALLY RECOMMENDED				Neither the MLV CCV vaccine nor the killed CCV vaccine has been shown to significantly reduce disease caused by a CCV + CPV challenge.

Continued

Table • 163-1

Canine Vaccine Recommendations—2005—cont'd

VACCINE	PRIMARY VACCINATION (PUPPY) ≤16 WEEKS	PRIMARY VACCINATION (ADULT) >16 WEEKS	REVACCINATION (BOOSTER) RECOMMENDATIONS	COMMENTS
Leptospira interrogans (*L. canicola* combined with *L. icterohaemorrhagiae*) (killed bacterin) (Also available with serovars *grippotyphosa* and *pomona*)	Administer 1 dose at 12 weeks and a second at 16 weeks of age. NOTE: For optimal response, do not administer to dogs less than 12 weeks of age.	2 doses, 2-4 weeks apart	Annual Some authors recommend a booster every 6 months in dogs known to be at *significant* risk of exposure, i.e., documentation of infections in the practice population or area. Arbitrary administration of leptospirosis vaccines every 6 months is NOT recommended.	***Optional.*** NOTE: Disease prevalence is likely to vary for each serovar. Vaccine recommendations are therefore difficult to make due the lack of information on prevalence of specific serovar infections among dogs living in various geographic regions of the U.S. Anecdotal reports from veterinarians and breeders suggest that the incidence of post-vaccination reactions (acute anaphylaxis) in puppies (less than 12 weeks of age) and small breed dogs is high. Reactions are most severe in young (<9 weeks of age) puppies. Routine use of the vaccine should be delayed until dogs are ≥12 weeks of age. Minimum DOI based on challenge studies has been shown to be approximately 12 months for serovars *L. canicola* and *L. icterohaemorrhagiae*. Efficacy, however, is <75%. (Data is not available on the DOI for *L. grippotyphosa* and *L. pomona*)
NONCORE				
Giardia lamblia (killed)	An initial dose may be given at 8 weeks of age; a second dose should be given 2-3 weeks later.	2 doses, 2-4 weeks apart	Annual (manufacturer's recommendation) The Task Force recommends that boosters are NOT necessary in dogs ≥1 year of age.	***Not Recommended***. The vaccine may prevent oocyst shedding but does not prevent infection. Infection in puppies (and kittens) is often subclinical. Although giardiasis is the most common intestinal parasite among people in the U.S. the source of human infection is contaminated water. Infections in dogs and cats are not considered to be zoonotic. The vaccine does NOT prevent infection, therefore a minimum DOI based on challenge is not reported.
NOT GENERALLY RECOM-MENDED				

Continued

Table 163-1

Canine Vaccine Recommendations—2005—cont'd

VACCINE	PRIMARY VACCINATION (PUPPY) ≤16 WEEKS	PRIMARY VACCINATION (ADULT) >16 WEEKS	REVACCINATION (BOOSTER) RECOMMENDATIONS	COMMENTS
Rabies **1-year** (killed) ROUTE OF ADMINISTRATION MAY *NOT* BE OPTIONAL — see product literature for details.	Administer 1 dose as early as 3 months of age.	Administer a single dose.	Annual. State, provincial, and/or local laws apply. The **1-year** rabies vaccine may be used as a booster vaccine when dogs are required, in accordance with local statutes, to be vaccinated annually against rabies.	***Required.*** MLV vaccines are no longer available for administration in the U.S. State and local statutes govern the frequency of administration for products labeled as "1-Year Rabies." NOTE: The Rabies (1-year) vaccine is generally administered as the initial dose followed, 1 year later, by administration of the Rabies (3-year) Vaccine. State and local statutes may dictate otherwise.
CORE Rabies **3-year** (killed) ROUTE OF ADMINISTRATION MAY *NOT* BE OPTIONAL— see product literature for details.	Administer 1 dose as early as 3 months of age. *NOTE: The 3-year rabies vaccine may be used as an alternative to the 1-year rabies vaccine for initial and subsequent doses. Local statutes apply.*	Administer a single dose. *NOTE: The 3-year rabies vaccine may be used as an alternative to the 1-year rabies vaccine for initial and subsequent doses. Local statutes apply.*	The **second** rabies vaccination is recommended 1-year following administration of the initial dose regardless of the animal's age at the time the first dose is administered. Depending on local statutes, booster vaccines should be administered annually or every 3 years thereafter.	***Required.*** State and local statutes govern the frequency of administration for products labeled as Rabies (3-year) ... these statutes vary throughout the U.S. and Canada. NOTE: The Rabies (1-year) vaccine is generally administered as the initial dose followed, 1 year later, by administration of the Rabies (3-year) Vaccine. State and local statutes may dictate otherwise. The Task Force recommends that every effort should be made to change laws that require vaccination with the 3-year rabies vaccine at any interval less than 3 years. Doing so does not increase efficacy and may actually be associated with adverse events.
CORE				

NOTE: Letter designation "r" preceding the name of the antigen indicates a recombinant vaccine.
NOTE: Route of administration is SQ or IM unless otherwise noted by the manufacturer.

CONCLUSION

In the absence of specific and reliable tests for immunity to infectious disease, each veterinarian must accept the responsibility of developing a rational vaccination protocol that, based on health risk profiling and vaccine(s) available, will best protect the individual patient at the most appropriate stages of life. The *Canine Vaccine Guidelines* have been specifically written to support safe, effective, and rational vaccination decisions.

CHAPTER • 164

Feline Vaccinations

James R. Richards

The overall objectives of feline vaccination are to vaccinate the largest possible number of cats in the population at risk, vaccinate each cat no more frequently than necessary, and vaccinate only against infectious agents to which the cat has a realistic risk of exposure and subsequent development of disease. Kittens less than 4 months of age are usually more susceptible to infection and disease than are adult cats, and they are the principle targets for vaccination.[1]

VACCINATION EFFICACY

The success of vaccination against an infectious agent rests upon the ability of the immune system to protect against the disease in question.[2] Vaccines against agents that do not establish persistent infections (e.g., feline panleukopenia virus) are the most successful. Vaccines against agents characterized by persistent infections (e.g., feline herpesvirus [FHV], feline calicivirus), that evade host defense mechanisms (e.g., feline leukemia virus [FeLV], feline immunodeficiency virus [FIV]), that mutate as they replicate within the host (e.g., FIV, feline calicivirus, feline coronavirus), or that use normal host defenses to cause disease (e.g., feline coronavirus) are generally less successful.

Vaccines do not induce the same degree of protection in all animals, nor do most vaccines induce complete protection from either infection or disease. Factors that negatively affect an animal's ability to respond to vaccination include maternal antibody interference, congenital or acquired immunodeficiencies, concurrent disease, inadequate sanitation, immunosuppressive medication, and stress due to overcrowding.[3] An optimal response to vaccination cannot be obtained until the influence of these factors is reduced.

The United States Department of Agriculture (USDA), under the authority granted by the Virus, Serum, Toxin Act of 1913, requires that vaccines produced for interstate sale be pure, potent, safe, and efficacious. Efficacy, as defined by the USDA, is an in vivo determination of a vaccine's ability to induce an immune response and is usually determined by either direct challenge exposure of test animals (usually 20 to 30 vaccinates and a smaller number of nonvaccinated controls) or by measurement of serologic response. Although such tests are necessary, they provide little information regarding whether the immune response induced by vaccination is clinically relevant. Several reasons exist for these shortcomings: the test animals tend to be of uniform age and lineage, the number used is usually small, the route and dose of challenge agent may not mimic natural exposure, and the virulence and genetic-antigenic diversity of field isolates may be highly variable and differ from the challenge agent. Studies that involve larger numbers of animals of diverse ages, health status, lineage, as well as those that are exposed under natural settings provide additional information, but they are expensive, difficult to control, and uncommonly performed.

VACCINATION SITES

Standardizing and recording parenteral vaccine sites in the patient's permanent record is important for monitoring local reactions and management of vaccine-associated sarcomas. Parenteral vaccines should not be administered in the dorsal spinal region or body wall. Limiting administration to the distal limbs provides the best opportunity for control of vaccine-associated sarcomas[4] (Table 164-1).

Text continued on p. 615.

Table • 164-1

Guidelines for Administration of Feline Vaccines

ANTIGEN	VACCINE TYPES[a]	PRIMARY VACCINATION		BOOSTER VACCINATION	COMMENTS
		Cats <12 Weeks Old	**Cats ≥12 Weeks Old**		
Feline parvovirus[b]	MLV vaccine for parenteral administration MLV vaccine for topical administration Adjuvanted inactivated-virus vaccine for parenteral administration	If ≥6 weeks old, clinician should vaccinate at initial visit and every 3 to 4 weeks until ≥12 weeks old[c]	2 doses, 3 to 4 weeks apart	1 year after primary vaccination, then no more frequently than every 3 years	*Highly recommended for all cats;* in most cats, protection derived after administration of booster vaccination 1 year after primary vaccination is sustained for at least 3 years and probably 5 to 6 years or more; MLV vaccines should *not* be administered to pregnant queens or kittens <4 weeks old

Continued

Table • **164-1**

Guidelines for Administration of the Vaccines—cont'd

ANTIGEN	VACCINE TYPES[a]	PRIMARY VACCINATION		BOOSTER VACCINATION	COMMENTS
Feline herpesvirus-1 (FHV-1) and feline calicivirus	Combined MLV vaccine for parenteral administration Combined adjuvanted inactivated-virus vaccine for parenteral administration	If ≥6 weeks old, clinician should vaccinate at initial visit and every 3 to 4 weeks until ≥12 weeks old[c]	2 doses, 3 to 4 weeks apart	1 year after primary vaccination, then every 3 years	*Highly recommended for all cats;* MLV vaccine should *not* be administered to pregnant queens
FHV-1 and feline calicivirus	Combined MLV vaccine for topical administration	If ≥6 weeks old, clinician should vaccinate at initial visit and every 3 to 4 weeks until ≥12 weeks old[d]	1 dose	1 year after primary vaccination, then every 3 years	*Highly recommended for all cats;* may be used as an alternative to the parenteral product; may be preferable to parenterally administered vaccines in cats reared in or entering environments in which viral upper respiratory tract disease is endemic (e.g., some catteries, boarding facilities, shelters); MLV vaccine should *not* be administered to pregnant queens
Rabies	Adjuvanted inactivated-virus vaccine for parenteral administration every year[e]	Not eligible for vaccination	1 dose	1 year after primary vaccination, then every year[e]	*Highly recommended for all cats;* rabies vaccination of cats is required by law in some regions of the country, and veterinarians should comply with state and local statutes regarding type of vaccine to be used and vaccination interval
Rabies	Adjuvanted inactivated virus vaccine for parenteral administration every 3 years[e]	Not eligible for vaccination	1 dose	1 year after primary vaccination, then every 3 years[e]	*Highly recommended for all cats;* rabies vaccination of cats is required by law in some regions of the country, and veterinarians should comply with state and local statutes regarding type of vaccine to be used and vaccination interval
Rabies	Canarypox virus–vectored recombinant vaccine for parenteral administration	1 dose to cats as young as 8 weeks old	1 dose	1 year after primary vaccination, then every year	The *recombinant* rabies virus vaccine can be used as an alternative to other products approved for annual use; this product does not contain an adjuvant, and postvaccination inflammation at the vaccine site appears minimal; however, whether use of this product will be associated with a decreased likelihood of vaccine-associated sarcoma formation is not presently known

Continued

Table • 164-1

Guidelines for Administration of the Vaccines—cont'd

ANTIGEN	VACCINE TYPES[a]	PRIMARY VACCINATION		BOOSTER VACCINATION	COMMENTS
Feline leukemia virus (FeLV)	Adjuvanted and nonadjuvanted inactivated-virus vaccines for parenteral administration	2 doses, 3 to 4 weeks apart to cats as young as 8 weeks old[f]	2 doses, 3 to 4 weeks apart[f]	Annually	Recommended for cats that are *not* restricted to a closed, indoor, FeLV-negative environment; most important for cats <16 weeks old; *not* recommended for cats ≥16 weeks old with minimal to no risk of exposure to FeLV-infected cats
Chlamydophila felis	MLV vaccine for parenteral administration Adjuvanted inactivated vaccine for parenteral administration	2 doses, 3 to 4 weeks apart to cats as young as 9 weeks old	2 doses, 3 to 4 weeks apart	Annually	Not recommended for routine use; can be considered for use in cats in multiple-cat environments where *C. psittaci* infections associated with clinical disease have been documented
Feline infectious peritonitis (FIP) virus	MLV vaccine for topical administration	Not approved for cats <16 weeks old	2 doses, 3 to 4 weeks apart to cats ≥16 weeks old	Annually	Not recommended; at this time, insufficient evidence exists to support the conclusion that the vaccine induces clinically relevant protection
Microsporum canis	Adjuvanted inactivated vaccine for parenteral administration	Not approved for cats <16 weeks old	First dose administered SC to cats ≥16 weeks old; second dose administered SC 12 to 16 days after the first dose; third dose administered SC 26 to 30 days after the second dose	Not stipulated	Not recommended for routine use; vaccination may be considered as one component of a comprehensive control program in multiple-cat environments in which *M. canis* infection is endemic or as adjunctive treatment to hasten resolution of clinical signs in individual cats
Bordetella bronchiseptica	MLV vaccine for topical administration	1 dose (0.2 mL) intranasally to cats ≥4 weeks old	1 dose (0.2 mL) intranasally	Not stipulated	Not recommended for routine use; vaccination may be considered for cats entering or residing in multiple-cat environments where *B. bronchiseptica* infections associated with clinical disease have been documented[g]
Giardia lamblia	Adjuvanted inactivated vaccine for parenteral administration	2 doses, 3 to 4 weeks apart to cats as young as 8 weeks old	2 doses, 3 to 4 weeks apart	Annually	Not recommended for routine use; vaccination may be considered as one component of a comprehensive control program in multiple-cat environments in which *G. lamblia* infections associated with clinical disease have been documented

Continued

Table 164-1

Guidelines for Administration of the Vaccines—cont'd

ANTIGEN	VACCINE TYPES[a]	PRIMARY VACCINATION		BOOSTER VACCINATION	COMMENTS
Feline immunodeficiency virus (FIV)	Adjuvanted inactivated whole virus vaccine for parenteral administration[h]	3 doses, 2 to 3 weeks apart to cats as young as 8 weeks old	3 doses, 2 to 3 weeks apart	Annually	Not recommended for routine use; vaccination may be considered for cats not restricted to a closed, FIV-negative environment.[i]

[a]Parenteral vaccines containing antigens limited to feline panleukopenia virus, FHV, and feline calicivirus (with or without *Chlamydophila felis*) should be administered as distally as possible on the lateral right forelimb. Monovalent parenteral FIV vaccines should be administered as distally as possible over the left forelimb. Vaccines containing rabies virus antigen (plus any other antigen) should be administered as distally as possible on the lateral right hindlimb. Vaccines containing FeLV antigen (plus any other antigen except rabies virus) should be administered as distally as possible on the lateral left hindlimb.
[b]Cause of feline panleukopenia.
[c]For kittens that are orphaned or at high risk of exposure, vaccination when as young as 4 weeks old may be indicated.
[d]For kittens that are orphaned or at high risk of exposure, vaccination when as young as 2 weeks old may be indicated.
[e]A specific route of administration may be required; see product information for details. Most often, the product approved for use annually is given for initial vaccination, followed 1 year later and every 3 years after that by administration of the product approved for use every 3 years; however, vaccination interval must comply with local and state statutes.
[f]FeLV testing is recommended before vaccination; infected cats do not derive any benefit from vaccination.
[g]This product is *not* the same as the *B. bronchiseptica* vaccine approved for use in dogs; the product approved for use in dogs should not be used in cats.
[h]This formulation of FIV vaccine is the only one available at the time of this writing.
[i]Some FIV vaccines induce antibodies indistinguishable by current tests from those induced by natural infection, and may confound attempts to diagnose infection. Cats should test negative for infection before such vaccines are initially administered.
MLV, Modified-live virus; *SC*, subcutaneously.
Adapted from the American Association of Feline Practitioners and Academy of Feline Medicine Advisory Panel on Feline Vaccines.
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INDIVIDUALIZING VACCINATION PROTOCOLS

The benefits of vaccination are well documented, but harmful effects can result in some individuals. As with any medical procedure, the benefits of vaccine administration should far outweigh any vaccine-associated risks. In deciding whether a particular vaccine antigen should be administered to a particular-cat, it is necessary to estimate several patient and vaccine variables. Patients should be evaluated based on their risk of exposure (which requires an understanding of the means of infectious agent transmission) and the expected response to exposure (likelihood of infection if exposed, likelihood and severity of disease if infected). Vaccine variables include the proportion of vaccinates expected to benefit from vaccination, the expected immune response to vaccination (sufficient to prevent infection, sufficient to reduce the severity of disease if infection occurs), and the likelihood and severity of vaccine-associated adverse events. The suggested vaccination protocol outlined in Table 164-1 takes these variables into consideration.

CHAPTER • 165

Diseases Caused by Systemic Bacterial Infections

Katrin Hartmann
Craig E. Greene

LEPTOSPIROSIS

Etiology

Leptospirosis, a zoonotic disease of worldwide significance in many animals and humans, is caused by infection with antigenically distinct serovars of the motile spirochetal bacterium *Leptospira interrogans sensu lato.* The bacterium can persist in wildlife reservoirs, contaminating the environment.[1] *Leptospira* organisms are thin, flexible, filamentous bacteria made up of fine spirals with hook-shaped ends. They are motile through writhing and flexing movements while rotating along their long axis.[2] Confusion may arise about the classification of leptospires because serogrouping used in the past overlaps with newer classifications based on genetic methodologies.

In all surveys of domestic animals, antibody prevalence is greater than clinical illness, suggesting that subclinical infections occur commonly. However, these spirochetes also can cause severe, sometimes fatal, disease. More than 200 different serovars have been identified in the *Leptospira interrogans* complex,[3] although the pathogenic importance of individual isolates is unknown.[4-6] Each serovar has a primary host that maintains the organism and contributes to its dissemination in the environment. Although all mammals are susceptible to infection, clinical signs are most severe with non-host-adapted serovars.[7] Leptospirosis is common in dogs, and its importance in veterinary practice may be underestimated. Reports of leptospirosis in cats are rare.

Canine leptospirosis was first described in 1899. Prior to 1960, serovars *icterohaemorrhagiae* and *canicola* were believed to be responsible for most clinical cases of canine leptospirosis. The disease, caused by acute or subacute hepatic and renal failure, typically was characterized by acute hemorrhagic diathesis, icterus, or uremia.[8] After a bivalent, serovar-specific vaccine against *canicola* and *icterohaemorrhagiae* came into widespread use, the incidence of "classic" leptospirosis in dogs appeared to have decreased.[9] However, these vaccines did not induce immunity against other serovars, leading to a relative increase in the incidence of disease attributed to serovars of other serogroups.

Awareness of leptospirosis has expanded as the range of tested serovars has increased. The serovar *grippotyphosa*, first discovered in kenneled hunting dogs in the southeastern United States, has been identified as a predominant serovar in dogs east of the Mississippi River. In the northeastern states, *pomona* has predominated; on the western coast, *bratislava* and *pomona*. Serogroup *Australis* has been incriminated in an outbreak in Canada and has been documented as the cause of chronic hepatitis in dogs in France. In Germany, the predominant serovars are *grippotyphosa, bratislava, saxkoebing,* and *sejroe;* a recent survey in Italy identified *bratislava* and *grippotyphosa.*[8-16]

Pathogenesis

Leptospires can be transmitted directly between hosts in close contact through urine, venereal routes, placental transfer, bites, or ingestion of infected tissues as the organism penetrates mucosa or broken skin. Shedding by infected animals occurs, usually via urine. The exact duration of shedding and potential spread to other dogs or humans is uncertain and may depend on the serovar. Recovered dogs can excrete organisms in urine intermittently for months to 4 years after infection.[17] Indirect transmission, which happens more often, occurs through exposure of susceptible animals to a contaminated environment (e.g., soil, food, or bedding). Water contact is the most common means of spread, and habitats with stagnant or slow-moving warm water favor organism survival. Leptospires in contaminated water invade the host through skin wounds or through intact mucous membranes. Because optimum survival conditions include a neutral or slightly alkaline pH, the organism survives only transiently in undiluted acidic urine (pH 5.0 to 5.5), whereas dilute urine provides a suitable habitat. Ambient temperatures between 0° and 25° C favor survival and replication, whereas freezing markedly decreases survival. Temperature and pH requirements explain the apparent increased incidence of canine leptospirosis in late summer and early fall, in the southern, semitropical belt of the United States, and in similar climatic regions worldwide. Clustering of cases depends on environmental factors. Seasonality is clearly associated with rainfall,[18-20] and disease outbreaks often occur during or immediately after periods of flooding.

Once in a susceptible host, leptospires begin to multiply as early as 1 day after entering the blood vascular space.[21] They invade many organs, including the kidneys, liver, spleen, central nervous system (CNS), eyes, and genital tract. Leptospires damage organs by replicating and causing inflammation. Initial replication mainly damages the kidneys and liver. The extent of damage to internal organs varies, depending on the virulence of the organism and host susceptibility.[22]

Recovery from infection depends on the production of specific antibodies. As serum antibodies increase, the organism is cleared from most tissues, except for the kidneys. Renal colonization occurs in most infected animals, and the organism usually persists in renal tubular epithelial cells, causing shedding from the kidneys for months to years after clinical recovery. The prognosis is highly dependent on conservation of renal function.

Clinical Signs

Signs of hepatic and renal dysfunction and of coagulation defects usually predominate in dogs with leptospirosis. The severity of clinical signs depends on the age and immunocompetence of the host, the environmental factors affecting the organisms, the serovar involved, and the virulence and quantity of the acquired bacteria. Younger dogs (less than 6 months) are more severely affected and develop more signs of hepatic dysfunction in any disease outbreak.

A majority of leptospiral infections in dogs are subclinical. Peracute leptospiral infections are characterized by massive leptospiremia, causing shock and often death with few

premonitory signs. Less severe infections are characterized by fever, anorexia, vomiting, dehydration, increased thirst, and reluctance to move.

Leptospiral infection can lead to similar clinical signs independent of the etiologic serovar, and reports on different clinical appearances may be more related to geographic distribution. Renal colonization occurs in most infected animals because the organism replicates and persists in renal tubular epithelial cells, even in the presence of neutralizing antibodies. Acute impairment of renal function may result from decreased glomerular filtration caused by swelling that impairs renal perfusion. Progressive deterioration in renal function results in oliguria or anuria. Renal function in some dogs that survive acute infections may return to normal within several weeks, or chronic compensated polyuric renal failure may develop.

The liver is another major parenchymatous organ damaged during leptospiremia. Profound hepatic dysfunction may occur without major histologic changes because of subcellular damage. The degree of icterus in both canine and human leptospirosis usually corresponds to the severity of hepatic necrosis. In contrast, the icterus, hemoglobinemia, and hemoglobinuria that develop in cattle with leptospirosis result from a specific hemolytic toxin produced by serovar *pomona*. In dogs, icterus is less likely a result of hemolysis because even decreased osmotic fragility has been detected in canine leptospirosis. Chronic active hepatitis and hepatic fibrosis have occasionally been demonstrated as sequelae to serovar *grippotyphosa* infection in dogs. Presumably, the initial hepatocellular injury and the persistence of the organism in the liver result in altered hepatic circulation and immunologic disturbances that perpetuate the chronic inflammatory response. This process may cause extensive hepatic fibrosis, cirrhosis, and failure.

Tissue edema and disseminated intravascular coagulation (DIC) may occur rapidly and result in acute endothelial injury and hemorrhagic manifestations. *Leptospira* lipopolysaccharides stimulate neutrophil adherence and platelet activation, which may be involved in inflammatory and coagulatory abnormalities.

Other body systems may also be damaged during the acute phase of infection. A benign meningitis is produced when leptospires invade the CNS; however, it is not as common as in humans. Uveitis occasionally is present in naturally occurring and experimentally induced canine leptospirosis. Abortion and infertility resulting from transplacental transmission of leptospires associated with serovar *bataviae* infection have been described. Pulmonary manifestations include labored respiration and coughing. Interstitial pneumonia has been documented as the cause in humans, whereas lung changes in dogs with leptospirosis are associated with pulmonary hemorrhage, most likely due to endothelial damage and vasculitis.[23]

Laboratory abnormalities usually include leukocytosis, thrombocytopenia, increased serum urea and creatinine, electrolyte disturbances, bilirubinemia, and increased serum hepatic enzyme activities. Coagulation parameters may be altered in severely affected animals. Urinalysis abnormalities include bilirubinuria, sometimes glucosuria, proteinuria, and increased numbers of granular casts, leukocytes, and erythrocytes in the sediment.

Diagnosis

Establishment of a diagnosis is important, because animals can serve as reservoirs and pose potential zoonotic risks. The diagnosis of leptospirosis can be accomplished by several techniques. Detection of antibodies using the microscopic agglutination test (MAT) is the most common diagnostic method[4,7,24,25]; however, other methods to detect antibodies, such as immunofluorescent assays or enzyme-linked immunosorbent assay (ELISA), have been used. The problem in interpretation of antibody test results is the high prevalence of subclinical infections and the persistence of antibodies. In addition, leptospiral vaccines induce antibodies, therefore the presence of antibodies in itself does not necessarily reflect disease. However, a high MAT titer to a nonvaccinal serovar and no (or only low) titers against vaccinal serovars, accompanied by clinical signs of leptospirosis, must be considered highly suggestive of active infection.[2,4,9] In some cases, cross-reactive results may make identification of the infecting serovar difficult. High titers to a specific serovar may not definitely identify the causative serovar, because shared epitopes among organisms of related serovars frequently induce production of cross-reactive antibodies.[25] Laboratory variation and differences in host-specific humoral immune responses sometime make correct assignment of antibody tests even more difficult.

Another diagnostic criterion is a fourfold increase in MAT titers. Because antibody test results are often negative in the first week of illness, especially in young dogs (less than 6 months of age), a second serum sample should be obtained within 1 to 2 weeks. Negative initial antibody tests can be explained by the 7 to 9 day period required before MAT antibodies are detected. MAT titers become positive after about 1 week, peak at 3 to 4 weeks, and remain positive for months after both natural infection and vaccination.[2] Therefore, to confirm current infection versus previous infection or vaccination, a rising titer should be demonstrated. Antimicrobial therapy early in the course of the disease may decrease the magnitude of the titer rise. Lower levels of antibodies to leptospiral antigens used in the MAT may also indicate exposure to infection with nonleptospiral spirochetes (e.g., oral spirochetal infections). However, dogs exposed to ticks harboring *Borrelia burgdorferi* that developed high titers to that organism did not show significant increases in anti-leptospira titers on the MAT. In contrast, leptospiral infections can affect antibody results for borreliosis. An advantage of the MAT is its serovar specificity; however, it cannot distinguish between IgM and IgG antibodies.

Besides the widely used MAT, a combined IgM/IgG ELISA[26-28] or immunofluorescent assay (IFA)[29] can be used to measure leptospiral antibodies. IgM antibodies increase within the first week of infection (before the MAT titer); the maximum IgM titer develops within 14 days and decreases thereafter. IgG antibody tests turn positive 2 to 3 weeks after infection and persist for months, with a maximum titer after 1 month.[2] A combined IgM/IgG test from a single sample is better suited to distinguishing natural infection from vaccine-induced immunity than is the MAT, because dogs that have been vaccinated and have received booster shots demonstrate a high IgG titer but low or negative IgM antibodies. However, these combined tests cannot distinguish between different serovars.

The organisms can be identified directly by means of several techniques, including visualization in fresh urine by dark-field microscopy or in tissue sections or on air-dried smears by light microscopy as well as by culturing the organism or by detection of deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR). However, all direct methods are reliable only with positive results. A negative result never excludes the presence of the infectious agent. Identification of leptospires in urine by dark-field microscopy[9,24,30] is frequently unrewarding, and both positive and negative results should be followed by culture or antibody testing. Leptospires sometimes can be seen by light microscopy in tissue sections or on air-dried smears with Giemsa stain or silver impregnation. Immunofluorescence and immunohistochemical staining techniques have been adapted to identify *Leptospira* organisms in tissues imprints of liver and kidney and in body fluids such as blood or urine, and these techniques potentially can be used to identify animals shedding organisms in urine when culture is impossible or too time-consuming.[31]

Although culture of the organism from blood, urine,[25] or cerebrospinal fluid[32] would be the ideal method, leptospires are difficult to culture and may take weeks to months to grow. They are fastidious, and sampling should always precede institution of antimicrobial therapy. Dogs are leptospiremic during the first week of infection, but the number of circulating organisms subsequently decreases as serum antibodies increase. Urine (sampled by cystocentesis to avoid overgrowth by normal flora) is the best fluid for culture. If animals are adequately hydrated, administration of a low dose of a diuretic such as furosemide (0.5 mg/kg) just before urine collection may facilitate recovery of organisms. Urine should be alkalinized to pH 8.0 or greater during transport. Special liquid, semisolid, or solid culture media should be used. Definitive differentiation of the etiologic serovar can also be accomplished using culture (if culture is successful).

PCR has been used to detect leptospires in blood, cerebrospinal fluid (CSF), aqueous humor, and urine. Because the concentration of leptospires is highest in urine, urine testing is recommended. PCR techniques for identifying the organisms in urine has been experimentally shown to be sensitive and specific and can help establish a diagnosis at an early stage of infection. In two studies comparing PCR, culture, and antibody testing in healthy and diseased animals, PCR was significantly more sensitive than the other methods in identifying shedders and diagnosing the disease.[33-35] Because culturing of urine is time-consuming and insensitive, the PCR approach may be most useful for direct detection of the organism. Unfortunately, PCR is not yet widely available. Recent advances in PCR techniques have allowed not only diagnosis of leptospirosis but also identification of specific *Leptospira* serovars.[36]

Treatment

Supportive therapy for animals with leptospirosis depends on the severity of the clinical signs, whether renal or hepatic dysfunction is present, and other complicating factors. Antimicrobial therapy is essential to terminate bacteremia. Treatment is divided into two stages. The goal of the first stage is to immediately inhibit multiplication of the organism and rapidly reduce fatal complications of infection, such as hepatic and renal failure. Penicillin and its derivatives are the antibiotics of choice for terminating leptospiremia. Initially, ampicillin (22 mg/kg given intravenously every 8 hours) or, preferentially, amoxicillin, if available for intravenous (IV) use (22 mg/kg given every 12 hours), can be administered parenterally to a vomiting, uremic, or hepatically compromised animal. These drugs prevent shedding and transmission of the organism within 24 hours of therapy. They do not, however, clear renal infections or eliminate the carrier state and chronic shedding. The goal of the second stage, therefore, is to eliminate the carrier state through administration of drugs such as tetracyclines, aminoglycosides, or the newer erythromycin derivatives. Doxycycline (5 mg/kg given orally every 12 hours for 3 weeks) is the drug of choice. Doxycycline treatment should start as soon as oral therapy is possible and liver function is uncompromised. Doxycycline is usually given orally because IV administration can cause shock and vomiting, and subcutaneous injection leads to abscessation. Oral administration, however, can cause gastrointestinal side effects. Doxycycline can be given regardless of the degree of renal dysfunction, whereas aminoglycosides must be strictly avoided if any degree of renal dysfunction is present. The doxycycline dose does not need to be adjusted in animals with renal failure because it is predominantly excreted in the feces. However, doxycycline can lead to liver toxicity. It should be started only after the animal stops vomiting and liver enzyme values have returned to the reference range. In animals with only mild clinical signs, doxycycline can be used for both initial and elimination therapy.

The extent of renal damage after treatment determines the overall prognosis for affected dogs. Some dogs have an apparent clinical recovery after treatment, whereas others develop persistent azotemia.

Prevention

Inactivated bacterins against *icterohaemorrhagiae* and *canicola* infection have been widely used, and this strategy has reduced the prevalence of highly virulent forms of illness. However, these vaccines are not cross-protective against the serovars responsible for most of the current infections in dogs. A recently developed bacterin vaccine that contains *grippotyphosa* and *pomona* strains, either as bivalent or quadrivalent products with the other two strains (Duramune LGP or Duramune LCI-GP, respectively; Fort Dodge Animal Health, Fort Dodge Iowa), is now on the market in the United States. The use of multistrain vaccines likely will reduce disease prevalence.[37] Because the highest titers are produced by multiple injections, yearly (and eventually biannual) vaccinations should be given to dogs in endemic areas, and all dogs should receive at least three injections in the primary vaccination series. IgG titers, which are primarily responsible for protection in dogs, are produced for at least 1 year after the third vaccination.

Debate has arisen over the necessity of routine vaccination in dogs. As inactivated bacterins, leptospiral vaccines have caused allergenic reactions, especially when combined with other adjuvanted agents. However, many manufacturers have improved and purified their leptospiral vaccines, producing safer multicomponent products. A number of these newer vaccines have been shown to protect against challenge for at least 1 year and to prevent the development of a carrier state in many vaccinated animals.[2] *Icterohaemorrhagiae* and *canicola* infections continue to occur in unvaccinated animals, which indicates that these agents have not been eradicated.

Doxycycline has been given at a low dose (200 mg once weekly) to humans in endemic areas for prophylaxis when vaccination with appropriate serovar bacterins is unavailable. Such therapy may result in the development of bacterial resistance and is not recommended for dogs (or humans).

Wild animal reservoirs and subclinically affected domestic animals continue to harbor and shed organisms. Therefore control of rodents in kennels, maintenance of environmental conditions to discourage bacterial survival, and isolation of infected animals are important steps in preventing the spread of disease. Control of shedding by wild animal reservoirs is impossible. For these reasons, vaccination of dogs is essential.

Leptospirosis in Cats

The prevalence of clinical illness is low in cats, despite the presence of leptospiral antibodies in the feline population and the exposure of cats to leptospires excreted by wildlife. Serovars *canicola*, *grippotyphosa*, and *pomona* have been isolated from cats. Outdoor cats have the highest antibody prevalence, and transmission from rodents is suspected. Cats may also be exposed to the urine of cohabiting dogs. Although cats develop antibodies after exposure, they appear to be less susceptible than dogs to both spontaneous and experimental infection. Clinical signs are usually mild or not apparent in feline leptospirosis, despite the presence of leptospiremia and leptospiuria and histologic evidence of renal and hepatic inflammation. The lack of clinical cases may be related partly to cats' aversion to water and partly to natural resistance to infection.

Public Health Considerations

The majority of leptospiral infections in humans are identified among those involved in water-related activities, either through work or leisure activities. In some outbreaks, simultaneous exposure of humans and dogs occurs. Urine from infected dogs can cause disease in humans when it comes in contact with mucosal

surfaces or a break in the epidermal barrier. Latex gloves are necessary when urine or urine-contaminated items are handled, and face masks and goggles should be worn when contaminated kennel areas are hosed down. Urine-contaminated areas should be cleaned with dry paper first (to avoid dilution of urine), then washed with detergent and treated with iodophor disinfectants, to which the organism is susceptible. All dogs known to be or suspected of shedding should be treated with doxycycline.

BORRELIOSIS

Etiology

Tick-borne spirochetoses are a group of diseases that affect humans and animals worldwide. They can be divided into the Lyme disease group (Lyme borreliosis), which is transmitted by *Ixodes* ticks, and the relapsing fever group, which is transmitted by soft ticks. The Lyme disease group was recognized more recently and is now the most commonly diagnosed vector-borne disease in humans.[1] Borreliosis has been known in Europe since the early 1900s; Alan Steere of Yale University first described the disease and the connection to tick bites after a 1975 outbreak in Lyme, Connecticut (which led to the name *Lyme disease*). However, evidence suggests that this infection in indigenous wildlife and their tick vectors is much older. Studies have demonstrated that ear skin samples from museum specimens of white-footed mice collected near Dennis, Massachusetts, in 1894 contained *Borrelia* DNA.[38] *Borrelia* organisms also were detected in British ticks from 1897.[39] Lyme disease now has been reported in North America, Europe, and Asia, with unconfirmed cases in Australia, South America, and Africa. Experimentally induced and naturally occurring Lyme borreliosis has been described in dogs, cats, and other domestic animals.[40] Antibody prevalence in dogs in endemic areas correlates with living in forested and urban areas and time spent outdoors.[41] In some endemic areas (e.g., Southern Germany), about 30% of ticks are infected,[42,43] and approximately 95% of dogs have antibodies indicating exposure.

Lyme disease is caused by *Borrelia burgdorferi sensu lato*, which comprises several species that affect humans and dogs worldwide. Like most spirochetes, *Borrelia* organisms are small, corkscrew-shaped, motile, microaerophilic bacteria of the order Spirochaetales that can move in connective tissue using their flagella. At least six species have been found in dogs and humans. *B. burgdorferi sensu stricto* predominates in humans and dogs in the United States. It also is found in Europe but only in about 10% of isolates. *B. garinii* and *B. afzelii* are the most common species in Europe. *B. japonica* has been isolated from ticks on humans and dogs in Japan. Recently, two new species (*B. lusitaniae* and *B. valaisiana*) have been detected. In cats, the natural disease is poorly documented, although cats can be infected experimentally. Cats seem to be less susceptible to clinical signs than dogs, and dogs less susceptible than humans.

The presence of disease and its clinical features depend on the isolate in a given geographic region. Genetic variability of isolates also occurs within each continent. In humans, different species are clearly associated with different tissue tropism and clinical problems; this is also likely in dogs. In humans, *B. burgdorferi sensu stricto* infection is associated with annular skin lesions, polyarthritis, and meningitis. Meningopolyneuritis (Bannwarth's syndrome) is the primary clinical sign in humans with *B. garinii* infection in Europe, whereas *B. afzelii* infection has been associated with chronic arthritis and dermatitis *(erythema chronicum migrans)*.[44]

Pathogenesis

Unlike *Leptospira* spp., *Borrelia* organisms do not survive free living in the environment. They are host associated and are transmitted between vertebrate reservoir hosts and hematophagous arthropod vectors. The principal vectors of *B. burgdorferi sensu lato* are various species of hard ticks of the *Ixodes* complex. *I. ricinus* and *I. persulcatus* are the primary vectors in Europe and Asia, respectively. In the United States, the closely related black-legged ticks *I. scapularis* (Northeast, Midwest, and Southeast) and *I. pacificus* (West) are the main vectors. These small *Ixodes* ticks (less than 3 mm) generally feed on more than one host during their life cycle. *I. scapularis* is a three-host tick with a 2-year life cycle. Infected nymphs overwinter, and in the spring they transmit infection to reservoir hosts, which in turn infect feeding larvae. Larvae and nymphs feed primarily on rodents and small mammals (northern *I. scapularis*) and reptiles (southern *I. scapularis*), whereas adult ticks feed on deer or larger mammals. Humans and pets are usually infected by nymphs or adult ticks. Because reptiles are not competent reservoir hosts, the infection rate of southern *I. scapularis* ticks is much lower than that of northern *I. scapularis* ticks. Furthermore, because the southern *I. scapularis* ticks do not always feed on mammals, the prevalence of *Borrelia* infection is relatively low in the southern regions.[40] Other ticks and insect vectors have been found to harbor *Borrelia* organisms but do not seem to maintain infection or to be important for transmission. Direct transmission of *Borrelia* spirochetes between reservoir hosts is unlikely, as is transovarial transmission in ticks. Canine urine is also an unlikely source of spread. In a natural infection model, control dogs in direct contact with infected dogs for up to 1 year did not develop antibodies, and organisms could not be isolated from the urine of infected dogs. These studies also did not document any evidence of *in utero* spread.[45] However, *Borrelia* organisms can survive freezing and storage, which makes artificial insemination a potential source of infection.[46] Blood transfusions offer another potential source of infection.

Natural spirochete transmission requires 48 hours of tick attachment, during which time organisms multiply and cross gut epithelium into the hemolymph, disseminate to the salivary glands, and infect the host through tick saliva.[47] Once in the body, *Borrelia* spirochetes usually cause persistent infection. Experimental evidence suggests that *Borrelia* organisms exist extracellularly and, in an undetermined way, can evade immune clearance. Organisms can persist and proliferate for extended periods (probably lifelong in most animals) in intercellular spaces in the skin at the site of the tick bite. Most infected animals never develop clinical signs. In dogs that do not develop clinical signs, it is likely that *Borrelia* organisms persist but do not invade connective tissues and therefore do not cause clinical signs but do cause persistent antibody response. In very few animals, *Borrelia* organisms proliferate and migrate from the skin at the site of the tick bite through connective tissues, including joints, beginning in close proximity to the tick bite. Clinical illness in these dogs results from the host's inflammatory response to their presence and migration. Despite treatment for months or years, *Borrelia* spirochetes can persist in the skin, connective tissues, joints, and nervous system and be detected by PCR or sometimes by culture of blood, cerebrospinal fluid, or urine.

It is still not known why a specific animal or human being develops clinical signs. Pathogenicity depends on the *Borrelia* species, and *B. burgdorferi sensu stricto* seems to be more pathogenic in dogs than the species mainly found in Europe. Evidence suggests that about 5% to 10% of dogs with antibodies in endemic areas in the United States develop clinical disease within 2 to 5 months of infection[48]; the percentage is much lower in endemic areas in northern Europe. Experimental studies have shown that the number of infected ticks that feed is critical. The age and immune status of the animal also seem to be important. Treatment with high doses of glucocorticoids at the time of infection has been shown to increase the likelihood of clinical signs. The development of immune complications,

such as arthritis, is probably related to host immunodeficiency. Humans with certain haplotypes of the major histocompatibility complex are prone to more severe clinical manifestations of the disease.[49]

Clinical Signs

All experimental infections in dogs have used *B. burgdorferi sensu stricto* strains, therefore the clinical condition caused by this organism is relatively well described. In experimentally infected dogs, clinical illness begins 2 to 5 months after tick exposure. Clinical signs include fever, inappetence, lethargy, lymphadenopathy, and episodic shifting limb lameness related to polyarthritis. Arthritis starts first in the joint that is closest to the tick bite. It has been shown that the release of proinflammatory cytokines and especially interleukin-8 (IL-8) plays an important role in the pathogenesis of acute arthritis.[50,51] Despite the transient nature of the arthritis, pathologic changes in the joints are progressive. Chronic nonerosive polyarthritis is the primary condition after prolonged infection, and it may persist despite antimicrobial therapy.

The clinical signs that develop in natural infection or in infections caused by other *Borrelia* species have been less definitively characterized. Glomerulonephritis and protein-losing glomerulopathy progressing to renal failure have been described in naturally infected dogs.[52,53] An acute, progressive renal failure associated with azotemia, uremia, proteinuria, peripheral edema, and body cavity effusions has been described in 49 dogs with positive antibody test results from *Borrelia*-endemic areas. Labradors and golden retrievers were commonly affected.[54] In Europe, glomerulonephritis is often found in Bernese Mountain dogs with high antibody titers to *Borrelia* organisms. *Borrelia* organisms are likely involved, but not yet proven, in this rapidly progressing glomerular disease. A dermatologic lesion of expanding erythema around the site of the tick bite has not been well documented in affected dogs. A small, reddened lesion, not as dramatic as the erythema migrans seen in humans, can be seen but disappears within the first week. However, the organism can be isolated from the skin area for an extended period. Neurologic manifestations caused by meningitis or encephalitis have not been well documented in either experimental or natural canine infection. Another nonarthritic syndrome that has been reported is cardiac arrhythmia from myocarditis, similar to that reported in humans.

No specific hematologic or biochemical changes are associated with Lyme disease. In contrast to leptospirosis, leukocytosis is not seen, probably because *Borrelia* organisms rarely spread hematogenously, but rather through connective tissue. Dogs with renal manifestation may have proteinuria due to glomerulonephritis sometimes secondary azotemia, hematuria, pyuria, and tubular casts. Synovial fluid analysis findings are typical for a suppurative polyarthritis, with leukocyte counts ranging from 2000 to 100,000 nucleated cells per microliter.

Diagnosis

Lyme borreliosis is likely overdiagnosed in human and veterinary medicine because it has become a "trendy" illness. Overestimation results from antibody cross-reactivity to other infectious agents, from the inaccuracies of antibody tests, and from the predominance of asymptomatic infections. The presence of antibodies to *Borrelia* organisms signifies exposure to a spirochete but does not prove that current clinical illness is caused by *Borrelia*. In endemic areas, most animals in the population have antibodies without ever developing clinical signs.

Various problems have been noted with antibody testing. First, no standardization exists for antigen preparations, techniques, and interpretation by different laboratories. Matched sera sent to 10 commercial laboratories for antibody testing found only 53% agreement.[55] Antibody screening procedures available for animals are ELISA and IFA techniques, usually using whole cells that contain many cross-reactive proteins to other bacteria, especially other spirochetes. In humans it has been shown that other inflammatory conditions, such as autoimmune diseases, rheumatoid arthritis, syphilis, and periodontal disease, can produce positive results.[2] *Leptospira*-positive canine sera also can have low levels of reactivity to *B. burgdorferi* in ELISA and IFA. In Great Britain, dogs with periodontal disease and presumed oral spirochetosis showed a higher level of antibodies against *B. burgdorferi* than healthy dogs from the same hospital population.[56] Some of the reports of human and animal Lyme disease in the western United States may actually be related to relapsing fever and the nonspecificity of whole-cell ELISA or IFA. Dogs vaccinated against borreliosis show antibodies in whole-cell ELISA and IFA for months to years after vaccination.

Paired titers are not helpful in the diagnosis of Lyme disease because high antibody titers usually persist for a long period. Simultaneous measurement of IgG and IgM in a single specimen theoretically would provide more information in other diseases. However, in naturally *Borrelia*-infected dogs and humans, IgM persists for many months, therefore a positive IgM titer does not help to confirm recent exposure or infection.[57,58]

False-negative antibody test results are rare. Early antibody tests are usually negative because the immune response to *B. burgdorferi* develops gradually. Experimentally infected dogs have ELISA-positive results by 4 to 6 weeks after exposure. Titers were at their highest levels by 3 months after exposure. Titer increases almost always precede clinical lameness and fever in experimentally infected dogs,[45] therefore a negative titer in an animal with clinical signs rules out Lyme disease with a high probability.

Because the routine antibody tests (ELISA and IFA) are nonspecific and because neither testing of paired samples nor IgM/IgG differentiation is useful, other confirmatory tests must be performed, such as the Western blot assay or the new C6 ELISA. These tests, which have higher specificity and sensitivity than whole-cell ELISA or IFA, can be used to detect antibodies that specifically indicate infection with *B. burgdorferi* and to exclude vaccination or contact with other bacteria. Western blot assays detect a spectrum of antibodies, and the pattern of antibody reactivity after natural infection differs from that produced after vaccination. After natural exposure to *B. burgdorferi*, antibodies develop to several proteins, including outer surface proteins. One of these outer surface proteins, OspC, appears to be expressed by *Borrelia* organisms in the host at warmer temperatures but is lost at lower temperatures in the tick or with *in vitro* cultivation. However, OspC is a prominent protein response to infection, and high amounts of anti-OspC antibodies are produced after natural infection. In contrast, the protein OspA is mainly expressed by *Borrelia* during the arthropod state (or if cultured *in vitro*). Therefore reactivity to OspA but not OspC occurs in vaccinated dogs (because the vaccine strains are cultured *in vitro*) but is lacking in naturally infected dogs. This effect is even more prominent if recombinant vaccines containing OspA are used rather than whole *Borrelia*. Thus the Western blot antibody pattern expressed by vaccinated dogs differs from that of naturally infected dogs.[59,60]

Newer ELISA tests that incorporate OspC also help differentiate between natural infection and vaccination.[61] Recently the antigenic properties of a 26 amino acid–long invariable region located within the central domain of the VlsE molecule, the variable surface of *B. burgdorferi*, were investigated. This region, named *IR* (invariable region) 6, was determined to be antigenetically conserved among strains of the *B. burgdorferi sensu lato* complex and to be immunodominant in both human and canine hosts.[62] A new, in-house

ELISA (C6 ELISA), designed using the IR6 sequence as a peptide (C6) biotinylated at the N-terminus, recently became available in the United States (SNAP 3Dx; IDEXX, Portland, Maine). The anti-C6 antibody response is highly specific for *B. burgdorferi* and is more sensitive than whole-cell tests in early infection, detecting antibodies as early as 3 weeks post exposure.[63] It also is more sensitive in detecting *Borrelia* infection in Europe than other commercial ELISA kits.[64] Dogs with leptospirosis, Rocky Mountain spotted fever, babesiosis, ehrlichiosis, and heartworm disease do not have antibodies to C6. Furthermore, C6 is not affected by the currently available Lyme vaccines.[65] C6 antibody levels also seem to correlate to *Borrelia* loads, dropping rapidly after treatment with antibiotics,[66] whereas conventional ELISA results stay at medium levels for a long time even after successful treatment.[67] Although already used in veterinary practice in endemic areas,[68] the C6 ELISA has not been validated in controlled studies. It must be considered that both the Western blot assay and the C6 ELISA, although more specific, only indicate natural exposure to *B. burgdorferi* and do not predict clinical disease.

In humans, CSF antibody titers have been compared with serum antibody titers in an attempt to diagnose neuroborreliosis. Intrathecal production of specific antibodies to *B. burgdorferi* can be demonstrated if the ratio of CSF to serum *B. burgdorferi* antibodies is greater than the CSF to serum concentration of albumin, total IgG, or specific IgG against another infectious agent. An increased intrathecal antibody concentration was demonstrated in dogs with neurologic dysfunction. The results of such reports are difficult to assess because the dogs were from endemic areas, and no supporting histopathology or culture findings were supplied.[40]

Culture of spirochetes from specimens of a diseased patient is the most definitive means of diagnosis but in most cases is difficult due to the low number of organisms present and the insensitivity of isolation methods. Special media (e.g., modified Barbour-Stoenner-Kelley medium) are required, but even then culturing is insensitive.[69] Skin appears to be the most consistent tissue for premortem or postmortem culture when specimens are taken at or near the site of tick attachment.[67] Xenodiagnosis, in which uninfected ticks become infected after feeding on suspect infected hosts, has proved reliable in a research laboratory setting but is too time-consuming and is not useful for routine clinical diagnosis.

PCR is highly specific. The best materials for diagnosis are skin samples, which should be taken at a location closest to the tick bite. If the tick bite location is unknown, a sample should be taken close to the joint in which the first lameness or swelling was observed. If no arthritis is or was present, the sample should be taken from an area that is generally most exposed to ticks (usually the front part of the dog). PCR can also be performed using urine,[70] which is slightly less sensitive. Blood is not useful, because *Borrelia* organisms rarely spread hematogenously. Joint fluid,[71] synovia samples, or CSF samples are excellent PCR material if clinical signs are present. PCR cannot distinguish between live and dead organisms. Research has shown that small DNA fragments of *Borrelia* may persist in synovial membranes after treatment,[67,72] and these fragments may induce positive PCR results. However, experimentally injected *Borrelia* DNA (without replicating *Borrelia*) was destroyed and was not detectable after 3 weeks. The sensitivity of PCR is high, but the sample must contain *B. burgdorferi* DNA. A negative PCR result, therefore, never excludes the presence of the organism elsewhere in the body.

Treatment

Because of the difficulty involved in obtaining an accurate diagnosis, antibiotics often are given empirically in an attempt to make a therapeutic diagnosis. Many reports exist of successful recovery after institution of antimicrobial therapy in dogs "diagnosed" with Lyme arthritis. However, clinical improvement after any therapeutic intervention should be viewed with caution, because acute limb and joint dysfunction is intermittent and often resolves after several days to weeks, regardless of whether antibiotics are given.[73] Doxycycline, the drug of choice, by itself has been shown to be chondroprotective in noninfectious arthritis in dogs[74] and thus leads to improvement also in arthritis not related to Lyme disease.

The antibiotics that are most effective for treating *Borrelia* infection are the tetracyclines, ampicillin or amoxicillin, some third-generation intravenous cephalosporins, and erythromycin and its derivatives. Doxycycline (10 mg/kg given orally every 12 hours for 30 days) is the first choice because it is a lipid-soluble tetracycline of relatively low cost. The other drugs are usually reserved for refractory or chronic infections. Improvement often occurs within 24 to 48 hours of initiation of antimicrobial therapy. The greatest success is achieved in the initial phases of clinical illness.

Research suggests that the organism is difficult to eliminate from animals with established infection and that relapses occur despite seemingly adequate treatment regimens.[73,75] Most treatment is instituted for a minimum of 30 days. However, on the basis of research studies, clearance of the organism after 30 days of treatment is questionable. Relapse can occur and PCR results can become positive after discontinuation of antimicrobials.[76,77] Also, inflammatory changes that occur in various tissues, such as the joints, may become self-perpetuating. Intra-articular persistence of *Borrelia* organisms may stimulate chronic immune and inflammatory processes. Animals with more chronic borreliosis are less likely to show improvement or to have relapses, even if treatment is continued for weeks to months. The current recommendations for treating chronic borreliosis are to repeat the 30-day antibiotic treatment four or five times in 3-month intervals. The *Borrelia* organisms may possibly be eliminated after years of such therapy.[77]

Nonsteroidal anti-inflammatory drugs may be helpful for pain relief during episodes of recurrent arthritis. Immunosuppressive doses of glucocorticoids definitely should be avoided, because immunosuppression may potentiate infection exacerbation.[76] Tick-exposed dogs that had recovered from clinical signs of Lyme disease and that were treated with oral prednisolone for a 2-week period 16 months after original exposure again demonstrated lameness and polyarthritis.[78]

Prevention

In United States, whole-cell bacterins and recombinant protein OspA vaccines for dogs are commercially available. Whole-cell bacterin vaccines should be avoided, because it is generally undesirable to have multiple components in a vaccine that are not involved in protection from infection and that have the potential to induce a delayed adverse response. Hamsters immunized with whole-cell bacterins and challenged by infected ticks developed arthritis several weeks to months later.[79] This concern has precluded development of a whole-cell bacterin from consideration as a human vaccine. All human vaccines that had been sold in the United States were based on recombinant DNA production of Osp products, but even they have been removed from the market. In Europe and other geographic areas, only whole-cell bacterins are available for dogs (and no vaccines are available for humans) because the multiplicity of infecting strains makes the development of a recombinant product that would protect against the different *Borrelia* species difficult. Multiplicity of infecting strains also makes questionable the protection induced by whole-cell vaccines (which are now on the market in Europe containing *B. burgdorferi sensu stricto* stains), because cross-protectivity between *B. burgdorferi* species could not be demonstrated.

The advantage of recombinant protein OspA vaccines is that they induce antibodies only to OspA, the protein that is expressed in the tick and not in the dog. Vertebrate hosts infected by *Borrelia* organisms through tick bites rarely develop antibodies to OspA. OspA is expressed by *Borrelia* in unfed ticks but is changed to OspC during transmission from the vector due to the warm conditions during feeding on the vertebrate host. During feeding, antibodies against OspA that are present in the vertebrate's blood due to vaccination enter the tick and neutralize *Borrelia* before the organism enters the host. Antibodies to OspA from the host cause an arrest of growth and salivary gland invasion in the ticks.[80] Spirochetes either are killed instantly by antibody-induced complement lysis or their mobility is reduced such that they cannot continue their migration to the salivary glands of the ticks.[81] In the vaccinated host, only OspA antibodies are present, and these cannot bind to *Borrelia* organisms expressing OspC. Thus the risk of the development of immune complex diseases is reduced compared with whole-cell *Borrelia* vaccines.

The disadvantage of vaccination in general is that the induced antibodies cause positive results on routine antibody testing for months to years. Western blot or C6 ELISA testing must be performed to distinguish vaccine induced from natural exposure antibodies. An additional disadvantage of the vaccine is the possibility that a hypersensitivity reaction may occur if the vaccine is given to a dog harboring the organism.[82] Vaccination of an already infected animal does not clear infection or prevent clinical illness. Local and systemic allergic reactions have been noted with whole-cell vaccines.[83] Vaccines might also be subject to breaks in protection in the future because *Borrelia* organisms are known to change their genotypic and phenotypic makeup, allowing survival despite organism-specific antibodies.

Vector control using residual insecticides or growth regulators is a supportive measure that can help reduce the prevalence of infection in humans and pets. Amitraz-impregnated collars may reduce transmission of *Borrelia* spirochetes in dogs.[84]

Borreliosis in Cats

Cats have been found to be antibody positive for *Borrelia*, and experimental infection has been produced, but naturally acquired disease has not been documented. Approximately 13% of cats tested in the United States had antibodies; however, there was no difference in positive results from cats with or without lameness.[40] In the United Kingdom, 4% of tested cats had antibodies.[85] Cats may be more resistant than dogs to the development of clinical signs. However, when cats were inoculated experimentally with organisms directly from arthropods, they developed multiple limb lameness and had joint, pulmonary, lymphoid, and CNS inflammation at necropsy. Arthritis and meningitis predominated.

Public Health Considerations

There is no evidence that infected pet dogs or cats pose a direct risk to humans except by introducing unfed tick stages into a household. The ticks do not survive long indoors and, if fed, tick stages do not reattach without moulting. However, partly fed ticks can refeed and can pose a greater risk of infection because of the shorter required period of attachment. Direct horizontal spread from dogs and cats to humans is unlikely. It has been speculated that urine from infected dogs could be a source of human infection. *Borrelia* organisms, however, deteriorate quickly in urine, and there is no evidence that human infections have occurred after contact with infected dogs.[86] In addition, in a recent study in the Netherlands, no positive correlation was observed between antibody prevalence in hunters compared with their dogs.[87] Although Lyme disease is classified as a zoonosis, dogs, cats, and humans are incidental hosts for a sylvan cycle that exists in nature. Lyme borreliosis in humans is usually associated with outdoor activities that result in exposure to tick vectors.

MYCOBACTERIOSIS

Etiology and Pathogenesis

Mycobacteriosis is caused by bacteria belonging to the genus *Mycobacterium*, family Mycobacteriaceae, order Actinomycetales.[40] Mycobacterioses are becoming increasingly important in dogs and cats (partly due to the increase in mycobacterial infections in humans and partly due to improved diagnostic methods), and their importance in veterinary medicine is probably underestimated. These diseases are more common in cats than dogs. In dogs and cats, mycobacteriosis can be divided into three groups, classic tuberculosis (tuberculous form),[88] opportunistic mycobacteriosis (opportunistic form),[89] and feline leprosy (lepromatous form).[90] All three groups can cause cutaneous signs (typically skin nodules with draining tracts and/or ulceration), but mycobacteria of the classic tuberculosis complex can also cause systemic disease. Classic tuberculosis can be caused by *Mycobacterium tuberculosis, M. bovis, M. avium, M. microti, M. microti*-like, and *M. simiae*. Opportunistic mycobacteria recognized as causes of disease in dogs and cats include *M. fortuitum, M. chelonae, M. smegmatis, M. phlei, M. thermosresistibile, M. terrae, M. genavense,* and *M. xenopi*. Feline leprosy is caused by *M. lepraemurium*.

Mycobacterium is a genus comprising morphologically similar, aerobic, environmentally resistant, non-spore-forming, acid-fast, gram-positive bacteria. Mycobacteria have the distinctive property of retaining hot carbolfuchsin and other stains after subsequent treatment with acid or alcohol, a property that facilitates diagnosis. This acid-alcohol fastness is due to the high lipid content of mycolic acid in the cell wall. Mycobacteria are more resistant to heat, pH change, and routine disinfection than other non-spore-forming bacteria. Most mycobacteria are found in habitats such as water or soil; however, a few can act as pathogens in animals and humans. They have a wide host affinity and pathogenic potential, and with their structural properties and ability to survive intracellularly, they produce granulomatous inflammation.

Classic tuberculosis has become increasingly important[89] in immunosuppressed individuals since the detection of the human immunodeficiency virus (HIV), and it has been caused by more resistant forms of mycobacteria. *M. tuberculosis, M. bovis, M. africanum,* and *M. microti* can cause the disease in humans. Currently, tuberculosis is the leading infectious cause of death in humans, and one third of the world's population is thought to be infected. However, only 10% of immunocompetent individuals develop active disease in their lifetime; the other 90% neither become ill nor transmit the organism. *M. tuberculosis* is the major cause of tuberculosis in humans, and humans are the only reservoir hosts. The inter-related factors of homelessness, illicit drug use, and HIV infection have resulted in an increased prevalence. Multiple-drug-resistant *M. tuberculosis* has emerged in these populations because of irregular compliance with drug therapy.

In dogs and cats, classic tuberculosis can be caused *M. tuberculosis, M. bovis, M. avium, M. microti, M. microti*-like, and *M. simiae*. Although *M. tuberculosis* can cause tuberculosis in dogs and cats,[91,92] it more commonly infects dogs. Dogs and cats are usually infected through direct contact with infected humans, and a canine or feline infection is considered an inverse zoonosis.[93] *M. tuberculosis* has an affinity for tissues with high oxygen content, which explains its common localization in the lungs. Animals with tuberculous pneumonitis

discharge organisms in the sputum, as do infected humans, and aerosolized droplets are the primary means of transmission of this disease. To be maintained in nature, *M. tuberculosis* requires infection of reservoir mammalian hosts, because environmental survival is limited to a maximum of 1 to 2 weeks. Although pets acquire the infection from humans and spread from dogs or cats to humans has not been reported, infected animals are a potential risk to humans, and euthanasia should be considered.

M. bovis is closely related to *M. tuberculosis* and difficult to distinguish except by biochemical tests and nucleic acid probes. Like *M. tuberculosis*, *M. bovis* does not exist long in the environment (4 days in summer, less than 28 days in winter), and reservoir hosts are essential for survival of the organism. *M. bovis* is the pathogen of classic "feline tuberculosis."[94] Cats are more commonly infected with *M. bovis* than dogs, and on an experimental basis, cats appear to be more susceptible to *M. bovis* than to *M. tuberculosis*. Dogs and cats are usually infected by means of unpasteurized milk, uncooked meat, or offal from infected cattle. Clinical disease, therefore, commonly involves the intestines. In areas in which bovine tuberculosis is well controlled, *M. bovis* infections have become extremely rare. In countries such as New Zealand, however, where *M. bovis* has become established in the wildlife population, domestic animals continue to become infected. Dogs and cats may be involved in the maintenance of *M. bovis* on farms, where it is enzootic, and may be responsible for transmission of *M. bovis* to humans. Orally infected dogs and cats usually excrete the organism through feces.

M. avium is a saprophytic organism that has been recognized in recent years as causing infection, especially in cats.[95-101] Poultry and swine are primarily susceptible to *M. avium* infection after contact with infected food or water. Dogs and cats seem to have innate resistance, but exposure is much greater than to *M. tuberculosis* and *M. bovis* because *M. avium* is ubiquitous in the environment. Certain breeds (e.g., Siamese cats[96] and basset hounds) seem to be more susceptible. Immunosuppression seems to play a role, and one case in a cat after renal transplantation has been described.[101] *M. avium* organisms are present in acidic conditions (pH 5.0 to 5.5) and in soils high in organic matter (e.g., acidic swamp areas, coastal plains, and brackish coastal waters). Unlike *M. tuberculosis* and *M. bovis*, *M. avium* organisms remain viable for at least 2 years in the environment. The feces of infected birds contain large numbers of *M. avium*, and infection of dogs and cats occurs from ingestion of infected meat or contact with infected soil contaminated by poultry carcasses or feces. There is no evidence of spread of *M. avium* between or within animals and humans. *M. avium* can cause disease in immunocompromised humans, but infection usually occurs through exposure to contaminated soil.

M. microti is a rodent pathogen that in earlier literature was reported to infect cats. A few cases in the Netherlands have been described in which hunting cats became infected.[102-104] *M. microti*-like is a new variant that has been identified as a common cause of tuberculosis in cats in Great Britain. It was predominantly found in rural cats with avid hunting behavior. and the source of infection is thought to be a prey species.[105,106]

M. simiae was recently found in an 8-year-old domestic short-hair cat with disseminated mycobacterial disease involving the skin, lungs, lymph nodes, and one eye. *M. simiae* is known to cause pulmonary, cutaneous, or disseminated infection in humans infection with HIV but has not been encountered as a pathogen in companion animals.[107]

Opportunistic mycobacteria that cause disease in companion animals include *M. fortuitum*, *M. chelonae*, *M. smegmatis*, *M. phlei*, *M. thermosresistibile*, *M. terrae*, *M. genavense*, and *M. xenopi*.[108-121] These saprophytic, nontuberculous, nonlepromatous, opportunistic species, also called *atypical mycobacteria*, are ubiquitous in nature, especially in water and wet soil, and are not pathogenic for animals under normal circumstances. Opportunistic mycobacteriosis appears to be more common in tropical and subtropical areas of the world; however, difficulties associated with diagnosis may underestimate the true prevalence. Cats are more often affected than dogs, and adult cats with a hunting or fishing lifestyle are more likely to be affected. Animal-to-animal transmission does not generally occur, and there is little zoonotic risk. Most opportunistic mycobacteria that infect dogs and cats are acquired from the environment after trauma to the skin or soft tissues (puncture or fight wounds) and cause localized tissue reactions in the skin (granulomas and abscesses) or deeper tissues. These organisms are particularly pathogenic if directly inoculated into adipose tissue. Entry through either the gastrointestinal or respiratory tracts is extremely rare. Although systemic immunosuppression has not always been apparent, *M. genavense* infection in a cat infected with the feline immunodeficiency virus (FIV) has been reported.[119]

Opportunistic mycobacteria can be characterized as slow-growing or fast-growing species. Fast-growing *M. fortuitum*, *M. chelonae*, *M. smegmatis*, *M. phlei*, and *M. thermosresistibile* are the species commonly isolated from cats and sometimes dogs with cutaneous lesions in the United States and Australia. Although the slow-growing opportunistic mycobacteria are responsible for several well-characterized cutaneous diseases in humans, they are less commonly isolated from dogs and cats, possibly because of the lengthy time needed for culture. However, the slow-growing species *M. terrae*, *M. genavense*, and *M. xenopi* have now been described in cats.

Feline leprosy, a disease seen only in cats and not in dogs or humans, is caused by *M. lepraemurium*, the agent of rat leprosy, and is usually introduced via bite wounds from rodents (possibly as soil contaminant) or contact with infected rats. There is no zoonotic risk. The disease is seen most in areas with a temperate maritime climate. Occurrence in cats has been confined to seaport cities of the western United States, New Zealand, Great Britain, Australia, and the Netherlands, with a greater incidence in winter. The organism cannot be cultivated by routine mycobacterial culture methods and requires special media. Feline leprosy is mainly a cutaneous syndrome; regional lymphadenopathy may be present, but systemic disease is rare. FIV or feline leukemia virus (FeLV) infection may play a role in the pathogenesis and predispose to septemic disease. Although the disease is more common in young cats, a clinical syndrome has been described in older cats in which disease progression was prolonged, typically taking months to years, and skin nodules did not ulcerate. This clinical picture was attributed to a *Mycobacterium* species closely related but slightly genetically different from *M. lepraemurium*.[122] In contrast to tuberculous and opportunistic mycobacterial infections, the prognosis in feline leprosy is good after surgical removal of the cutaneous lesion. Spontaneous resolution of lesions does occur.

Clinical Signs

Infection with tuberculosis-causing mycobacteria in dogs and cats is often asymptomatic or insidious. It is unclear what factors contribute to the host's resistance. Cell-mediated immunity typically is associated with protection against facultative intracellular pathogens such as mycobacteria and seems to be associated with enhanced capacity of activated macrophages to kill mycobacteria or to inhibit their intracellular multiplication. When clinical signs occur, they reflect the site of granuloma formation. Skin lesions (found on the face, neck, forepaws and, less frequently, ventral thorax and tail base) include dermal nodules or nonhealing wounds with draining sinus tracts, often accompanied by enlarged regional lymph nodes. In pulmonary disease that occurs mainly in *M. tuberculosis* infection,

bronchopneumonia, pulmonary nodule formation, and hilar lymphadenopathy are seen, causing fever, weight loss, anorexia, and harsh, nonproductive coughing. Intestinal localization, more common in *M. bovis* infection, can cause weight loss, anemia, vomiting, and diarrhea as signs of intestinal malabsorption. Mesenteric lymph nodes may be palpably enlarged, and abdominal effusion is present in some cases. Oropharyngeal lesions can cause dysphagia, retching, hypersalivation, and tonsillar enlargement. Tuberculous choroiditis and retinal detachments, granulomatous uveitis, and CNS signs occasionally occur. A granulomatous myelitis has been described in a dog with *M. avium* infection.[123] Lameness and fractures may be observed with bone localization.

Clinical laboratory findings in tuberculosis are frequently nonspecific, although leukocytosis and hyperglobulinemia may be present. Radiographically visible masses and tracheobronchial lymphadenopathy may be apparent in the thoracic cavity. Abdominal radiography and ultrasonography may reveal enlargement of parenchymatous organs such as liver and spleen or solitary abdominal masses. Fluid may be present in the abdominal cavity, and calcified mesenteric lymph nodes may be noted. Osteoproliferative lesions may be found in the axial or appendicular skeleton.

Opportunistic mycobacteriosis in cats most commonly occurs as skin lesions with multiple fistulous draining tracts associated with purulent drainage into the caudal abdominal, inguinal, and lumbar subcutaneous tissues. Most cats, even those with extensive cutaneous involvement, remain active and normal except for the draining tracts. Fever occasionally occurs, but anorexia, weight loss, and other features of chronic infection are usually absent. Dogs with opportunistic mycobacteriosis usually have a history of fight wounds or trauma followed by granulomatous proliferation of cutaneous tissues with serous or seropurulent drainage. Clinical laboratory findings are usually unremarkable in opportunistic mycobacteriosis, although hypercalcemia occurred in one cat with granulomatous skin masses.[124]

Feline leprosy is characterized by soft, fleshy, focal nodules in the skin and subcutis of the head and extremities. The lesions develop rapidly and are usually freely movable and painless. They may be haired or superficially ulcerated, and regional lymph nodes may be enlarged. Clinical laboratory findings are unremarkable.

Diagnosis

The diagnosis of classic tuberculosis can be established by demonstrating acid-fast organisms within a lesion by means of biopsy and histologic examination or by direct smears of exudates or fluids. The acid-fast staining method is ideal for aspirates of tissue and granulomas and for identifying organisms in bacterial cultures. Mycobacteria can be stained with carbolfuchsin or fluorescent dyes. Fluorochrome stains are more sensitive and technically less difficult to examine than conventional carbolfuchsin stains. Although often present in low numbers, intracellular mycobacteria are recognized by their clubbed shape and beaded appearance. In *M. avium* infection, higher numbers usually can be seen. Granulomatous lesions consist of areas of focal necrosis surrounded by infiltrations of plasma cells and macrophages and an outer connective tissue capsule. Calcification of granulomas may occur.

Intradermal skin testing is used as an aid in the diagnosis of human mycobacterial infections and to evaluate delayed-type hypersensitivity in animals. Intradermal skin testing is generally useful in diseases in which the cellular immune response should be tested because humoral immunity does not play a role. Although useful in humans, intradermal tuberculin testing is inconsistent and unreliable in dogs, and is not useful in cats.[125,126] If dogs are tested, the highest concentration of the tuberculin solution used for testing humans is needed, and the inner surface of the ear pinna should be injected.[88]

Testing of antimycobacterial antibodies is unreliable in dogs and cats because antibodies are produced inconsistently. Antibody tests include hemagglutination and complement fixation but should be critically interpreted due to their inaccuracies.

Culture is the definitive means of diagnosing tuberculosis and of identifying the specific mycobacteria species involved. Mycobacteria of the tuberculosis complex are slow growing, often requiring 4 to 6 weeks to establish visible colonies. The different species can be identified by colony growth and biochemical characteristics. Culture and identification of the specific organism is helpful for definitive diagnosis, long-term management, and prognosis and for calculating the zoonotic risk.

PCR testing has been developed for species relevant in human medicine, and animal specimens can also be evaluated.[127] Commercial kits (e.g., AccuProbe; Gen-Probe, San Diego, California) simplify the identification. Although final identification in culture takes up to 6 weeks, PCR followed by restriction analysis and nucleic acid hybridization can shorten this time to a few days. Unfortunately, PCR does not exist for all species that are relevant in dogs and cats.

Confirmation of opportunistic mycobacteriosis is not always easy because a diligent search for organisms in impression smears from exudates or tissue biopsy is usually required. Histology is characterized by extensive granulomatous to pyogranulomatous inflammation of the dermis and associated panniculitis. Application of acid-fast stains may reveal a few organisms within extracellular lipid vacuoles surrounded by neutrophils and macrophages. Bacterial culture of deep tissue (especially the panniculus) biopsy specimens and identification of the organism are essential for definitive diagnosis, but cultures from multiple tissue samples may be necessary. Fast-growing mycobacteria grow within 3 to 5 days, whereas the slow-growing types require 4 to 6 weeks. A 16S rRNA PCR and partial sequencing has been used to identify *M. genavense* infection in a cat.[119]

Diagnosis of feline leprosy is made by finding large numbers of acid-fast mycobacteria on histologic or cytologic samples or impression smears. A diffuse, granulomatous inflammatory infiltrate composed of vacuolated macrophages is present on histologic examination, and numerous mycobacteria are noted within macrophages or extracellularly within dermal vacuoles. Culture results are routinely negative with standard mycobacterial media, and specific media are needed (e.g., 1% Ogawa egg yolk medium). Animal inoculation using guinea pigs, rabbits, mice, or hamsters has been performed historically to identify *M. lepraemurium*, but this technique is obsolete. A PCR amplifying a sequence of the 16S rRNA gene has been developed to detect *M. lepraemurium*,[122,128] but its availability is limited.

Treatment

The decision to treat a dog or cat with classic tuberculosis is controversial. The zoonotic risk of pets that may harbor *M. tuberculosis* or *M. bovis* must be considered. Species differentiation by culture or PCR is recommended, especially if the animal has generalized disease, respiratory tract involvement, or extensive draining cutaneous lesions. If treatment is opted, the owner must know that it is long term and difficult to maintain (especially in cats). The inherent toxicity of some drugs and the financial costs must be explained. In some cases, the drugs may at best suppress the disease and indefinite treatment may be required. Surgical excision of small cutaneous lesions may be considered but is successful in only a few cases, and systemic therapy should accompany the surgical procedure. Debulking of larger lesions risks wound dehiscence and local recurrence of infection.

Pending a definitive diagnosis, interim therapy with fluoroquinolones is recommended. If signs of regional spread or

systemic involvement are present, double or triple therapy should be initiated immediately. Ideally, treatment should consist of an initial and a continuation phase. The initial phase usually requires at least three drugs and should last 2 months; the continuation phase requires two drugs and lasts at least an additional 4 months, depending on the type and extent of disease. Some animals require lifelong treatment. If triple therapy is not feasible (e.g., in difficult cats), treatment should at least involve two drugs, which should be given for a minimum of 9 months.

Traditionally, a combination of rifampin, isoniazid, and ethambutol (a common combination for humans) has been considered the most effective regimen for treatment of tuberculosis in animals. These drugs are relatively hepatotoxic for dogs and cats. The results of recent studies suggest less toxic combinations that are equally effective. The current treatment recommendation is an initial phase of 2 months involving a combination of rifampin (10 mg/kg given orally every 12 hours), enrofloxacin (5 mg/kg given orally every 24 hours), and azithromycin (10 mg/kg given orally every 12 hours), followed by a continuation phase of rifampin *plus* either enrofloxacin or azithromycin in these dosages. When resistance develops, a combination of rifampin, isoniazid, and ethambutol may be considered. If necessary, pyrazinamide or dihydrostreptomycin (if available) can be substituted for ethambutol. If *M. bovis* infection has been confirmed, however, pyrazinamide is not recommended due to the organism's natural resistance. Rifampin and isoniazid are more effective and less toxic than ethambutol and dihydrostreptomycin and consequently more appropriate choices if only two drugs are given. The prognosis depends on the extent and severity of infection but is generally guarded, especially when systemic disease is present. Uncomplicated cutaneous cases carry the best prognosis.[129]

In opportunistic mycobacteria infection, species identification should be performed and antibiotic susceptibility testing should be requested. A fluoroquinolone should be used pending diagnosis. Treatment after diagnosis should be tailored to the individual case. *M. fortuitum* and *M. smegmatis* are usually sensitive to high dosages of fluoroquinolones (ciprofloxacin, enrofloxacin, and ofloxacin), whereas *M. chelonae* is not. In contrast, *M. chelonae* is usually sensitive to clarithromycin. Double or triple therapy should be considered, as for tuberculosis, and antibiotic therapy should be continued for at least 2 months. In some cases clinical cure was achieved only after 6 to 8 months of therapy; other patients have required lifelong treatment. Surgical resection or debulking of large granulomatous masses has been more beneficial in dogs. Cats may improve with surgical resection of small lesions, but dehiscence, proliferation of the wound margins, and further progression of lesions are common sequelae. Surgical intervention should be radical and planned as for removing a locally invasive neoplasm. Antibiotic therapy is always necessary in combination with surgery. The prognosis is poor to guarded and is worse if previous attempts at surgery have failed. Dogs apparently have a better prognosis for remission. Despite expensive, long-term therapy, an infected pet that has continual serous drainage occasionally must be euthanized.

In feline leprosy, surgical removal of lepromatous granulomas is the desired treatment. Complete surgical excision of all nodules has proved beneficial in many cats. A fluorquinolone should be used pending the diagnosis. When surgery is not feasible or when removal is incomplete, treatment with clofazimine (8 mg/kg given orally every 24 hours), rifampin (15 mg/kg given orally every 24 hours), or clarithromycin (5 mg/kg given orally every 12 hours) has proved successful.[122,129] Clofazimine appears to have minimal toxicity in cats. Dapsone may be another alternative to surgery but is considered relatively toxic in cats. In contrast to other mycobacterial infections, the prognosis is good, and spontaneous resolution without treatment may occur.[130]

Prevention and Public Health Considerations

Mycobacterial infections are a major public health problem. Humans are susceptible to all mycobacteria that cause classic tuberculosis in dogs and cats. Identification of cases of *M. tuberculosis* infection in humans and outbreaks of *M. bovis* infection in cattle should be followed by evaluation of pet contacts. However, diagnosis of exposure in a healthy animal is difficult, because intradermal skin tests and antibody tests are not reliable. Euthanasia of animals infected with *M. tuberculosis* or *M. bovis* is generally recommended due to the public risk. *M. avium*, *M. microti*, *M. microti*-like, and *M. simiae* are just as likely to be acquired from environmental sources by humans as by pets, therefore treatment can be considered. However, to avoid any potential concern, families with members who are immunocompromised generally should be advised not to keep mycobacteria-infected pets. Vaccines are available to protect humans against infection with *M. tuberculosis*, but their efficacy is questionable. The attempt to control tuberculosis in dogs with modified live vaccines has had moderate success in that some dogs have shown resistance to infection; however, the immunity was only partial, therefore vaccination has not been generally recommended.

Opportunistic mycobacteria are free-living saprophytes, and there is little risk of transmission of these infections from animal to animal or animal to human. However, wound disinfection and contact precautions are usually advised, especially if immunosuppressed individuals are present in the same environment. Subcutaneous inoculation of *M. chelonae* organisms into a person reportedly occurred through penetration of dog hair into the owner's Achilles tendon by means of prolonged, vigorous rubbing of the person's ankle. Human hospital–acquired infections have also occurred.

There is no zoonotic risk in feline leprosy. Because the disease is acquired from rodents, prevention of exposure to rodents likely minimizes the possibility of disease in cats.

BRUCELLOSIS

Etiology

Canine brucellosis is caused by *Brucella canis*, a small, gram-negative, aerobic, coccobacillary bacterium that naturally infects dogs, causing an insidious bacteremia and reproductive disturbances.[1] *B. canis* has a limited host range; only dogs and wild Canidae have been found to be susceptible in nature. A survey testing free-ranging coyotes in Yellowstone National Park in Wyoming did not find antibodies to *B. canis*.[132] Cats can be infected experimentally with *B. canis* but are relatively resistant. Rabbits and nonhuman primates (but no other animal species) can also be experimentally infected. Human cases have been reported as a result of laboratory accidents or contact with infected dogs, but people are relatively resistant to *B. canis*. Dogs also are susceptible to infection with *Brucella abortus* and *Brucella suis*, which they can acquire naturally through ingestion of contaminated placentas and aborted fetuses from livestock.[133]

Pathogenesis

A relatively low prevalence of *B. canis* infections has been reported in the United States and Japan (1% to 18%), with a higher rate seen in the southern United States (approximately 8%). The prevalence is higher in Central and South America, with rates as high as 28%, as well as in Asia and North Africa. *B. canis* infections are extremely rare in northern Europe, but cases have been reported in southern and eastern European countries, (e.g., Spain and Czechoslovakia). The prevalence of infection varies according to a number of factors, including the age of the investigated population, housing condition, breed, and geographic location. Pet dogs in urban environments have

a lower prevalence compared with stray dogs in economically depressed areas, which may reflect increased population density and uncontrolled breeding of dogs.

B. canis is most commonly transmitted venereally; the organism penetrates the mucous membranes and enters the lymphoreticular system. The infection rate is high during breeding or after abortion. The highest number of organisms is found in aborted material. Shedding of *B. canis* may occur for up to 6 weeks after an abortion. The milk of infected bitches contains lower concentrations of organisms and appears to be less important in the transmission of infection to surviving pups, most of which having already been infected *in utero*. Although only low numbers of organisms are seen in semen and urine, seminal fluid and urine have been incriminated as sources of infection in male dogs that harbor the organisms in the prostate and epididymides. Alternative means of transmission occur less frequently under natural circumstances. Transmission via fomites has been reported after vaginoscopy, blood transfusion, artificial insemination, and use of contaminated syringes. *B. canis* is short lived outside the dog and is easily inactivated by common disinfectants.

After invading the mucous membranes, the bacteria enter phagocytic cells (and persist intracellularly in mononuclear phagocytes) and are transported to lymphatic and genital tract tissues. A leukocyte-associated bacteremia occurs beginning 1 to 4 weeks after infection and can last 6 to 64 months. *B. canis* may also spread to nonreproductive tissues, such as the intervertebral disks, eyes, and kidneys. The greatest numbers of *B. canis* organisms are found in the lymph nodes, spleen, and tissues of gonadal steroid dependency. As with other intracellular pathogens, cell-mediated immunity is probably the most important defense mechanism against *B. canis*. Persistent, nonprotective antibodies are characteristic of such infections; they appear to have little influence on the level of bacteremia or the number of organisms in tissues but characteristically cause hyperglobulinemia.

Spontaneous recovery from infection may occur within 1 to more than 5 years after infection. Some dogs may have persistent bacteremia throughout this time, whereas others can harbor bacteria in tissues for several months after bacteremia ceases. Dogs that recover naturally have low or negative antibodies and yet are immune to reinfection, which also suggests that protective immunity is cell mediated.

Clinical Signs

Despite generalized systemic infection with *B. canis*, adult dogs rarely are seriously ill. Fever is uncommon, and lymph node or spleen enlargement may rarely be noted. Except in males that commonly have epididymitis, most infections are not diagnosed through intact history or a routine physical examination. Dry, lusterless coats, loss of vigor, and decreased exercise tolerance are occasionally reported by owners of working dogs. Nongravid females mostly show no signs of illness.

The primary problems in intact male dogs are epididymitis, scrotal enlargement, and scrotal dermatitis. Inflammation of the epididymides and testes in males causes sperm leakage, which provokes the immune system to produce a complex of antisperm agglutinating antibodies and delayed-type hypersensitivity reactions against sperm that are unrelated to the antibodies against *B. canis*. The immune responses produced against spermatozoa contribute to the epididymitis, infertility, and eventual spermatogenic arrest seen in most infected male dogs.[133]

Bitches in late gestation (40 to 60 days) usually abort dead puppies but show no other clinical signs. Puppies are usually partly autolyzed. Some puppies are stillborn or weak. Conception failures also occur, but infection with *B. canis* does not interfere with normal estrous cycles. A high proportion of bitches that abort may subsequently have normal litters. However, some infected bitches show intermittent reproductive failures.

Less often, *B. canis* may localize in nonreproductive tissues such as the end-arterial circulation of the intervertebral disk, causing diskospondylitis.[134] Other tissues that filter blood-borne organisms or immune complexes also may become involved, including eyes (uveitis), kidneys (glomerulonephritis), and meninges (meningoencephalitis). Dogs with diskospondylitis initially experience spinal pain and later paresis and ataxia if spinal cord compression develops. Osteomyelitis of the appendicular skeleton causes lameness of the affected limb. Meningoencephalitis has been reported after experimental and natural infections; however, neurobrucellosis in dogs, as in humans, is uncommon.[135] Chronic multifocal pyogranulomatous dermatitis that resembled lick granuloma lesions also has been reported, but a direct causal relationship was not established. Recurrent anterior uveitis with corneal edema has been detected in infected dogs, either alone or in combination with other signs.[133]

Hematologic and biochemical values are either unaltered or nonspecific in canine brucellosis. Hyperglobulinemia with concomitant hypoalbuminemia has been the most consistent finding in chronically infected dogs. Some dogs have a positive Coombs' test in the absence of hemolytic anemia. CSF analysis may reveal pleocytosis, primarily consisting of neutrophils, and an increased protein concentration with meningoencephalitis, but it is unremarkable when diskospondylitis alone is present. Urinalysis is usually normal despite the variable presence of bacteriuria unless glomerulonephritis is present. Semen abnormalities include immature sperm, deformed acrosomes, swollen midpieces, detached tails, and head-to-head agglutination of sperm, often accompanied by neutrophilic and mononuclear inflammation.

Diagnosis

Antibody testing is the most frequently used diagnostic method for detecting canine brucellosis. Antibody tests available to veterinarians, however, pose a particular dilemma because several tests currently in use by diagnostic laboratories have not been evaluated critically and may provide false-positive results.[136] These tests are subject to considerable interpretive error because lipopolysaccharide antigens of several bacterial species cross-react with *B. canis*. False-negative results are rare, but antibody tests are usually negative during the first 4 weeks after infection despite the presence of bacteremia by 2 weeks after infection. Antibiotic therapy may suppress bacteremia and the associated antibody response, contributing to negative antibody tests and failure to isolate the organism in infected dogs.

ELISA and IFA for antibody detection exist, but they have not been well standardized or widely evaluated. Some newer ELISAs have been developed,[137-139] but no comparison studies involving large numbers of canine sera samples are available to assess the usefulness of these tests. The 2-mercaptoethanol rapid slide agglutination test (ME-RSAT) (D-Tec CB; Synbiotics, San Diego, California) is preferred as an in-office screening procedure because it is inexpensive, rapid, and sensitive and it detects antibodies early. There is a high correlation between a negative test and lack of infection. However, false-positive test results are possible. *B. canis* cross-reacts with other *Brucella* species and other bacterial species, such as *Pseudomonas*, *Bordetella bronchiseptica*, *Actinobacillus equilli* and, possibly, others. Some breeds (e.g., Irish wolfhounds and Old English sheepdogs) have an exceptionally high false-positive rate, for unknown reasons. The tube agglutination test (TAT) is used by some laboratories after a positive ME-RSAT result to obtain confirmation and quantitative titers. Unfortunately, it suffers from the same nonspecific results and has not been well standardized among laboratories. Nevertheless, results of the ME-RSAT correlate well with the ME-TAT, both of which

should be considered as screening tests. The agar gel immunodiffusion (AGID) test is a sensitive procedure for antibody detection. Two antigens, either from the cell wall or cytoplasm (Cp), have been used in this test. The better CpAg-AGID uses cytoplasmic antigens and is highly specific for *Brucella* infection in dogs.[140] This test is performed by certain commercial laboratories and should be used as a confirmatory antibody testing procedure.

Culture, if positive, is the only definitive way to diagnose brucellosis. Isolation of *B. canis* is time-consuming but not difficult, because the organism grows well aerobically on conventional media used for all *Brucella* species. Negative results, however, may occur in chronically infected dogs with intermittent bacteremia. Blood is the best source for isolating the organism. Whole blood should be cultured, because the organisms are associated with the leukocyte fraction. Bacteremia is detected 2 to 4 weeks after oronasal infection and, if left untreated, can persist for as long as 5 years.[133] Culture of the organism from urine or semen is less reliable. However, urine culture can be positive in some dogs, especially males, when blood cultures are negative; only cystocentesis urine should be used to avoid overgrowth of other bacteria. Collection of semen by ejaculation is valuable for culture during the first 3 months of infection, when the concentration of organisms is greatest. *B. canis* can also be isolated at necropsy from several tissues.

A PCR has been developed for humans that identifies all *Brucella* species relevant for human medicine; the test uses genus-specific primers that bind to a conserved region of the 16S rRNA gene. With carbohydrate profiling, *B. canis* can be differentiated from the other species.[141,142] This PCR could be used in dogs.

Treatment

Treatment of *B. canis* infection is difficult because of the intracellular persistence of the organism. Relapses are common after antimicrobial therapy stops. Bacteremia often recurs days to months after treatment is discontinued, making follow-up evaluation essential because animals still can harbor infection in certain tissues. For these reasons and because of the zoonotic risk, client education is critical, and euthanasia may be considered. If treatment is an option, infected pets should be neutered and given a strict regimen of antibiotic therapy to reduce the chance of family members becoming infected through genital secretions. The organism can persist in the tissues of neutered animals, but shedding is believed less likely. Treatment of intact breeding dogs should be considered only under exceptional circumstances. Infected male dogs rarely, if ever, recover; they usually become sterile. Infected female dogs have recovered in some instances and have been returned to breeding programs. Aborting females may subsequently produce normal litters, but even in those cases the success of therapy is uncertain. Thus breeding of such animals should be done only when it is considered essential (e.g., loss of a valuable blood line) and after the risk has been explained to the owner.

Various antimicrobial agents have been considered for treatment. Repeated courses of antibiotic therapy are recommended on the basis of follow-up antibody testing and blood cultures. Cure of brucellosis must not be assumed, because bacteremia may recur weeks or months after antibiotics are discontinued, and reports of successful cures should be viewed with caution unless subsequent cultures and antibody tests have been performed for at least 6 months. Infected dogs respond poorly or not at all to drugs when they are given alone or for a single course of therapy. *In vitro*, synergy has been noted among tetracyclines and fluoroquinolones and aminoglycosides and sulfonamides,[143] and combination therapy, usually performed with tetracyclines and aminoglycosides, offers the best chance of eliminating infection. Unfortunately, the best known regimen (minocycline *plus* dihydrostreptomycin) is unobtainable in many countries because of the restricted availability of dihydrostreptomycin. Gentamicin has been substituted for dihydrostreptomycin, but the efficacy is less than with dihydrostreptomycin.[133] The recommended treatment regimen is gentamicin (5 mg/kg subcutaneously every 24 hours for 7 days) administered twice in the first and fourth week, in combination with high-dose oral minocycline (25 mg/kg orally every 24 hours) for 4 weeks. Eventually, generic doxycycline can be substituted for minocycline at the same dosage at lower cost. Renal function must be closely monitored during gentamicin treatment phases. Lower dosages of this combination or other antibiotics alone or in combination are not as effective. Infected animals may have to be treated with two or more courses of this antimicrobial treatment regimen. Sequential antibody tests at 3- to 6-month intervals are recommended to monitor treatment efficacy.

Prevention

There is no vaccine for brucellosis, and the results of experimental vaccination studies have been unsatisfactory. The desirability of a vaccine is questionable, especially with the available diagnostic testing, because an effective vaccine would be required to provide serviceable immunity but not confound the antibody tests.

Control of canine brucellosis in a kennel with confirmed cases is a difficult, time-consuming, and agonizing experience both for dog owners and veterinarians. A kennel should be quarantined as soon as the diagnosis of *B. canis* infection is ascertained, and infected animals should be promptly eliminated. Appropriate disinfection procedures should be implemented to arrest the spread of infection via fomites. All dogs and discharges or secretions in an infected kennel should be handled with gloves until antibody testing can be done to determine the extent of the infection. Animals should not be admitted to or released from the kennel until the disease is eradicated. Movement of dogs within a colony also should be restricted to removal of proven and suspect cases to isolation quarters. New additions are at high risk for infection, especially if dogs are not individually penned, which also increases the number of animals requiring repeated testing during the eradication process. Animals must not be released for sale or any other purpose. All dogs in an infected kennel should be antibody tested for at least 3 months after a negative status is achieved, especially before each breeding, even by artificial insemination. If animals are retained as pets or working dogs or if treatment is contemplated, the animals should be neutered and moved to separate housing. Prevention is accomplished by quarantine of all new acquisitions until two antibody test results at l-month intervals are negative. Animals used for breeding should be tested 3 to 4 weeks before each mating to allow time for test results to be reported. Brood bitches should not be mated unless both male and female have been tested and certified negative. If dogs leave a colony, they should be tested before readmission.[133]

Brucellosis in Cats

Cats can be infected experimentally and develop bacteremia but are relatively resistant and do not develop clinical signs. The relevance of *B. canis* infection in cats in the field is unknown.

Public Health Considerations

Pathogenic *Brucella* species in humans include *B. melitensis*, *B. abortus*, *B. suis*, and *B. canis*. Human brucellosis caused by other *Brucella* species is still prevalent in many southern countries, especially in the Mediterranean basin, and ingestion of raw milk and milk products is the most common mode of transmission.[142,144-146] Humans are relatively resistant to infection

with *B. canis*, and the disease is relatively mild compared with infections caused by other *Brucella* species. However, more than 40 cases of human infection caused by *B. canis* exist in the literature. Natural and laboratory-acquired infections have been reported in several countries; however, the actual number of cases is unknown because human infections are often undiagnosed. Contact with aborting bitches was the source of infection for the majority of infected pet owners. A proportion of cases are asymptomatic and can be detected only by testing for antibodies. Fever, chills, fatigue, malaise, lymphadenomegaly, and weight loss have been seen in symptomatic patients. Rare complications include endocarditis,[147] meningitis, arthritis, hepatitis, and visceral abscesses. Two infected adolescent boys had pleural effusion and pulmonary nodules.[148] Human infections are readily and effectively treated with tetracyclines.

Clients should always be informed about the potential health hazard in keeping *B. canis*–infected pets. Laboratory workers should use caution in handling or pipetting samples submitted for diagnostic testing. Veterinarians should practice good hygiene when examining suspected dogs, especially aborting bitches.

TETANUS

Etiology

Tetanus is caused by the action of a potent neurotoxin formed in the animal or human body by *Clostridium tetani*, a motile, gram-positive, nonencapsulated, anaerobic, spore-forming bacterium.[1] Although strain differences of C. *tetani* exist throughout the world, the toxin produced by all strains is antigenically homogeneous. Resistant spores of the organism can be found in the environment, especially in rich soil. Spores can survive adverse weather conditions in the absence of direct sunlight for months to years and can be found readily in dust and debris in indoor environments. Organisms can be isolated from the feces of many domestic animals, including dogs and cats, and humans without pathogenetic significance.[149] The prevalence of the disease in dogs and cats is relatively low[150] compared with that in other domestic animals (e.g., horses) and humans. However, a number of cases in dogs[151-160] and cats[161-167] are reported in the literature. The low prevalence in dogs and cats is mainly related to the natural resistance of dogs and cats to the toxin. It could be shown that this resistance is caused by the inability of the toxin to penetrate and bind to nervous tissue, because direct CNS injection of toxin produce equivalent signs in all species.[168]

Pathogenesis

Tetanus develops when spores are introduced into wounds or penetrating injuries. Most cases develop after penetrating skin wounds, but tetanus has also been described in female dogs after parturition[169] or ovariohysterectomy.[170,171] The spores vegetate in response to anaerobic conditions at the site of the injury. Two toxins have been identified from C. *tetani*. Tetanolepsin causes hemolysis of erythrocytes *in vitro* but is not considered clinically significant. In contrast, tetanospasmin enters the body from the wound site and has marked effects on neurologic function. It is not absorbed from the gastrointestinal tract, where it is usually destroyed by digestive enzymes. Its high molecular weight (176,000) precludes its entry into the placenta.

Tetanospasmin enters the axons of the nearest motor nerves at the neuromuscular endplate and migrates by retrograde transport within motor axons to the neuronal cell body in the spinal cord or brain stem. It can spread in the CNS in this fashion. Alternatively, it can be transported in the bloodstream from the area of the wound to nerves at distant sites. Thus the condition can cause localized, progressive illness or a more generalized syndrome. Tetanospasmin blocks inhibitory transmission to motor neurons. It has additional effects on the neuromuscular junction and autonomic ganglia that can cause further visceral and motor neuron disturbances.

Clinical Signs

Clinical signs of tetanus usually occur within 5 to 10 days of injury, but because of the higher resistance of dogs and cats, the onset may be delayed up to 3 weeks. This may account for the absence of a detectable wound by the time dogs show clinical signs. Because cats have an even more pronounced innate resistance, their wounds are usually so extensive that they are still obvious at presentation. Wounds nearer the head are associated with more rapid onset and generalized tetanus than are injuries to distant extremities.

The clinical signs of tetanus can be explained by the pathophysiologic effects of tetanospasmin on the nervous system. The toxin inhibits release of glycine and gamma-aminobutyric acid (GABA) neurotransmitters of inhibitory neurons of the brain and spinal cord. It has an affinity for gangliosides in the gray matter of the CNS, which may explain the cerebral signs that appear in some cases without obvious spinal cord involvement. Tetanospasmin also has an affinity for binding at the neuromuscular junction, which can induce direct neuromuscular facilitation before the migration of toxin to the CNS. The toxin may affect sympathetic preganglionic neurons in a manner similar to that in the lower motor neurons in the spinal cord and cause signs of autonomic dysfunction.[168]

Localized tetanus is more common in cats than in dogs and more common in dogs than in other domestic animals or humans because of the relative resistance of carnivores to the toxin. This condition is characterized by increased stiffness of a muscle or an entire limb, first noted in close proximity to the wound site. The stiffness usually spreads gradually and eventually may involve the entire nervous system.

Animals affected with generalized tetanus generally have a stiff gait and an outstretched or dorsally curved tail. They have difficulty standing or lying down in comfortable positions because of their extreme muscle rigidity. The rectal temperature is usually elevated due to excessive muscular activity. The ears are held erect, the lips are drawn back, and the forehead is often wrinkled as a result of facial muscle spasm. The animal characteristically appears to be continuously smiling *(risus sardonicus)*. Protrusion of the third eyelid and enophthalmus result from retraction of the globe from hypertonus of extraocular muscles. Trismus (lockjaw) is caused by contraction of masticatory muscles. Increases in salivation and the respiratory rate, as well as laryngeal spasm and dysphagia, can result from involvement of parasympathetic and somatic cranial nerve nuclei. Regurgitation and gastroesophageal reflux may result from esophageal hiatal hernia and megaesophagus,[172] potentially leading to aspiration pneumonia, a major complication in many animals with tetanus. Animals become apprehensive and react strongly to tactile or auditory stimulation. Dogs and cats usually remain conscious until they develop convulsions. The signs may proceed to periodic generalized tonic contraction of all muscles with opisthotonus or grand mal convulsions.

Bradycardia associated with tetanus probably results from vagal-parasympathetic hyperactivity. Tetanospasmin also blocks neurotransmitters in the parasympathetic cardiac inhibitory center of the nucleus ambiguous, resulting in increased vagal tone and pronounced bradyarrhythmias. Increased catecholamine release associated with adrenergic stimulation can cause episodes of hypertension or tachycardia.[173]

Hematologic abnormalities, including leukocytosis with neutrophilia and left shift, are the result of large wounds or

aspiration pneumonia that may be present. Serum biochemistry and CSF values are unaffected, except for increased muscle enzyme activities (creatine kinase, aspartate aminotransferase).

The progression of clinical signs culminates in death, which is usually caused by respiratory compromise as a result of rigidity of the respiratory musculature, reflex spasms of the larynx, increased airway secretions, and central respiratory arrest from medullary tetanospasmin effects or anoxia. Dogs and cats not as severely affected may recover. The binding of tetanospasmin to presynaptic sites of inhibitory neurons is irreversible; recovery depends on sprouting of new axon terminals.

Diagnosis

Tetanus is one of the few infectious diseases that can be diagnosed by "classic" clinical signs. Measurement of serum antibody titers to tetanospasmin has been used to substantiate the diagnosis. Values must be compared with those of control animals. Antibody measurements might be helpful in a clinical setting to confirm the cause of undiagnosed muscle stiffness. Isolation of *C. tetani* from wounds is usually unrewarding. The organisms are only present in low concentrations, and although Gram-stained smears may demonstrate gram-positive rods and dark-staining spherical endospores, the morphology is similar to that of many other anaerobic bacteria. If culture is attempted, it should be done under strict anaerobic conditions at 37° C for at least 2 weeks.

Treatment

Treatment of severely affected animals is costly and time-consuming, and owners must be advised of the possibility of complications and lengthy hospitalization. Mildly diseased animals recover from the neurologic dysfunction with wound management alone. More severe cases, if left untreated, can prove fatal. These animals are suffering, therefore euthanasia must be the alternative to treatment.

The immediate concern in treating tetanus is administration of antitoxin to neutralize any toxin that is unbound to the CNS or has yet to be formed. The timing and route of antitoxin administration are important in determining effectiveness. Use of antitoxin should be a routine measure; however, elimination of bound toxin by the affected animal occurs gradually, and administration of antitoxin does little to hasten the process. Therefore recovery in most cases is slow and progressive. Intravenous administration of antitoxin is superior to intramuscular or subcutaneous administration for producing a rapid and marked increase of circulating antitoxin. The equine antitoxin (2.5 to 25 IU/kg) should be given slowly intravenously over 5 to 10 minutes. Larger animals should receive a proportionally lower dose on the basis of body weight. Intravenous administration of antitoxin is commonly associated with anaphylaxis, warranting appropriate precautions. An initial test dose (0.1 to 0.2 mL) of antitoxin should be given intradermally 15 minutes before IV administration. Epinephrine, glucocorticoids, and antihistamines should be readily available in case of an adverse reaction, or the latter two may be given before the intravenous injection, depending on the intradermal test outcome. A therapeutic blood level of antitoxin persists in dogs for 14 days after injection; repeated administration is usually unnecessary and increases the chance of an anaphylactic reaction. Local intramuscular injection of a small dose of antitoxin (1000 IU) around and proximal to the wound site has been shown to be beneficial in experimental studies. Intrathecal injection of antitoxin in laboratory animals has been shown to be beneficial; however, use in affected humans has not proven to be effective.

Local and parenteral antibiotic therapy should be instituted in an attempt to kill any vegetative *C. tetani* organisms present in the wound. Although antibiotics by themselves do not neutralize circulating toxin, they significantly reduce the amount of antitoxin released in experimental tetanus. Penicillin G is the drug of choice and should be given intravenously (as potassium or sodium salt) at a high dose (20,000 to 50,000 IU/kg every 6 hours for 10 days). A portion of the dose can be injected intramuscularly (as procaine salt) in close proximity to an identified wound site. Penicillin derivatives, such as ampicillin, are not as effective against the organism, and their use may cause little or no response. Metronidazole (10 mg/kg orally every 8 hours for 10 days) may be more active than penicillin G because it is bactericidal against most anaerobes and achieves effective therapeutic concentrations even in anaerobic tissues. Some treatment regimens recommend a combination of penicillin G and metronidazole; however, metronidazole toxicity has to be considered, and only low dosages should be used (not more than 250 mg total every 12 hours in cats). Clindamycin (5 mg/kg intravenously every 8 hours for 10 days) also has been used in some cases.

Surgery may be required if tissue necrosis or abscess formation is extensive. Antitoxin should be administered before surgery because of the release of toxin in the circulation during tissue manipulation. General anesthesia is usually required to debride wounds and remove necrotic tissue. The prognosis for recovery is always greater if the wound site is located and can be debrided.

Supportive measures are imperative in the successful management of an animal with tetanus. Sedation is usually needed for an excitable animal, and phenothiazines appear to be highly effective, even though they are contraindicated in most seizure disorders. Fluids are needed for hydration. Tracheostomy may be required if laryngeal spasm is severe. Esophagostomy or gastrostomy tubes may be needed if trismus prevents eating.

In mildly affected animals, normal function usually returns within 3 weeks of the initiation of treatment. The prognosis for severely affected animals is extremely guarded, and many die as a result of complications associated with respiratory or cardiovascular dysfunction or uncontrollable muscle spasms.

Prevention

Active immunoprophylaxis with tetanus toxoid is not recommended for dogs and cats; it is used in more susceptible species such as humans and horses. Appropriate care of infected wounds and rational antibiotic therapy should minimize the occurrence of tetanus.

Tetanus in Cats

Cats are even more resistant to tetanus toxin than dogs and more commonly develop only localized tetanus.[161-167]

Public Health Considerations

There is no risk of transmission from dogs or cats to humans.

BOTULISM

Etiology

Clostridium botulinum is a gram-positive, spore-forming, saprophytic, anaerobic rod that is distributed in soil worldwide. Botulism is an intoxication caused by a neurotoxin produced by the organism that causes neuromuscular paralysis.[1] In humans, outbreaks of botulism are commonly described in the literature; the contaminated food sources are variable and have included canned beef stew,[174] home-canned mushrooms,[175] and restaurant potato salad.[176] Sources of recent outbreaks include a commercial canned cheese sauce in the United States,[177]

a mascarpone cream cheese dessert in Italy,[178] and a locally produced cheese in Iran.[179]

To cause disease, either the organism or its spores must contaminate a food source. Most cases in animals are caused by ingestion of the preformed toxin in food. Naturally occurring botulism in dogs has been mainly attributed to the eating of carrion or raw meat. The disease in cats is similar to that in dogs under experimental conditions, although there are no reports of naturally occurring disease.

Seven subtypes of C. *botulinum* (A, B, C, D, E, F, and G) have been identified on the basis of their antigenically distinct neurotoxins. All have similar structure and the same neurotoxic effect. Subtypes A, B, E, and F are associated with human disease. Most cases in animals are caused by subtypes C and D, which are closely related immunologically. All canine cases to date have been caused by subtype C toxin[180-186] with the exception of two cases of subtype D reported from Senegal.[187,188]

Clostridial spores are resistant to heat, light, drying, and radiation, and specific conditions are necessary for germination. The organism grows best in anaerobic and warm conditions (15° to 45° C). All types of botulinal toxin are inactive when initially released by bacterial lysis, and bacterial or tissue proteases are necessary to cleave them to generate the active dichain neurotoxin.

Pathogenesis

Botulism is usually caused by ingestion of the preformed toxin, although a variant of the disease in humans, infant botulism, is induced by ingestion of spores, mostly present in honey. Adults are usually resistant to intestinal colonization with C. *botulinum*, mainly thanks to the intestinal microflora.

Once ingested, the toxin is absorbed from the stomach and upper small bowel and enters the lymphatic system. It circulates by unknown transport mechanisms to the neuromuscular junction of cholinergic nerves, where it exerts its effects. A metalloproteinase similar to tetanus toxin, the botulinal toxin, prevents the presynaptic release of acetylcholine at the neuromuscular junction; both the spontaneous release of acetylcholine and its release caused by a nerve action potential are inhibited. Binding of the toxin occurs very quickly and is irreversible, unaffected by temperature and independent of neural activity. The cell membrane receptors for the toxin have a very high affinity for it because very small quantities (less than 10 mol) are sufficient to cause death, making it the most potent toxin known.[189] Variations in receptor affinity for different types of toxin explain the different sensitivities of animal species to the different botulinal toxins.

Clinical Signs

The incubation period after ingestion of contaminated food in dogs ranges from hours to 6 days. The earlier the signs appear, the more serious the disease. The duration of illness in dogs that have recovered ranged from 14 to 24 days. The severity of signs varies with the amount of toxin ingested and the individual susceptibility.

The blockage of acetylcholine release results in generalized lower motor neuron and parasympathetic dysfunction. Clinical signs are characterized by a symmetric, ascending weakness from the rear to the forelimbs that can result in quadriplegia. Limb reflexes are depressed, and cranial nerve motor responses are affected, causing mydriasis, decreased jaw tone, decreased gag reflexes, and excess salivation. Megaesophagus may be present. Pain perception is intact; muscle atrophy and hyperesthesia do not develop. Death may result from respiratory paralysis.

Hematologic and biochemical parameters are unaffected. Electromyography shows conduction defects primarily in the neuromuscular junction and less in the peripheral nerve.

Blockage of neurotransmission can cause death of the affected animal from inability to breathe. If recovery occurs, it is complete. Botulinal neurotoxin does not cause death of the affected neuron; it only causes paralysis and degeneration of the intoxicated synapse. If the animal survives, recovery occurs by development of new terminal axons with functional neuromuscular junctions. Cranial nerve, neck, and forelimb functions tend to return first during recovery. Thus the effect of botulinal neurotoxin always has the potential for a complete reversal.

Diagnosis

Botulism is usually suspected from the history and clinical signs. Confirmatory diagnosis is based on finding the toxin in serum, feces, vomitus, or samples of the food ingested. Serum should be collected as early in the disease course as possible and when clinical signs are maximal. About 10 mL of serum or 50 g of feces, vomitus, or food are needed. The preferred method for identifying the toxin still is the neutralization test in mice. Serum or an extract of contaminated material is injected alone and in combination with type-specific antitoxin into the peritoneal cavity of mice. The mice are then observed for signs of botulism. Survival of one group protected with one type of antitoxin and death of the other groups with signs consistent with botulism confirm the presence of botulinal toxin. Newer *in vitro* tests, including radioimmune assay (RIA), passive hemagglutination, ELISA,[190] and PCR, have been developed to identify botulinal toxin but have not replaced the mouse test to date due to lack of accuracy.

Treatment

Antitoxin is not effective after the toxin has penetrated the nerve endings, which occurs rapidly after the toxin enters the bloodstream. However, antitoxin may prevent further toxin binding if intestinal absorption and circulation are still occurring. Most cases in dogs are type C; thus type C antitoxin should be given. The recommended dose for treating dogs is the same as that for treating human adults (10,000 to 150,000 IU/dog IV or IM, two doses 4 hours apart). Because the antitoxin remains in circulation for 40 days after administration, there is no need for further administration. Anaphylaxis is a potential risk. Intradermal skin testing can be performed with 0.1 mL 20 minutes before intravenous injection. Any immediate reaction at the test site is a warning that an allergic response may occur, and glucocorticoids and antihistamines should be applied *before* application of the antitoxin in these cases.

The use of antibiotics in botulism is the subject of debate. Penicillin and metronidazole have been administered in dogs and humans in an attempt to reduce any potential intestinal growth of C. *botulinum*. The efficacy of these drugs is doubted because the disease occurs usually due to ingestion of preformed toxin and because neither drug is certain to eradicate C. *botulinum* from the intestine. The possibility that these drugs could make the disease worse by releasing more toxin through bacterial lysis is discussed. Even in infant botulism, which may involve intestinal colonization with C. *botulinum*, penicillin has no effect on recovery. Antibiotics also can alter the intestinal microflora, which might allow C. *botulinum* to grow. Therefore antibiotics should only be given if secondary infection (e.g., aspiration pneumonia) develops. Aminoglycosides should be avoided because they also have the potential to block neuromuscular function.

Supportive treatment, which can be time-consuming and expensive, is the most important intervention in the therapy of animals with botulism. Spontaneous and complete recovery occurs in moderately affected animals if respiratory and urinary tract infections can be avoided. Affected animals should

be padded when recumbent and assisted to eat and drink. Several drugs, including guanidine hydrochloride, 4-aminopyridine, and 3,4-diaminopyridine, have been used as neuromuscular potentiators but without demonstrable efficiency in clinical cases in humans or animals.

Prevention

Preventing access to carrion and thorough cooking of any food fed to dogs and cats prevents the disease. Botulinal toxin is destroyed by heating food to 80° C for 30 minutes or to 100° C for 10 minutes. Vaccination with a toxoid has been successful in cattle and in exposed laboratory workers but has not been used in dogs or cats is not recommended because of the low prevalence of the disease.

Botulism in Cats

Although botulism has been experimentally produced in cats, no natural cases of botulism have been reported. A cat that ate contaminated yogurt did not become ill, even though two humans eating the same yogurt did. Botulism has been reported in lions, but jaguars and coatis eating the same food as the lions were not affected.[191] Produced under experimental conditions, the disease in cats is similar to that occurring in dogs because botulinal neurotoxins cause similar signs in all species. Although there are no reports of natural disease in cats, cats can be the source of outbreaks in cattle. In one case, 427 Holstein cattle that had been fed a rotten bale of oat hay contaminated with a dead cat died from botulism, and the presence of botulinum toxin type C was identified.[192]

Public Health Considerations

The disease is not transmitted from animals to humans.

CHAPTER 166

Obligate Intracellular Bacterial Pathogens

Edward B. Breitschwerdt

GENERAL CONSIDERATIONS

From an evolutionary and clinical perspective, several groups of bacteria have developed an obligate intracellular life style that facilitates their existence within an insect vector or within one or more animal hosts. Due to the persistent nature of many of these intracellular infections, the factors that ultimately predispose to the development of pathology in many animal hosts are as yet incompletely understood. Recent genetic analyses of 16S rRNA genes, heat shock, and surface protein genes have resulted in a substantial reclassification of the genera *Anaplasma*, *Ehrlichia*, *Cowdria*, *Neorickettsia*, and *Wolbachia*.[1] As a result, the genus *Ehrlichia* is now comprised of: *E. canis*, *E. chaffeensis*, *E. ewingii*, *E. muris*, and *E. ruminantium*. The genus *Anaplasma* is now comprised of: *A. phagocytophilum*, (previously *E. equi*, *E. phagocytophila*, or the human granulocytic ehrlichia [i.e., the HGE agent]), *A. bovis*, and *A. platys*. *E. risticii* has been transferred to the genus *Neorickettsia*, which includes: *N. sennetsu*, *N. helminthoeca*, *N. risticii*, and the salmon fever agent. Organisms within the genus *Wolbachia* are currently recognized as arthropod pathogens or symbiotes but appear to be of emerging importance as vertebrate pathogens. Within the genera *Rickettsia*, *Ehrlichia*, *Anaplasma*, and *Neorickettsia*, numerous species can be pathogenic for animals, including man. Many of these organisms are found throughout the world and can be transmitted by ticks, fleas, chiggers, or the ingestion of insects or flukes. These organisms can induce disease manifestations that range in severity from subclinical to life threatening.

Because of this reclassification, clinicians will have to reorganize the nomenclature that involves pathophysiology, diagnosis, treatment, and preventive strategies related to these organisms.[1,2] Although a currently cumbersome task, the recent reclassification should result in enhanced clarity when considering similarities and differences among organisms in the same or different genera. The terms *rickettsioses*, *ehrlichioses*, *anaplasmoses*, and *neorickettsial infections* have taken on new clinical meaning as a result of advances in microbial genetics and clinical medicine. A more detailed description of Rocky Mountain spotted fever (RMSF), typhus group rickettsiae, canine ehrlichiosis, salmon-poisoning disease, and *Coxiella burnetii* infection is provided in the fifth edition of this text (see Chapter 86, The Rickettsioses).

RICKETTSIOSES: THE SPOTTED FEVER GROUP RICKETTSIAE

Spotted fever group (SFG) rickettsiae have been described from all continents. The group includes nine species: *Rickettsia rickettsii* (the type species), *R. africae*, *R. akari*, *R. australis*, *R. conorii*, *R. montana*, *R. parkeri*, *R. rhipicephali*, *R. sibirica*, and *R. felis*, although many other SFG rickettsiae have been described. *Dermacentor*, *Rhipicephalus*, *Haemaphysalis*, and *Amblyomma* species ticks transmit SFG rickettsiae. Rickettsia-induced endothelial cell damage results in vasculitis, altered vascular permeability, edema, and necrosis. *R. felis*, which is transmitted by fleas, is recognized as a cause of human febrile illness in the United States and Central and South America. The pathogenicity of *R. felis* in cats or dogs has not been established. As the most pathogenic of the SFG rickettsiae, *R. rickettsii* will be considered in detail.

ROCKY MOUNTAIN SPOTTED FEVER

RMSF is a tick-transmitted rickettsial disease of dogs, people, and other vertebrate species. The causative agent is *Rickettsia rickettsii*. Veterinarians should anticipate a spectrum of illness

after naturally occurring infection with *R. rickettsii* in endemic regions. Clinical abnormalities associated with RMSF include fever, anorexia, depression, mucopurulent ocular discharge, scleral injection, tachypnea, coughing, vomiting, diarrhea, muscle pain, neutrophilic polyarthritis, and a diverse group of neurologic signs including hyperesthesia, ataxia, vestibular signs, stupor, seizures, and coma. In some dogs, weight loss is very severe, considering the short duration of illness. Poorly localizing joint, muscle, or neurologic pain that is suggestive of polyarthritis, polymyositis, or meningitis may represent the only or most prominent clinical finding. Retinal hemorrhages are a consistent finding but may be absent early in the course of the disease. Epistaxis, melena, hematuria, and petechial-to-ecchymotic hemorrhages occur in some dogs but may not develop unless diagnosis and treatment are delayed for 5 or more days after the onset of clinical signs. Scrotal edema, hyperemia, hemorrhage, and epididymal pain are frequently observed in male dogs. Signs associated with cardiovascular collapse, oliguric renal failure, or brain death can develop in the terminal stages of the disease.[3,4] Gangrene affecting the distal extremities, scrotum, mammary glands, nose, or lips is associated with severe vascular obstruction and can induce substantial tissue loss, necessitating reconstructive surgery.

Diagnosis

Seasonal occurrence, history of tick infestation, fever, and combinations of the previously described clinical findings should suggest the possibility of RMSF. Due to marked variation in clinical presentation, confirmation of the diagnosis of RMSF is important for the clinician to gain familiarity with the disease. In addition, confirmation of RMSF in household pets warrants owner education as to the enhanced risk associated with tick exposure in that environment. Thrombocytopenia, generally mild in degree, is the most consistent hematologic finding.

Leukopenia generally occurs during the early stages of infection (first 24 to 48 hours), followed by progressive leukocytosis, which increases in proportion to the severity of vascular injury. Toxic granulation of neutrophils, metamyelocytes, eosinopenia, lymphopenia, and monocytosis may accompany the more typical changes in platelet and neutrophil number. A mild anemia may occur. Severe anemia, leukopenia, and thrombocytopenia can accompany fulminant canine RMSF.[4] Biochemical abnormalities reflect the effects of generalized vascular damage and vary with the severity and duration of infection. Hypoproteinemia, hypoalbuminemia, azotemia, hyponatremia, hypocalcemia, and increased liver enzymes (serum alkaline phosphatase, alanine aminotransferase) may occur in dogs with RMSF. Bilirubinuria and bilirubinemia also occur in dogs with RMSF. Synovial or cerebrospinal fluid (CSF) analysis will generally reflect a mild increase in protein and cells, which, in the early disease process, are composed of a high percentage of neutrophils and later, mononuclear cells.

Confirmation of a diagnosis requires either direct immunofluorescent testing for *R. rickettsii* antigen in tissue biopsy or necropsy specimens, serologic testing, or polymerase chain reaction (PCR) amplification of rickettsial DNA. Using the indirect fluorescent antibody (IFA) test, documentation of a fourfold or greater increase in antibody titer between acute and convalescent sera confirms a diagnosis of RMSF. To facilitate the accurate interpretation of serologic results, it is important to obtain the acute-phase sample as early in the disease course as possible and the convalescent sample 2 to 3 weeks thereafter. If acute-phase sera are obtained several days after the onset of clinical signs, a high antibody titer may be found. Although early initiation of antirickettsial antibiotic therapy will slightly decrease the intensity of the humoral immune response to *R. rickettsii* antigen, experimental studies indicate that collection of appropriately timed serum samples should still facilitate an accurate diagnosis of RMSF in dogs.[5] Direct immunofluorescent testing or PCR amplification of *Rickettsia* DNA provides the opportunity for rapid diagnosis by demonstrating *R. rickettsii* in skin biopsies or by detecting DNA in blood or tissue samples.[6] Prior initiation of antibiotic therapy can cause a false-negative test results with both direct immunofluorescent testing and PCR.

Treatment

Tetracycline (22 mg/kg three times a day for 14 days) or doxycycline (5 mg/kg twice a day for 14 days) is effective for treatment of SFG rickettsiae infection. Fluoroquinolones, such as enrofloxacin, appear to be equally effective for treating RMSF but not ehrlichiosis. After initiation of treatment, a rapid clinical response occurs in dogs without severe vascular damage or neurologic sequela. Defervescence should be anticipated within 24 hours after the initiation of antibiotics. Delay in diagnosis or the use of antibiotics such as penicillin, cephalosporin derivatives, or aminoglycosides that lack antirickettsial spectrums, may result in increased morbidity or mortality. Due to severe vascular damage, fluid therapy should be used with extreme caution. Prednisolone administered at anti-inflammatory or immunosuppressive doses in conjunction with doxycycline does not potentiate the severity of *R. rickettsii* infection in experimentally infected dogs.[5]

Prevention

Immunity after natural infection is probably permanent. It is possible that undiagnosed mild or asymptomatic *R. rickettsii* infections, or repeated exposure to nonpathogenic SFG rickettsiae, can also contribute to the prevention of severe RMSF in dogs with heavy tick exposure in endemic regions. Minimizing tick exposure, using acaracidal preparations, and routinely removing ticks from dogs represent the most effective means of prevention. After infection with *R. rickettsii*, the duration of rickettsemia is brief, approximately 5 to 14 days.[5,6] Therefore infected dogs do not play an important reservoir role and pose a minimal zoonotic threat to humans. In contrast, if RMSF is diagnosed in a household pet, the dog serves as a valuable environmental sentinel for potential human exposure to infected ticks. Care should be exercised in removing ticks, so as not to contaminate one's hands with infective hemolymph from ticks. Although the risk of inadvertent transmission is small, contact with rickettsemic blood during intravenous catheter placement, blood collection procedures, or laboratory sample analysis should be avoided. Zoonotic warning labels are recommended for blood samples obtained from dogs in which a differential diagnosis of RMSF is being considered. The role of typhus group rickettsiae as canine pathogens is yet to be established.[7]

CANINE EHRLICHIOSIS

Canine ehrlichiosis is an infectious disease of dogs, caused by *E. canis*, *E. chaffeensis*, *E. ewingii*, and potentially *E. ruminantium*.[2,8] Although the clinicopathologic course of disease can vary depending upon the infecting *Ehrlichia* species, illness is typically characterized by an acute reduction in cellular blood elements, most often thrombocytopenia. Investigators from South Africa have obtained molecular evidence (16S rDNA sequencing) that supports infection of dogs and people with an organism that is identical or closely related to *E. ruminantium* (previously *Cowdria ruminantium*). The implications of this recent finding could prove to be of great importance, if *E. ruminantium*, the organism that causes heartwater in cattle in Africa, could be introduced into the United States by way of dog transport.

Historically, *Ehrlichia* species were designated by their cellular tropism (i.e., monocytes, granulocytes, platelets).

With the advent of species-specific molecular diagnostic testing, defining an infection in an animal based solely upon the putative cell tropism is of minimal scientific or medical utility for several reasons. As an example, granulocytic morulae can be found on stained blood smears from dogs infected with *E. ewingii* or *A. phagocytophilum*. Based upon current nomenclature, one dog has ehrlichiosis and the other anaplasmosis. In addition, detection of morulae is a highly insensitive means of diagnosis, which further limits the clinical utility of a cell tropism–based classification.

The distribution of canine ehrlichiosis is related to the distribution of the vector ticks, *Rhipicephalus sanguineous*, the brown dog tick and vector for *E. canis* throughout the world, as well as *Amblyomma americanum*, the lone star tick and primary vector for *E. chaffeensis* and *E. ewingii* in the United States. It is probable that other tick species transmit known and yet to be characterized *Ehrlichia* spp. to wild and domestic animals in Europe, Asia, Africa, and South America. Although ehrlichiosis is diagnosed most frequently in dogs living in the Southeastern and Southwestern United States, the disease has been reported from nearly every state. Because of chronic, subclinical infection,[9] a dog can be transported from an endemic to a nonendemic region and subsequently develop disease manifestations years after the initial infection.

E. canis and *E. chaffeensis* are small, pleomorphic bacteria that most frequently infect circulating mononuclear cells. *E. canis* infections have been reported in dogs that have a concurrent infection with *Anaplasma platys, Babesia canis* or *Hepatozoon canis, Bartonella vinsonii (berkhoffii)* or in conjunction with *E. chaffeensis* or *E. ewingii*. In some instances simultaneous transmission of organisms from vector ticks occurs, whereas in other instances coinfection reflects frequent tick exposure and multiple independently obtained chronic infections. Concurrent infection with phaeohyphomycosis or cryptococcosis may represent coincidental infections, or it may represent secondary opportunistic infection associated with chronic ehrlichiosis.

Clinical signs during the acute phase of disease will vary from depression, anorexia, and fever to severe loss of stamina, weight loss, ocular and nasal discharges, dyspnea, lymphadenopathy, and edema of the limbs or scrotum. Acute-phase clinical signs are transient and usually resolve in 1 to 2 weeks without treatment. Thrombocytopenia and leukopenia generally occur 10 to 20 days after infection. Despite moderate to severe thrombocytopenia, hemorrhages are rarely observed. A variety of ocular and central nervous system (CNS) signs, including hyperesthesia, muscle twitching, and cranial nerve deficits, may occur due to inflammation or bleeding into the eye or meninges respectively.[9,10] Clinical findings in the acute phase of ehrlichiosis can be identical to canine RMSF. Clinical signs associated with the chronic phase of the disease would be characterized as mild to asymptomatic in some dogs and severe in other dogs. A combination of bleeding tendencies, pallor due to anemia, severe weight loss, debilitation, abdominal tenderness, anterior uveitis, retinal hemorrhages, and neurologic signs consistent with meningoencephalitis, typify dogs that develop disease manifestations during chronic infection with *E. canis*, *E. chaffeensis*, or *E. ewingii*. Concurrent bacterial infections may be documented, particularly in neutropenic dogs. Numerous patterns of hemorrhage may occur in dogs with ehrlichiosis. Epistaxis, once considered a hallmark of the disease, is reported infrequently in more recent case series.

In addition to hematologic abnormalities that would be consistent with *E. canis* (anemia, neutropenia, thrombocytopenia, lymphocytosis, monocytosis, and eosinophilia) infection with *E. ewingii* causes neurologic dysfunction and lameness involving one or more limbs, muscular stiffness, a stilted gait, reluctance to rise, an arched back posture, and joint swelling and pain.[11,12] Polyarthritis or meningoencephalitis, characterized by a predominantly neutrophilic inflammatory response and generally accompanied by fever, is frequently reported. Morulae can be found in joint or CSF and have been observed most frequently in peripheral blood neutrophils from dogs receiving glucocorticoid or cancer chemotherapeutic drugs. Although the importance of this clinical observation is unclear, it may suggest that chronically infected dogs develop ehrlichiemia if immunosuppressed or that immunosuppression potentiates morulae development during an acute infection. Asymptomatic infections with *E. ewingii* have been documented with PCR testing.[11,12]

In addition to clinical signs that may be suggestive of ehrlichiosis, severe laboratory abnormalities can contribute to the index of suspicion for the disease.[13,14] Hematologic abnormalities including pancytopenia, aplastic anemia, neutropenia, or thrombocytopenia, would be consistent with canine ehrlichiosis. Thrombocytopenia is the most consistent hematologic abnormality in both the acute and chronic stages of ehrlichiosis.[14,15] However, after experimental infection, platelet numbers are frequently in the low laboratory reference range. Pancytopenia is documented in less than 25% of dogs in retrospective clinical studies. Profound lymphocytosis, accompanied by atypical or reactive lymphocytes, has been associated with ehrlichiosis. Because *E. canis* causes defective platelet function, bleeding can be detected in dogs with normal, increased, or mildly suppressed platelet counts. Moncytic morula in peripheral blood smears or buffy coat smears is consistent with a diagnosis of *E. canis* or *E. chaffeensis*, whereas neutrophilic morulae are consistent with a diagnosis of *E. ewingii*, which has been most frequently described in dogs in Missouri, Oklahoma, Tennessee, North Carolina, and Virginia. Anemia, if present, will vary in degree of severity among affected dogs. Positive Coombs' tests suggest that immune damage, due to circulating erythrocyte antibodies, can contribute to an acute hemolytic crisis in some dogs with ehrlichiosis. In this situation, a regenerative anemia may be encountered; however, a nonregenerative anemia is most frequently documented in chronically infected dogs. Although highly variable, bone marrow examination usually reveals a hypocellular marrow with varying degrees of suppression of the erythroid, myeloid, and megakaryocytic series. Hyperplasia of the bone marrow, especially megakaryocytic hyperplasia, occurs during the acute phase of the disease. Although encountered in other chronic inflammatory diseases, plasmacytosis is a frequently reported bone marrow finding in ehrlichiosis.

Serum proteins are increased above expected values in approximately 50% to 75% of *E. canis* seropositive dogs.[13] Hyperglobulinemia is characterized by increased beta or gamma globulins (or both). Serum protein electrophoresis may reveal a polyclonal or monoclonal gammopathy. A monoclonal gammopathy, in association with severe bone marrow plasmacytosis, could be easily misdiagnosed as a plasma cell myeloma or, when found in association with lymphocytosis, misdiagnosed as lymphocytic leukemia. Hypoalbuminemia occurs in association with protein-losing nephropathy (PLN) or a reciprocal decrease in albumin associated with hyperglobulinemia. Experimentally, a transient, spontaneously reversible PLN associated with ultrastructural glomerular damage occurs 2 to 5 weeks postinoculation. In the chronic disease phase, *E. canis* can induce a severe PLN most likely related to immune complex glomerulonephritis. Less frequently encountered laboratory abnormalities include azotemia, and increased serum alanine aminotransferase and alkaline phosphatase activities, and increased total bilirubin.

Diagnosis of ehrlichiosis requires visualization of morulae, detection of *E. canis* antibodies, or PCR amplification of *E. canis*, *E. chaffeensis*, or *E. ewingii* DNA.[16-19] The IFA technique, dot enzyme-linked immunosorbent assay (ELISA) test, or recombinant ELISA test is available for detection of *Ehrlichia* species antibodies.[16-18] Due to cross-reactivity to immunoreactive proteins, most dogs infected with *E. canis* or *E. chaffeensis* will

have positive IFA or ELISA test results, whereas less than half of the dogs infected with *E. ewingii* will have measurable cross-reacting antibodies.[12] Although interlaboratory variation in serologic results occurs due to interpretation error, the IFA test for *E. canis* is highly sensitive. Serologic cross-reaction has not been reported in association with *R. rickettsii*, *B. canis*, *A. platys*, or *A. phagocytophilum*. A positive titer is considered indicative of infection, because most experimentally infected dogs become seronegative within 6 to 9 months after effective treatment, whereas untreated dogs remain seropositive. Infection with *E. canis* does not infer protective immunity; therefore subsequent exposure to infected ticks after treatment will result in disease recurrence, generally of decreased severity. After antibiotic treatment some dogs become asymptomatic but maintain high *E. canis* antibody titers for years.[20] Clinically, dogs are assumed to have eliminated the infection with an *Ehrlichia* spp. if hyperglobulinemia resolves progressively after treatment or if *Ehrlichia* spp. DNA cannot be amplified from EDTA blood samples. Infrequently, a dog maintains a high antibody titer or a hematologic abnormality such as thrombocytopenia persists for years after antibiotic therapy.[21] Although it is unclear whether these dogs are chronically infected with *E. canis*, infected with other pathogens, or if the persistent hematologic abnormalities are mediated through altered immunoregulation induced by the organism, little evidence exists to support antimicrobial resistance among *Ehrlichia* spp. that leads to persistent infection. Increasingly, PCR is becoming an important clinical diagnostic tool to differentiate the infecting *Ehrlichia* spp. and to determine if treatment has effectively eliminated the infection.[17,19] In dogs with persistently high *E. canis* antibody titers, PCR testing is indicated, preferably when antibiotics are not being administered.

Tetracycline (22 mg/kg three times a day for 21 days) or doxycycline (5 mg/kg twice a day for 21 days) are currently recommended for treatment of canine ehrlichiosis.[21,22] Experimentally, enrofloxacin will suppress the infection and may result in clinical and hematologic improvement but does not eliminate the infection.[23] Although imidocarb dipropionate has gained clinical acceptance in some endemic regions for treating severe, chronic, or presumed refractory cases of ehrlichiosis, lack of efficacy has been demonstrated in treating some dogs with ehrlichiosis.[22] Clinical improvement may be observed with penicillin or sulfonamides, but the response is variable and infection generally persists.

The short-term prognosis for canine ehrlichiosis is generally good. Dramatic clinical improvement usually occurs within 24 to 48 hours after initiation of tetracycline or doxycycline in dogs with acute-phase or mild chronic-phase disease. Following treatment, rapid clinical improvement is frequently noted in chronically infected dogs; however, periods up to a year may be necessary for complete hematologic recovery. The long-term prognosis is variable, potentially related to failure to diagnose concurrent infections.[24] Continuous or long-term administration of antibiotics, such as tetracycline, has apparently contributed to delayed hematologic recovery in dogs with obvious clinical improvement. Hemorrhage or concurrent infection may contribute to death of chronically infected dogs, despite the initiation of tetracycline therapy. The duration of doxycycline treatment for chronically affected dogs or those with severe pancytopenia or aplastic anemia remains controversial. Supportive therapy, including fluids, blood transfusion, vitamins, and anabolic steroids is required in some dogs. Long-term tetracycline prophylaxis (6.6 mg/kg once daily), repositol oxytetracycline (200 mg intramuscularly [IM] twice weekly), and topically applied acaracides have been used in military working dogs to prevent *E. canis* infection in highly endemic regions. This approach may be appropriate for recurrent infections in kennels if tick control measures are of limited effectiveness. Because of extensive dog transport and chronic asymptomatic *E. canis* infection, the establishment of new endemic foci in previously naive regions is possible. Tick control measures are very important but may not always provide an effective means to prevent infection with an *Ehrlichia* spp.[25] No vaccine is currently available.

It appears that most *Ehrlichia* spp. are capable of infecting people; however, for various reasons dogs play a seemingly minor role in the acquisition of human infections. Early reports suggested that nonhuman primates could be infected with *E. canis* and, more recently, an organism genetically related to *E. canis* was isolated from a veterinarian in Venezuela.[26] Both *E. chaffeensis* and *E. ewingii* can cause serious disease manifestations in people, including meningoencephalitis, acute renal failure, and acute respiratory failure.[27,28]

CANINE ANAPLASMOSIS

In endemic regions, *Ixodes scapularis*, *I. pacificus*, or *I. ricinus* (Europe) transmit *Anaplasma phagocytophilum* to cats, dogs, sheep, horses and human beings.[29] Numerous species of small rodents, including *Peromyscus leucopus*, the white-footed mouse, serve as reservoirs for the organism in nature.[30] Infection has also been documented in numerous species of wild and domestic animals. California, Minnesota, Wisconsin, and several New England states (areas endemic for *I. scapularis* or *I. pacificus*) report a particularly high prevalence of infection, generally in dogs, horses, and human beings. Fever, lethargy, and a reluctance to move, accompanied by lymphopenia, thrombocytopenia, elevated serum alkaline phosphatase and amylase activities, and hypoalbuminemia are the most common clinical abnormalities reported in dogs. In the Northeast and North Central United States, acute disease occurs most frequently in the fall months during the period that adult *I. scapularis* ticks are active. Granulocytic morulae can be found within neutrophils and acute and convalescent serology is recommended to document seroconversion to *A. phagocytophilum* antigens in acutely ill dogs, cats, or horses. Infection with *A. phagocytophilum* can also be confirmed by PCR. Both ELISA and IFA tests using *E. canis* antigens will in most instances not detect cross-reacting antibodies in dogs with anaplasmosis. Therapeutically, tetracycline hydrochloride or doxycycline elicit rapid improvement in clinical status. The extent to which *A. phagocytophilum* induces chronic infection in dogs in North America is unclear; however, in Sweden, chronic infection with *A. phagocytophila* has been documented in experimentally infected dogs for up to 6 months after infection.[31] Administration of corticosteroids facilitated the detection of neutrophilic inclusions.

CANINE CYCLIC THROMBOCYTOPENIA

Canine cyclic thrombocytopenia is caused by *A. platys*, a bacterial organism that replicates only in platelets.[32,33] The mode of *A. platys* transmission is presumed to be by tick vector, but experimentally, *Rhipicephalus sanguineous*, the vector for *E. canis*, did not transmit *A. platys* infection. In the United States, *A. platys* is generally considered to be minimally pathogenic, and is usually recognized as an incidental observation during blood smear examination. The distribution of *A. platys* infection in the United States has not been established; however, most reports have originated from the South and Southeast, with occasional reports from the North and North Central portion of the country. With the exception of a single case report of uveitis, naturally occurring and experimental infections have not been associated with clinical signs. Similar to anaplasmosis in cattle, *A. platys* causes cyclic bacteremia, accompanied by thrombocytopenia, at approximately 10 to 14 day intervals.

At its nadir, thrombocytopenia can be severe (20,000 to 50,000 platelets/μl), and platelets are hypoaggregatable. A mild normocytic, normochromic, nonregenerative anemia, leukopenia, hypoalbuminemia, and hyperglobulinemia, has been reported in association with experimental *A. platys* infection. On Giemsa-stained blood smears, *A. platys* appears as single or less frequently multiple basophilic inclusions within platelets. The duration of infection in untreated dogs has not been clearly established.

Diagnosis of *A. platys* requires visualization of platelet inclusions, detection of serum antibodies by indirect immunofluorescence, or PCR amplification. Sera from *A. platys*–infected dogs does not cross-react serologically with *E. canis*, *A. phagocytophilum*, or *N. risticii* antigens. Antibodies appear in the serum 2 to 3 weeks after experimental infection and are usually detectable during the initial thrombocytopenic episode. In a study of thrombocytopenic and healthy kennel dogs in Louisiana, seroprevalence to *A. platys* was 40.7% in the thrombocytopenic group and 54.2% in healthy kennel dogs. *Anaplasma platys* morulae were detected in only one of the thrombocytopenic dogs. These results suggest that exposure to *A. platys* in southern states is extensive, and that premunition most probably develops after several cycles of thrombocytopenia. Coinfection with *E. canis* and *A. platys* is common, and it has been theorized that *A. platys* infection might intensify the clinical course of canine ehrlichiosis.

Treatment with oral tetracycline (22 mg/kg every 8 hours for 14 days), or presumably doxycycline (5 mg/kg every 12 hours for 14 days), should eliminate the organism. Because experimental studies have not identified abnormal clinical signs associated with *A. platys* infection, caution should be exercised in ascribing clinical illness to *A. platys*. In such cases, other infectious and noninfectious causes of thrombocytopenia should be pursued diagnostically.

NEORICKETTSIA RISTICII

In 1994, Kakoma and colleagues reported serologic evidence of over 100 cases of "atypical canine ehrlichiosis" with 3 fatalities.[34] These dogs were not seroreactive to *E. canis* antigens by IFA but were reactive to *N. risticii* antigens at generally low antibody titers. *Neorickettsia risticii* is the cause of Potomac horse fever.[35] Serum samples in this study were derived from California, Texas, Arizona, Illinois, Washington, Florida, and Michigan. Isolates obtained from 3 dogs were morphologically and genetically (based on partial 16S rRNA gene sequence) indistinguishable from *N. risticii*.[34] Successful experimental transmission of a dog isolate has not been reported. Clinical abnormalities, described for 6 dogs, included lethargy, vague signs of abdominal discomfort with intermittent vomiting, persistent bleeding or petechial hemorrhages, polyarthritis, dependent edema, and posterior paralysis. Hematologic abnormalities were variably present and included anemia, thrombocytopenia, prolongation of prothrombin time (PT), and hypercalcemia. Therapy with tetracycline also appears to be variably efficacious for treatment of this infection, with substantial improvement in some dogs and a complete lack of response in other dogs. The authors propose that pending additional research, the canine isolate be referred to as *N. risticii* subsp. *atypicalis*. The definitive pathophysiologic characterization of this organism as a cause of disease in dogs awaits additional study.

FELINE EHRLICHIOSIS, ANAPLASMOSIS, AND NEORICKETTSIOES

Morulae-like inclusion bodies have been observed in monocytes, lymphocytes, or granulocytes of cats living in Kenya, France, Sweden, and the Northeastern, Midwestern and Western United States.[36–38] Antibody reactivity to *E. canis* or *N. risticii* antigens has also been reported.[38] Although the precise clinical significance of these observations awaits the results of future studies, it seems probable that cats can be infected by one or more members of the genus *Ehrlichia*, *Anaplasma*, and *Neorickettsia*. Experimentally, inoculation of cats with *A. phagocytophilum* resulted in asymptomatic infection, or mild fever and depression, and the development of neutrophilic and eosinophilic morulae. Recently, several laboratories have amplified *A. phagocytophila* DNA from the blood of acutely ill cats with fever, lethargy, inappetence, and thrombocytopenia.[37,39] These feline cases have been identified in geographic regions that are endemic for canine, equine, or human anaplasmosis.

Anorexia, loss of body condition, fever, splenomegaly, lymphadenopathy, normocytic normochromic anemia, radiographic evidence of interstitial lung disease, and mononuclear intracytoplasmic inclusions typical of the genus *Ehrlichia* were described in three cats from Kenya. Neutropenia and hyperglobulinemia were each reported in one cat. These cats were infested with *Haemaphysalis laechi* ticks. Resolution of disease signs was reported after treatment with either tetracycline hydrochloride or imidocarb dipropionate. Intracytoplasmic inclusions resembling morulae have been observed during cytologic evaluation of a lymph node aspirate from a cyclically febrile, anorexic cat from Colorado. Laboratory abnormalities included a normocytic normochromic nonregenerative anemia, hyperglobulinemia, and pyogranulomatous lymphadenitis. Serum immunoglobulin G (IgG) antibodies to *E. canis* antigen were detected, and the cat responded rapidly to doxycycline despite a previous lack of response to several other antibiotics. Serologic evidence of ehrlichiosis was reported in 12 sick cats with clinical and laboratory abnormalities including fever, malaise, weight loss, anorexia lymphadenopathy, nonseptic suppurative polyarthritis, anemia, thrombocytopenia, neutropenia, and polyclonal or monoclonal gammopathy.[36,38] Each of these cats responded favorably to doxycycline. Based upon PCR amplification and DNA sequencing, *E. canis*-like infection has been reported in cats from the United States, Canada, and France.[40,41] Consistent with previous reports, these cats had polyarthritis or bone marrow suppression accompanied by anemia, thrombocytopenia or pancytopenia. However, despite chronic illness and the detection of antinuclear antibodies (ANAs), IFA testing using *E. canis* antigens was negative. Antibody reactivity (IFA and Western immunoblot) to *N. risticii* antigens was described in five cats from California.[38] Hematologic abnormalities included leukopenia, anemia, and thrombocytopenia. All attempts to isolate, transmit, or detect *E. risticii* by PCR were unsuccessful. Additional studies are needed to isolate and genetically characterize feline *Ehrlichia*, *Anaplasma*, and *Neorickettsia* organisms to clarify further the pathogenic importance of these organisms in cats.

COINFECTION WITH MULTIPLE TICK-TRANSMITTED PATHOGENS

Recent serologic and PCR evidence indicates that coinfection with *Ehrlichia*, *Babesia*, *Rickettsia*, and *Bartonella* spp. occurs more frequently in dogs than previously realized.[42–45] The extent to which infection with multiple organisms complicates the clinical, diagnostic, and therapeutic features that would be anticipated if a dog were infected with only one organism is not clear. In general, coinfection should be considered in dogs with unusually severe clinical presentations. For example, infection with *Bartonella* in dogs concurrently infected with *Ehrlichia canis* may contribute to the tendency

to develop epistaxis. Recent observations also illustrate the difficulty in attributing causation to a single organism in dogs or people coinfected with multiple tick-transmitted pathogens.[45] As certain *Borrelia, Ehrlichia, Babesia,* and *Bartonella* spp. can cause chronic, insidious infection in dogs, the relative role of each organism to the pathogenesis of specific disease manifestations in a sick, naturally infected dog will remain difficult to establish. From an evolutionary perspective, it is obvious that vectors, vector-borne intracellular organisms, and animal and human hosts have developed a highly adapted form of interaction. In general, vectors need blood for nutrition; the bacterial, rickettsial, and protozoal organisms need an intracellular environment to survive; immunologically, most hosts appear to be able to support chronic infection with many vector-borne organisms for months to years without obvious deleterious effects. Certainly more recent evidence indicates that clinicians should screen for a panel of intracellular pathogens when dealing with sick dogs with a history of tick and flea exposure. This same evidence emphasizes the importance of strategies to control ticks and fleas on dogs and cats.

CHAPTER 167

Canine Bartonellosis

Edward B. Breitschwerdt

Bartonella species are fastidious gram-negative bacteria that are highly adapted to a mammalian reservoir host and within which the bacteria usually cause a long-lasting intraerythrocytic bacteremia.[1,2] In the natural host, chronic bacteremia with a *Bartonella* species can frequently be detected by culture or PCR in seemingly healthy individuals. Until recently, mechanisms that facilitate persistent *Bartonella* bacteremia in mammals were not well understood. Recent studies, have identified an intraerythrocytic localization for these bacteria, which is a unique strategy for bacterial persistence.[1-6] Nonhemolytic intracellular colonization of erythrocytes would preserve the organisms for efficient vector transmission, protect *Bartonella* from the host immune response, and potentially contribute to decreased antimicrobial efficacy.[3] *Bartonella* spp. are an important cause of bacillary angiomatosis, peliosis hepatis, fever of unknown origin, endocarditis, granulomatous hepatitis, and a rapidly expanding spectrum of less frequently diagnosed medical conditions in people.[7-9]

Bartonella vinsonii (berkhoffii) was isolated from a dog with endocarditis in 1993.[10,11] Retrospectively, long-term administration of immunosuppressive doses of corticosteroids for a presumptive diagnosis of systemic lupus erythematosus (SLE) may have facilitated the isolation of *B. vinsonii (berkhoffii)* from this dog. Subsequent attempts to isolate *B. vinsonii* from immunocompetent dogs with serologic or molecular evidence of *Bartonella* infection have not been successful in most instances. When using the currently recommended microbiologic techniques, there appears to be considerable variation in the degree of difficulty associated with the isolation of different *Bartonella* spp. from the blood of different animal species. *Bartonella vinsonii (berkhoffii)* is difficult to isolate, as compared with the relative ease of isolating *B. henselae* from the blood of infected cats. For this reason, sensitive molecular-based detection methods are proving to be diagnostically useful.

SEROPREVALENCE

Due to the relatively recent recognition that dogs can be infected with *B. vinsonii (berkhoffii)* and potentially other *Bartonella* spp., seroprevalence data is limited.[12-15] Seroprevalence was determined in 1920 sick dogs from North Carolina or surrounding states that were evaluated at a veterinary teaching hospital.[12] Using a reciprocal titer of greater than 64, 3.6% of the dogs had antibodies to *B. vinsonii (berkhoffii)*. Risk factors that could be associated with seroreactivity included heavy tick exposure (odds ratio, 14.2), cattle exposure (odds ratio, 9.3), rural versus urban environment (odds ratio, 7.1), and heavy flea exposure (odds ratio, 5.6). These data were interpreted to support the possibility that exposure to *B. vinsonii (berkhoffii)* was more likely in dogs in rural environments that were allowed to roam and were likely to have a history of heavy tick infestation. Using sera from dogs experimentally infected with *R. rickettsii* or *Ehrlichia canis*, cross reactivity to *Bartonella* antigens was not detected. However, 36% and 52% of serum samples derived from dogs naturally infected with *E. canis* or *B. canis* were reactive to *B. vinsonii* antigens. Because both *E. canis* and *B. canis* are transmitted by *Rhipicephalus sanguineous*, this tick may be involved in the transmission of *B. vinsonii*. The possibility of tick transmission was further supported by two additional studies involving dogs infected with one or more *Ehrlichia* spp. from the same geographic region, in which seroreactivity to *B. vinsonii (berkhoffii)* antigens was 30% and 89%, respectively.[16,17] Seroprevalence, using *B. vinsonii (berkhoffii)* antigens, was 10% (4 of 40 dogs) in dogs with suspected tick-borne illness from Israel and 36% in dogs with fever and thrombocytopenia from Thailand.[15,18] Using an ELISA assay, 35% of 869 samples (derived from coyotes in California) contained antibodies to *B. vinsonii (berkhoffii)* antigens.[19] These data suggest that *B. vinsonii (berkhoffii)* is distributed throughout the world.

DISEASE MANIFESTATIONS

The spectrum of disease associated with *Bartonella* infection in dogs and most other animal species is currently unknown. Endocarditis, caused by *B. vinsonii (berkhoffii)*, occurs in large breed dogs with a potential predisposition for aortic valve involvement.[10,20,21] Intermittent lameness, bone pain or fever of unknown origin (FUO) can precede the diagnosis of endocarditis by several months. Multifocal areas of severe myocardial inflammation can be found in some dogs with *B. vinsonii* endocarditis. Recently *B. vinsonii (berkhoffii)*, originally isolated

from a dog, was isolated from a human endocarditis patient.[22] Considering these preliminary observations, derived from naturally infected dogs and people, the role of *Bartonella* spp. as a cause of myocarditis in companion animals deserves additional research consideration.

Bartonella-induced granulomatous lymphadenitis, involving the left submandibular lymph node, was diagnosed in a dog on the basis seroreactivity to *B. vinsonii (berkhoffii)* antigens, visualization of Warthin-Starry silver staining bacteria within the lymph node, and PCR amplification followed by Southern blot hybridization.[23] Seven days prior to enlargement of the lymph node, the owners removed an engorged tick from the left ear. This case may be illustrative of a clinical presentation that is analogous to acute bartonellosis (cat scratch disease) in people, where a scratch or bite injects the inoculum, as compared with direct inoculation by the bite of a tick.

Based on recently obtained serologic evidence in dogs, *B. vinsonii (berkhoffii)* or closely related *Bartonella* species appear to contribute to the development of dermatologic lesions indicative of a cutaneous vasculitis, anterior uveitis, polyarthritis, meningoencephalitis, and immune-mediated hemolytic anemia.[24] Thrombocytopenia is found in approximately half of the dogs with disease manifestations. Eosinophilia is also found in approximately one third of infected dogs.

Based upon current evidence, *B. vinsonii (berkhoffii)* is considered the most frequent *Bartonella* species that causes disease in dogs. However, this conclusion may not be accurate, because sera from dogs have not been screened systematically against a large panel of *Bartonella* species antigens. Studies from Hawaii, the United Kingdom, and Japan identified *B. henselae* seroprevalences of 6.5% (2 of 31 dogs), 3.0% (3 of 100 dogs), and 7.7% (4 of 52 dogs).[25-27] However, it is becoming increasingly clear that other *Bartonella* species can infect dogs. For example, *B. henselae* was amplified and sequenced on two independent occasions from the liver of a dog with peliosis hepatis.[28] This is a unique pathologic lesion that is induced only by *B. henselae* infection in people.[1,8] Recently, *B. henselae* DNA was amplified from a dog with granulomatous hepatitis, a histopathologic lesion that is reported with some frequency in children infected with *B. henselae*.[29] Similarly, *B. clarridgeae* was cultured, and DNA was amplified from the aortic valve of a dog with vegetative valvular endocarditis.[21] *Bartonella clarridgeae* was also amplified and sequenced from the liver of a Doberman pincher with copper storage disease.[29] *Bartonella elizabethae*, a species that infects rodents, was PCR amplified and sequenced from an ethylenediamine tetra-acetic acid (EDTA) blood sample obtained from a dog that had experienced chronic weight loss culminating in sudden unexplained death.[30] The clinical importance of these observations, particularly as relates to causation, is unknown. However, although presumably infrequent, *Bartonella* spp. that frequently infect cats or rodents and are transmitted by fleas among reservoir hosts, may occasionally be found in dogs with disease manifestations.

DIAGNOSTIC CONSIDERATIONS

Thrombocytopenia, anemia (which frequently can be immune-mediated), and neutrophilic leukocytosis are the most commonly detected hematologic abnormalities. Monocytosis and eosinophilia can also occur in *B. vinsonii*–infected dogs. During a 149-day study, after experimental inoculation of SPF dogs with culture grown *B. vinsonii (berkhoffii)*, there was sustained suppression of peripheral blood CD8+ lymphocytes, accompanied by an altered cell surface phenotype and an increase in CD4+ lymphocytes in the peripheral lymph nodes.[31] Therefore infection with *B. vinsonii (berkhoffii)* could induce a degree of chronic immunosuppression that might predispose to secondary infections and result in a wide array of clinical manifestations in dogs naturally infected with *Bartonella* species. Because blood culture is insensitive, serology and PCR amplification of *Bartonella* DNA are the mainstays of diagnosis. As seroprevalence to *B. vinsonii (berkhoffii)* antigens is infrequently detected (<4%) in sick dog populations in endemic regions, detection of antibodies in a sick dog provides strong clinical evidence for prior exposure and potentially active infection. For this reason, treatment of seroreactive dogs is recommended. A reciprocal titer of 64 or greater is considered indicative of prior exposure to or active infection with *B. vinsonii (berkhoffii)*. Testing against other *Bartonella* spp. antigens, such as *B. henselae*, may prove to be of clinical use in the future.

TREATMENT

To date, an optimal protocol has not been established for the treatment of *Bartonella* infections in cats, dogs, or people.[32,33] Regardless of the antibiotic used for treatment, a long duration of antibiotic administration (4 to 6 weeks) may be necessary to eliminate the infection. Macrolides (erythromycin, azithromycin) most probably represent the oral antibiotic class of choice for treating *Bartonella* infections.[32,33] Fluoroquinolones alone (or in combination with amoxicillin) have also elicited a positive therapeutic response in dogs, which is accompanied by a progressive decrease in *B. vinsonii* antibody titers.[24] Doxycycline may be effective for treatment of *B. vinsonii (berkhoffii)* in dogs, but data from cats experimentally or naturally infected with *B. henselae* or *B. clarridgeae* indicates that a high dose (10 mg/kg every 12 hours) for 4 to 6 weeks may be necessary to eliminate *Bartonella* infection in dogs, cats, or other animal species.[34] Recently, retrospective analysis of the treatment of human *Bartonella* endocarditis identified a more favorable outcome if an aminoglycoside was prescribed for a minimum of 2 weeks.[35] In those situations in which *Bartonella* infection poses serious risk in dogs, such as endocarditis, myocarditis, or meningoencephalitis, use of an aminoglycoside may be warranted.

PREVENTION

Increasingly, veterinarians play an important role in advising the public as to the epidemiologic and zoonotic implications of vector-borne pathogens. Nondomestic animals frequently serve as the primary reservoir for *Bartonella* species. For example, the coyote appears to be an important reservoir host for *B. vinsonii (berkhoffii)*.[36] Although somewhat circumstantial, increasing evidence suggests that *Bartonella* species can be transmitted by fleas and ticks to cats, dogs, or human beings.[12,23,37] Therefore minimizing or eliminating flea and tick exposure is perhaps of greater public health importance today than during any previous time. When rigorous flea and tick control measures are instituted, it is highly probable that transmission of *Bartonella* species will be greatly reduced or eliminated.[38]

CHAPTER 168

Protozoal and Miscellaneous Infections

Michael R. Lappin

Multiple pathogenic protozoans infect dogs and cats. The group can be divided into amoeba, ciliates, coccidians, flagellates, Microspora, and Piroplasmia. Protozoans generally cause gastrointestinal (GI) tract disease (enteric protozoans), polysystemic disease, or in the case of *Toxoplasma gondii*, both enteric and polysystemic disease.

ENTERIC PROTOZOAL DISEASES

The most common protozoal agents infecting the GI tract of dogs and cats are *Giardia* spp., *Cryptosporidium* spp., *Cystoisospora* spp., *Sarcocystis* spp., *Besnoitia* spp., *Hammondia* spp., *T. gondii*, *Neospora caninum*, *Entamoeba histolytica*, *Balantidium coli*, and *Tritrichomonas foetus*.[1-3] *Giardia* and *T. foetus* are flagellates, *Cystoisospora* spp., *Sarcocystis* spp., *Besnoitia* spp., *Hammondia* spp., *N. caninum*, *T. gondii*, and C. *parvum* are coccidians, *B. coli* is a ciliate, and *E. histolytica* is an amoeba. *Cystoisospora* spp., *Sarcocystis* spp., *Besnoitia* spp., *Hammondia* spp., *N. caninum*, and *T. gondii* only complete the intestinal cycle in one species. Some isolates of *Cryptosporidium* spp., *Giardia* spp., *E. histolytica*, and *B. coli* will replicate in multiple warm-blooded vertebrates and therefore can potentially be zoonotic.

Fecal oral transmission occurs with all the enteric protozoans. The coccidians produce oocysts. *Cryptosporidium* spp. oocysts are immediately infectious when passed by the host; *T. gondii*, *N. caninum*, and *Cystoisospora* spp. must sporulate outside the host to be infectious. Both trophozoites and cysts of *Giardia* spp. are potentially infectious; however, transmission occurs most frequently after ingestion of cysts because gastric secretions generally kill trophozoites. Ingestion of the organism in the tissues of transport hosts can also result in infection by *Cystoisospora* spp., *Besnoitia* spp., *Hammondia* spp., *N. caninum*, and *T. gondii*. Carnivorism can result in infection by *Cryptosporidium* spp., *Giardia* spp., *E. histolytica*, and *B. coli* if the organisms are present in the intestines of the prey species. Infections can be self-limiting for each of the agents; however, with the exception of *T. gondii*, fecal shedding periods are variable. After tissue cyst ingestion, infected cats rarely shed oocysts of *T. gondii* for more than 2 weeks.[4]

The enteric protozoans have worldwide distribution. Because they are maintained in nature primarily by fecal-oral transmission, more cases are associated with crowded and unsanitary environments. In general, *Giardia* spp., *T. gondii*, *Cystoisospora*, and *Cryptosporidium* spp., *T. foetus* (cats) infections are common in the United States; *E. histolytica*, *B. coli*, and infections are rare. Antibodies against *T. gondii* (40%) and *Cryptosporidium* spp. (8.3%) are commonly detected in serum from client-owned cats, suggesting that exposure is common.[4,5] Prevalence of the agents varies by region in coprologic studies.

Pathogenic mechanisms have not been ascertained for each of the enteric protozoans. *Cystoisospora* spp. and *T. gondii* replicate in intestinal cells and may result in clinical illness from cell destruction. Tissue invasion also can occur with *E. histolytica*.[6,7] *Giardia* spp. and *Cryptosporidium* spp. are found on the surface of enterocytes, so pathogenesis is unlikely secondary to direct cell damage. Some of the pathogenic mechanisms proposed for these enteric agents include production of toxins, disruption of normal flora, induction of inflammatory bowel disease (IBD), inhibition of normal enterocyte enzymatic function, blunting of microvilli, and induction of motility disorders. *Cystoisospora* spp. generally are only pathogens resulting in clinical disease in puppies or kittens, and *Sarcocytis* spp., *Besnoitia* spp., and *Hammondia* spp. are almost never pathogenic in dogs or cats. All other enteric protozoans can cause disease regardless of age. Clinical disease is more common, and duration of organism shedding into the environment may be prolonged in dogs and cats with immunodeficiency inducing concurrent diseases.

Owner concerns in dogs or cats with enteric protozoal infections generally are vomiting, inappetence, or diarrhea; fever is uncommon. *Giardia* spp., *Cryptosporidium* spp., and *T. gondii* infections are most commonly associated with small-bowel diarrhea; *E. histolytica*, *B. coli*, and *T. foetus* infections are most commonly associated with large-bowel diarrhea. *Cystoisospora* spp. infections can cause clinical signs of large or small-bowel diarrhea. Physical examination findings in dogs or cats with enteric protozoal infections are nonspecific but can include abdominal discomfort, increased gas or fluid in the intestinal tract, or thickened intestinal loops.

All dogs and cats with large, small, or mixed bowel diarrhea should be assessed for enteric protozoal infections. Diagnosis of GI protozoal infection is based primarily on documentation of oocysts, trophozoites, or cysts on direct fecal examination or fecal flotation.

A direct smear of diarrheic stool can be used to examine for trophozoites of *E. histolytica*, *B. coli*, *T. foetus*, or *Giardia*. More frequently, a small quantity of fresh feces or mucous is mixed with a drop of 0.9% NaCl on a clean microscope slide and examined at 100X after placing a cover slip. When a motile organism is noted, examining at 400X assesses structural features. Application of a stain like Lugol's solution, methylene blue, or acid methyl green to the wet mount at the edge of the cover slip will aid in visualizing internal structures of protozoa.[8] Trophozoites are rarely found in formed stools. Duodenal aspiration for cytologic examination for *Giardia* trophozoites is effective for the diagnosis of giardiasis in the dog. However, this technique is not effective in the cat because the organism lives in the distal small intestine.

Protozoal cysts or oocysts are best demonstrated after fecal concentration; Sheather's sugar centrifugation and zinc sulfate centrifugation are two techniques commonly used in clinical practice.[8] These solutions are inexpensive and generally effective. Sugar solution is hypertonic and will distort *Giardia* spp. cysts; the cytoplasm is pulled to one side and appears as a half- or quarter-moon. Zinc sulfate centrifugation is considered by some to be the flotation solution of choice for *Giardia* spp. cysts.

Due to small size and limited number in feces of infected dogs and cats, *Cryptosporidium* spp. oocysts are almost never seen when concentrated feces are examined at 100X.

Acid-fast staining or fluorescein-labeled monoclonal antibody staining of a fecal smear and fecal antigen testing can aid in the diagnosis of cryptosporidiosis in dogs and cats. Oocysts stain pink with acid-fast stain. A fluorescein-labeled monoclonal antibody system is also available for identification of *Giardia* spp. cysts. Antigens of *Giardia* spp. and *Cryptosporidium* spp. can be detected in feces by enzyme-linked immunosorbent assay (ELISA). However, it is now known that dog- and cat-specific *Giardia* spp. and *Cryptosporidium* spp. exist[9-12]; most currently available tests were titrated using isolates from human feces. Thus results of indirect fluorescent antibody (IFA) and antigen assays should be interpreted with results from fecal examination techniques. Polymerase chain reaction (PCR) assays for demonstration of *Giardia* spp. and *Cryptosporidium* spp. DNA in feces is being studied.

The presence of enteric protozoans in diarrheic stool does not prove that disease was due to the organism. Some enteric protozoans, especially *Giardia* spp., *Cryptosporidium* spp., *T. foetus*, and *Cystoisospora* spp. live chronically in the intestinal tract of normal animals; other conditions causing GI tract disease can induce shedding. Thus animals with enteric protozoal infections that do not respond to therapy should be evaluated for underlying causes of disease. *Giardia* spp., *Cryptosporidium* spp., *Cystoisospora* spp., and *Sarcocystis* spp. are commonly found in animals with normal stools; therefore yearly fecal examinations are indicated in all dogs and cats.

Withholding food for 24 to 48 hours is indicated for animals with acute vomiting or diarrhea. Highly digestible, bland diets are used most frequently if vomiting and small-bowel diarrhea are the primary manifestations of disease. High-fiber diets are generally indicated if large-bowel diarrhea is occurring. Feeding a high-fiber diet may also aid in the treatment of giardiasis due to inhibition of trophozoite attachment to duodenal epithelial cells.

Entamoeba histolytica, *Giardia* spp., and *T. foetus* generally respond clinically to the administration of metronidazole, but infection is usually not eliminated (Table 168-1). Because dogs or cats with giardiasis could also be infected with these other potentially zoonotic enteric protozoans, metronidazole is a logical primary drug. Metronidazole also helps correct the anaerobic bacterial overgrowth that commonly accompanies giardiasis. If inflammatory changes exist, metronidazole may also be beneficial due to inhibition of lymphocyte function. In a recent study of cats, administration of liquefied metronidazole benzoate for 7 days was 100% effective during the time period studied.[13] Central nervous system (CNS) toxicity occasionally occurs with this drug; it is unlikely if no more than 50 mg/kg is given orally per day.[14,15] Fenbendazole and albendazole are commonly prescribed alternate anti-*Giardia* spp. drugs; albendazole is associated with neutropenia in dogs and cats and so should not be used.[16-19] Furazolidone (cats); paromomycin (dogs or cats); and febantel, pyrantel, and praziquantel (dogs) are other drugs with anti-*Giardia* effects.[20] Lastly, use of the commercially available *Giardia* spp. vaccines as immunotherapy has given variable treatment responses.[21-23] Diarrhea due to *T. foetus* can sometimes be controlled by the administration of fenbendazole or enrofloxacin, but infection is not eliminated.

Paromomycin, tylosin, and azithromycin have all been used to lessen diarrhea in dogs and cats with cryptosporidiosis, but no treatment has consistently stopped *Cryptosporidium* spp. oocyst shedding.[24,25] The most commonly prescribed drugs to treat *Cystoisospora* spp. infections of dogs and cats are trimethoprim-sulfonamide, sulfadimethoxine, furazolidone, amprolium, or amprolium-sulfadimethoxine. Quinacrine, spiramycin, toltrazuril, and roxithromycin have been used on a limited basis. However, no drug eliminates infection.

Cryptosporidium spp., *T. gondii*, *Giardia*, *E. histolytica*, and *B. coli* are potentially zoonotic. *Entamoeba histolytica* and *B. coli* infections are extremely uncommon, and pets are unlikely sources of human infections. Most people are infected with *Cryptosporidium* spp. or *Giardia* spp. from contaminated food or water, not contact with pets.[26-28] It is now known that *Cryptosporidium* spp. and *Giardia* spp. exist that are specific to people or pets. For example, in one recent study of *C. hominis* of people, the organism failed to infect dogs and cats.[29] In one enzootic area, people were infected with a human *Giardia* and dogs were infected with a dog *Giardia*; cross-infection did not seem to occur.[11] Thus not all *Cryptosporidium* spp. and *Giardia* spp. are zoonotic. However, it is impossible to determine clinically if an individual strain is infectious to people; therefore infected animals should be managed as a potential zoonotic risk. (See the following section for a discussion of *T. gondii* associated zoonotic disease.)

POLYSYSTEMIC PROTOZOAL DISEASES

The primary protozoans that induce polysystemic disease in dogs and cats are *Acanthomoeba* spp., *Hepatozoon canis*, *Neospora caninum*, *Toxoplasma gondii*, *Leishmania* spp., *Trypanosoma cruzi*, *Cytauxzoon felis*, *Babesia* spp., and *Pneumocystis carinii*.

COCCIDIANS

Toxoplasmosis

Toxoplasma gondii is one of the most prevalent parasites infecting warm-blooded vertebrates.[4] Only cats complete the coccidian life cycle and pass environmentally resistant oocysts in feces. Dogs can pass oocysts in feces after the ingestion of feline feces.[30] Sporozoites develop in oocysts after 1 to 5 days of exposure to oxygen and appropriate environmental temperature and humidity. Tachyzoites disseminate in blood or lymph during active infection and replicate intracellularly rapidly until the cell is destroyed. Bradyzoites are the slowly dividing, persistent, tissue stage that form in the extraintestinal tissues of infected hosts as immune responses attenuate tachyzoite replication. Tissue cysts form readily in the CNS, muscles, and visceral organs.[4] Infection of warm-blooded vertebrates occurs after ingestion of any of the three life stages of the organism or transplacentally. Most cats are not coprophagic and are usually infected by ingesting *T. gondii* bradyzoites during carnivorous feeding; oocysts are shed in feces from 3 to 21 days. Sporulated oocysts can survive in the environment for months to years and are resistant to most disinfectants. Bradyzoites may persist in tissues for the life of the host. Approximately 30% to 40% of cats and people and 20% of the dogs in the United States are seropositive and therefore presumed to be infected.[4] Prior to 1988 many of the dogs diagnosed with toxoplasmosis based on histologic evaluation were truly infected with *Neospora caninum* (see Neosporosis section).[31]

Clinical disease associated with the intestinal phase of infection is rare. Approximately 10% to 20% of experimentally inoculated cats develop self-limiting, small-bowel diarrhea after primary oral inoculation with *T. gondii* tissue cysts. Detection of *T. gondii* oocysts in feces is rarely reported in studies of naturally exposed cats with diarrhea.

Death in dogs and cats can develop from overwhelming intracellular replication of tachyzoites after primary infection; hepatic, pulmonary, CNS, and pancreatic tissues are commonly involved.[32,33] Transplacentally or lactationally infected kittens develop the most severe signs of extraintestinal toxoplasmosis and generally die of pulmonary or hepatic disease.[34,35]

Common clinical findings in cats with disseminated toxoplasmosis include depression, anorexia, fever followed by hypothermia, peritoneal effusion, icterus, and dyspnea.[32]

Table • 168-1

Drugs Used in the Management of Protozoal and Miscellaneous Diseases

ORGANISM/DRUG NAME	COMMON CANINE DOSE	COMMON FELINE DOSE
Babesia spp.		
Clindamycin hydrochloride	12.5 mg/kg, q12h, for 14 days, PO	NA
Imidocarb dipropionate	5-6.6 mg/kg, q14 days, SC or IM	NA
Metronidazole	25 mg/kg, q8-12h, for 14 days PO	NA
Pentamidine isethionate	15 mg/kg, q24h, daily for 2 days, SC	NA
Balantidium coli		
Metronidazole	10-25 mg/kg, q12h, for 8 days, PO	NA
Tetracycline	22 mg/kg, q8h, for 7-10 days, PO	NA
Cryptosporidium spp.	Unknown	10 mg/kg, q24h, for 7-21 days, PO
Azithromycin	As for cats	10 mg/kg, q12h, for 5-7 days, PO
Paromomycin	As for cats	150 mg/kg, q12-24h, for 5 days, PO
Tylosin	As for cats	10-15 mg/kg, q12h, for 21 days, PO
Cystoisospora spp.		
Trimethoprim-sulfonamide	15-30 mg/kg, q12h, for 5 days, PO	15 mg/kg, q12h, for 5 days, PO
Sulfadimethoxine	50-60 mg/kg, daily, for 5-20 days, PO	50-60 mg/kg, daily, for 5-20 days, PO
Furazolidone	8-20 mg/kg, q12-24h, for 5 days, PO	8-20 mg/kg, q12-24h, for 5 days, PO
Amprolium	300-400 mg, daily, for 5 days	60-100 mg, daily, for 5 days
Paromomycin	As for cats	165 mg/kg, q12h, for 5 days, PO
Cytauxzoon felis		
Buparvaquone	NA	10 mg/kg, q24h, IM or SC
Diminazene	NA	2 mg/kg, q14 days, IM
Imidocarb	NA	2 mg/kg, q14 days, IM
Parvaquone	NA	10-30 mg/kg, q24h, IM or SC
Entamoeba histolytica		
Metronidazole	10-25 mg/kg, q12h, for 8 days, PO	25 mg/kg, q12h, for 7 days, PO
Giardia spp.		
Fenbendazole	50 mg/kg, q24h, for 3-7 days, PO	50 mg/kg, q24h, for 3-7 days, PO
Giardia vaccine	1 dose, q21days, for 2-3 inoculations	1 dose, q21days, for 2-3 inoculations
Metronidazole	10-25 mg/kg, q12h, for 8 days, PO	25 mg/kg, q12h, for 7 days, PO
Praziquantel, pyrantel and febantel	Daily PO for 3 days	NA
Hepatozoon americanum		
Clindamycin*	10 mg/kg, q8h, for 2-4 weeks, PO	NA
Decoquinate*	10 to 20 mg/kg, q12h, for life, PO	NA
Pyrimethamine*	0.25 mg/kg, q24h, for 2-4 weeks, PO	NA
Trimethoprim-sulfadiazine*	15 mg/kg, q12h, for 2-4 weeks, PO	NA
Imidocarb dipropionate	5-6 mg/kg, q14 days, IM or SQ	NA
Leishmania spp.		
Allopurinol	15 mg/kg, q12h, for months, PO	NA
Amphotericin B	3.0-3.3 mg/kg, q48h, 3-5 times, IV	NA
Meglumine antimonite	100 mg/kg, q24h, IV,IM, SC	NA
Sodium stibogluconate	30-50 mg/kg, q24h, IV, SC	
Neospora caninum		
Clindamycin*	10 mg/kg, q8h, for 4 weeks, PO	NA
Pyrimethamine*	1 mg/kg, q24h, for 4 weeks, PO	NA
Trimethoprim-sulfadiazine*	15 mg/kg, q12h, for 4 weeks, PO	NA
Pneumocystis carinii		
Pentamidine isethionate	4 mg/kg, q24h, for 2 weeks, IM	NA
Trimethoprim-sulfonamide	15-30 mg/kg, q8-12h, for 2 weeks, PO	NA
Tritrichomonas foetus		
Metronidazole	10-25 mg/kg, q12h, for 8 days, PO	25 mg/kg, q12h, for 7 days, PO
Toxoplasma gondii		
Azithromycin	5-10 mg/kg, q12h, for 5-7 days, PO	7-15 mg/kg, q12h, for 5-7 days, PO
Clindamycin hydrochloride	12.5 mg/kg, q12h, for 28 days, PO, IM	12.5 mg/kg, q12h, for 28 days PO, IM
Pyrimethamine	0.25-0.5 mg/kg, q24h, for 28 days PO	Usually not used due to toxicity
Trimethoprim-sulfonamide	15 mg/kg, q12h, for 28 days, PO	15 mg/kg, q12h, for 28 days, PO

*Used in combination.
IM, Intramuscular; *IV*, intravenous; *SC*, subcutaneous; *PO*, oral; *NA*, not applicable.

If a host with chronic toxoplasmosis is immunosuppressed, bradyzoites in tissue cysts can replicate rapidly and disseminate again as tachyzoites. Disseminated toxoplasmosis has been documented in cats concurrently infected with feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), feline infectious peritonitis (FIP) virus, and after renal transplantation.[4]

Chronic toxoplasmosis occurs in some dogs and cats. *Toxoplasma gondii* infection should be on the differential diagnoses list for cats with anterior or posterior uveitis, fever, muscle hyperesthesia, weight loss, anorexia, seizures, ataxia, icterus, diarrhea, and pancreatitis.[4,36] Based on results of *T. gondii*–specific aqueous humor antibody and PCR studies, toxoplasmosis appears to be a common infectious cause of uveitis in cats.[37,38] Kittens infected transplacentally or lactationally commonly develop ocular disease.[39] Immune complex formation and deposition in tissues and delayed hypersensitivity reactions may be involved in chronic, subfatal clinical toxoplasmosis. Because none of the anti-*Toxoplasma* drugs totally clear the body of the organism, recurrence of disease is common.

In dogs, respiratory, GI, or neuromuscular infection resulting in fever, vomiting, diarrhea, dyspnea, and icterus are most common and occur most frequently in immune-suppressed dogs, such as those with canine distemper virus (CDV) infection or those receiving cyclosporine to prevent rejection of a transplanted kidney.[4,40,41] Neurologic signs are dependent on the location of the primary lesions and include ataxia, seizures, tremors, cranial nerve deficits, paresis, and paralysis. Dogs with myositis have weakness, stiff gait, or muscle wasting. Rapid progression to tetraparesis and paralysis with lower motor neuron dysfunction can occur. Some dogs with suspected neuromuscular toxoplasmosis probably had neosporosis.[31] Myocardial infection resulting in ventricular arrhythmias occurs in some infected dogs. Dyspnea, vomiting, or diarrhea occur in dogs with polysystemic disease. Retinitis, anterior uveitis, iridocyclitis, and optic neuritis occur in some dogs with toxoplasmosis but are less common than in the cat.

Dogs or cats with clinical toxoplasmosis can have a variety of clinicopathologic and radiographic abnormalities but none document the disease. Nonregenerative anemia, neutrophilic leukocytosis, lymphocytosis, monocytosis, neutropenia, eosinophilia, proteinuria, bilirubinuria, increases in serum proteins and bilirubin concentration, as well as creatinine kinase, alanine aminotransferase, alkaline phosphatase, and lipase activity occurs in some animals.[4] Pulmonary toxoplasmosis most commonly causes diffuse interstitial to alveolar patterns or pleural effusion.[42] Cerebrospinal fluid (CSF) protein concentrations and cell counts are often higher than normal. The predominant white blood cells (WBCs) in CSF are small mononuclear cells, but neutrophils also are commonly found.

The antemortem definitive diagnosis of toxoplasmosis can be made if the organism is demonstrated; however, this is uncommon. Bradyzoites or tachyzoites are rarely detected in tissues, effusions, bronchoalveolar lavage fluids, aqueous humor, or CSF. Detection of 10 × 12 μm oocysts in feces in cats with diarrhea suggests toxoplasmosis but is not definitive, because *Besnoitia* and *Hammondia* infections of cats produce morphologically similar oocysts.

Toxoplasma gondii–specific antibodies (dogs or cats), antigens (cats), immune complexes (cats), and DNA (cats) can be detected in the blood of normal animals, as well as in those with clinical signs of disease; therefore it is impossible to make an antemortem diagnosis of clinical toxoplasmosis based on these tests alone.[4,37,38,43] Of the serum tests, IgM correlates the best with clinical toxoplasmosis because this antibody class is rarely detected in serum of healthy animals. The antemortem diagnosis of clinical toxoplasmosis can be tentatively based on the combination of the following:

- Demonstration of antibodies in serum that documents exposure to *T. gondii*
- Demonstration of an IgM titer greater than 1:64 or a fourfold or greater increase in IgG titer that suggests recent or active infection
- Clinical signs of disease referable to toxoplasmosis
- Exclusion of other common causes of the clinical syndrome
- Positive response to appropriate treatment

Some animals with clinical toxoplasmosis will have reached their maximal IgG titer or will have undergone antibody class shift from IgM to IgG by the time they are serologically evaluated, so the failure to document an increasing IgG titer or a positive IgM titer does not exclude the diagnosis of clinical toxoplasmosis. Because some healthy animals have extremely high serum antibody titers and some clinically ill animals have low serum antibody titers, the magnitude of titer is relatively unimportant in the clinical diagnosis of toxoplasmosis. Because the organism cannot be cleared from the body, most animals will be antibody-positive for life; therefore repeating serum antibody titers after clinical disease has resolved is of little use.

The combination of aqueous humor or CSF *T. gondii*–specific antibody detection and organism DNA detection by PCR is the most accurate way to diagnose ocular or CNS toxoplasmosis in cats (Diagnostic Laboratory, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO 80523). Although *T. gondii*–specific IgA, IgG, and organism DNA can be detected in aqueous humor and CSF of both normal and clinically ill cats, *T. gondii*–specific IgM has only been detected in the aqueous humor or CSF of clinically ill cats and so may be the best indicator of clinical disease. Because *T. gondii* DNA can be detected in blood of healthy cats, positive PCR results do not correlate to clinical disease.

Supportive care should be instituted as needed. Clindamycin hydrochloride, trimethoprim-sulfonamide combination, and azithromycin have been used successfully for the treatment of clinical toxoplasmosis.[4,36] Pyrimethamine combined with sulfa drugs is effective for the treatment of human toxoplasmosis but commonly results in toxicity in cats. Cats or dogs with uveitis should be treated with topical, oral, or parenteral glucocorticoids to avoid secondary glaucoma and lens luxations.[4,44] *T. gondii* seropositive animals with uveitis that are otherwise normal can be treated with topical glucocorticoids alone, unless the uveitis is recurrent or persistent. In these situations, administration of a drug with anti-*T. gondii* activity may be beneficial.

T. gondii is a significant zoonosis. Primary infection of mothers during gestation can lead to clinical toxoplasmosis in the fetus; stillbirth, CNS disease, and ocular disease are common clinical manifestations. Primary infection in immunocompetent individuals results in self-limiting fever, malaise, and lymphadenopathy. As T-helper cell counts decline, approximately 10% of people with acquired immunodeficiency syndrome (AIDS) develop toxoplasmic encephalitis from activation of bradyzoites in tissue cysts. People most commonly acquire toxoplasmosis by ingesting sporulated oocysts, tissue cysts, or they acquire it transplacentally. To prevent toxoplasmosis, eating undercooked meats or ingesting sporulated oocysts should be avoided. Although owning a pet cat was epidemiologically associated with acquiring toxoplasmosis in one study of pregnant women,[45] touching individual cats is probably not a common way to acquire toxoplasmosis for the following reasons:

- Cats generally only shed oocysts for days to several weeks after primary inoculation.
- Repeat oocyst shedding is rare, even in cats receiving glucocorticoids, and in those infected with FIV or FeLV.[46,47]
- Cats with toxoplasmosis inoculated with tissue cysts 16 months after primary inoculation did not shed oocysts.[47]

- Cats are fastidious and usually do not allow feces to remain on their skin for time periods long enough to lead to oocyst sporulation; the organism was not isolated from the fur of cats shedding millions of oocysts 7 days previously.[48]
- Increased risk of acquired toxoplasmosis was not associated with cat ownership in human immunodeficiency virus (HIV)-infected people or in veterinary health care providers.[49]

If infection is suspected on fecal examination, the oocyst shedding period can be shortened by administration of clindamycin (25 to 50 mg/kg a day orally), sulfonamides (100 mg/kg a day orally), or pyrimethamine (2.0 mg/kg a day orally).[4] Because humans are not commonly infected with *T. gondii* from contact with individual cats, testing healthy cats for toxoplasmosis is not recommended. No serologic assay accurately predicts when a cat shed *T. gondii* oocysts in the past, and most cats that are shedding oocysts are seronegative. Most seropositive cats have completed the oocyst shedding period and are unlikely to repeat shedding; most seronegative cats would shed the organism if infected. If owners are concerned that they may have toxoplasmosis, they should see their doctor for testing. Avoiding sporulated oocysts and tissue cysts in undercooked meat can lessen the risk of acquiring toxoplasmosis.

NEOSPOROSIS

Neospora caninum is a coccidian previously confused with *T. gondii* due to similar morphology.[31,50,51] The sexual cycle is completed in the GI tract of dogs and results in the passage of oocysts in feces.[52-55] Sporozoites develop in oocysts within 24 hours of passage. Tachyzoites (rapidly-dividing stage) and tissue cysts containing hundreds of bradyzoites (slowly-dividing stage) are the other two life stages. Dogs are infected by ingestion of bradyzoites but not tachyzoites.[53] Infection has been documented after ingestion of infected bovine placental tissue. Transplacental infection has been well documented; dams that give birth to infected offspring can repeat transplacental infection during subsequent pregnancies.[56] Although organism replication occurs in many tissues, clinical illness primarily reflects neuromuscular infection in dogs. Although encephalomyelitis and myositis develops in experimentally infected kittens, clinical disease in naturally infected cats has not been reported.[57] Canine neosporosis has been reported in many countries around the world. Whether other intermediate hosts play a role in maintenance of infection is unknown, but white-tailed deer are commonly seropositive.[58] Because repeated transplacental infections occur, increased risk exists for puppies from a bitch that has previously birthed infected puppies.

Congenitally infected puppies develop ascending paralysis with hyperextension of the hindlimbs; muscle atrophy occurs in many cases. Polymyositis and multifocal CNS disease can occur alone or in combination. Clinical signs can be evident soon after birth or may be delayed for several weeks. Neonatal death is common. Although disease tends to be most severe in congenitally infected puppies, dogs as old as 15 years have been clinically affected. In some dogs, myocarditis, dysphagia, ulcerative dermatitis, pneumonia, and hepatitis occur.[59-63] Glucocorticoid treatment may activate bradyzoites in tissue cysts resulting in clinical illness. CNS inflammation is usually with mononuclear cell infiltrates, which suggests an immune-mediated component to the pathogenesis of disease. If not treated, most affected dogs die.

No specific hematologic or biochemical findings exist, but increased creatine kinase (CK) and aspartate transaminase (AST) activities are common in dogs with myositis. CSF abnormalities include increased protein concentration (20 to 50 mg/dL) and a mild, mixed inflammatory cell pleocytosis (10 to 50 cells/dL) consisting of monocytes, lymphocytes, neutrophils, and rarely, eosinophils. Interstitial and alveolar patterns can be noted on thoracic radiographs. Demonstration of the organism in CSF or tissues gives a definitive diagnosis. Tachyzoites are rarely identified on cytologic examination of CSF, imprints of dermatologic lesions, and bronchoalveolar lavage. Mixed inflammation with neutrophils, lymphocytes, eosinophils, plasma cells, macrophages, and tachyzoites was noted on transthoracic aspirate of one dog with lung disease.[63]

Oocysts can be detected in feces by microscopic examination after flotation or by PCR. *Neospora caninum* tissue cysts have a wall greater than 1 μm; *T. gondii* tissue cysts have a wall less than 1 μm. The organism can be differentiated from *T. gondii* by electron microscopy, immunohistochemistry, and PCR.[61]

The clinician can make a presumptive diagnosis of neosporosis by combining appropriate clinical signs of disease and positive serology or presence of antibodies in CSF with the exclusion of other causes inducing similar clinical syndromes, in particular, *T. gondii*. Immunoglobulin G antibody titers greater than or equal to 1:200 have been detected in most dogs with clinical neosporosis; minimal serologic cross-reactivity with *T. gondii* occurs at titers greater than or equal to 1:50.

The prognosis for dogs with severe neurologic involvement is grave. Some have survived after treatment with trimethoprim-sulfadiazine combined with pyrimethamine, sequential treatment with clindamycin hydrochloride, trimethoprim-sulfadiazine, and pyrimethamine, or clindamycin alone.[59-62]

Neospora caninum antibodies have been detected in people,[64] but in one study there was no link to repeated abortion.[65] There has been an epidemiologic link between dogs and cattle; therefore efforts should be made to lessen dog fecal contamination of livestock feed, and dogs should not be allowed to ingest bovine placentas.[66] White-tailed deer are commonly seropositive, so it is possible that intermediate hosts play a role in canine infection. Bitches that whelp clinically affected puppies should not be bred. Glucocorticoids should not be administered to seropositive animals, if possible, because a potential exists for activation of infection.

HEPATOZOONOSIS

Hepatozoonosis in dogs is caused by *Hepatozoon canis* and *H. americanum*.[67,68] In North America, *H. americanum* predominates, is transmitted by *Amblyomma maculatum*, and is most common in the Texas Gulf Coast, Mississippi, Alabama, Georgia, Florida, Louisiana, and Oklahoma.[69] In Africa, southern Europe, and Asia, *H. canis* predominates and is transmitted by *Rhipicephalus sanguineous*. A *Hepatozoon* species is occasionally found in the blood of cats in Europe.[71-73] The tick ingests the organism from infected dogs during a blood meal and oocysts develop. After a dog ingests an infected tick, sporozoites are released and infect mononuclear phagocytes and endothelial cells of the spleen, liver, muscle, lungs, and bone marrow, and they ultimately form cysts containing macromeronts and micromeronts. Clinical disease results from pyogranulomatous inflammation; glomerulonephritis or amyloidosis may occur secondary to chronic inflammation and immune complex disease.

H. americanum has resulted in illness in all age groups, but disease is most commonly recognized in puppies.[73-74] Fever, weight loss, and severe hyperesthesia over the paraspinal regions are common findings. Anorexia, pale mucous membranes from anemia, depression, oculonasal discharge, and bloody diarrhea occur in some dogs. Clinical signs can be intermittent and recurrent. Clinical disease associations are currently unclear, but the cats are commonly coinfected with FeLV or FIV.

Neutrophilic leukocytosis (20,000 to 200,000 cells/μL) with a left shift is the most common hematologic finding. Thrombocytopenia is unusual unless coinfection by *Ehrlichia canis* occurs. Normocytic, normochromic nonregenerative anemia is common and is likely from chronic inflammation. Increased activity of alkaline phosphatase but not creatine kinase occur in *H. americanum* infected dogs. Hypoalbuminemia, hypoglycemia, and rarely, polyclonal gammopathy occur in some dogs. Periosteal reactions from the inflammatory reaction directed at tissue phases in muscle can occur in any bone excluding the skull, are most common in young dogs, do not occur in every case, and are not pathognomonic for hepatozoonosis. Presence of serum antibodies against *H. americanum* were compared with tissue biopsy; the sensitivity and specificity were 93% and 96%, respectively.[75] Definitive diagnosis is based on identification of gamonts in neutrophils or monocytes in Giemsa- or Leishman's-stained blood smears or by demonstration of the organism in muscle biopsy sections.

For treatment of *H. americanum*, the combination of trimethoprim-sulfadiazine, pyrimethamine, and clindamycin for 14 days is successful in the short-term.[73,74] Administration of decoquinate mixed with food lessens the likelihood of recurrence of clinical disease and prolongs survival time. Imidocarb dipropionate is the drug of choice for treatment of *H. canis* and may also be effective for *H. americanum*. Administration of nonsteroidal anti-inflammatory drugs (NSAIDs) may lessen discomfort for some dogs. No therapeutic regimen has been shown to eliminate *H. canis* or *H. americanum* infection from tissues.

Tick control is the best form of prevention. Glucocorticoid administration should be avoided because it may exacerbate clinical disease. No evidence exists for zoonotic transfer of *H. americanum* or *H. canis* from infected dogs to people.

PIROPLASMIA

Babesiosis

Multiple *Babesia* spp. infect dogs throughout the world.[76-85] *Babesia canis* has worldwide distribution including Africa, Asia, Australia, Europe, Central America, South America, Japan, and the United States. *B. canis rossi* is transmitted by *Haemaphysalis leachi* and is the most pathogenic. *B. canis canis* is transmitted by *Dermacenter reticulatus* and is moderately pathogenic. *B. canis vogeli* is the least pathogenic and is transmitted by *Rhipicephalus sanguineus*. *Babesia gibsoni* infects dogs in the United States, Japan, India, Sri Lanka, Korea, Malaysia, and Egypt. North American and Asian isolates of *B. gibsoni* vary genetically enough to be proposed as different species.[81] In countries other than the United States, *H. bispinosa* and *H. longicornis* are known vectors for *B. gibsoni*. *R. sanguineus* is proposed but not proven to be a vector in the United States. A *Babesia* spp. that genetically varies considerably from other *B. canis* or *B. gibsoni* isolates was described in Oklahoma. None of the *Babesia* spp. that infect cats—*B. cati* (India), *B. felis* (South Africa and Sudan), *B. herpailuri* (South America and Africa), or *B. pantherae* (Kenya)—are found in the United States.[85] *Babesia* spp. can also be transmitted by blood transfusion.

The organisms replicate intracellularly in red blood cells (RBCs) resulting in intravascular hemolytic anemia. Immune-mediated reactions against the parasite or altered self-antigens worsens the hemolytic anemia and commonly results in positive Coombs' test. Severity of disease depends on the species and strain of *Babesia* and the host immune status; chronic, subclinical infection can occur. Peracute or acute *Babesia* infections result in anemia and fever leading to pale mucous membranes, tachycardia, tachypnea, depression, anorexia, and weakness. Icterus, petechiation, azotemia, and hepatosplenomegaly are present in some dogs depending on the stage of infection and the presence of disseminated intravascular coagulation (DIC).[83-88] Severe, acute anemia potentiates the development of DIC, metabolic acidosis, and renal disease. The primary differential diagnosis for acute babesiosis is primary immune-mediated hemolytic anemia. Chronically infected dogs commonly have weight loss and anorexia. Ascites, GI signs, CNS disease, edema, and clinical evidence of cardiopulmonary disease occur in some dogs with atypical infection. Subclinical infection occurs as well. Administration of glucocorticoids or splenectomy may activate chronic disease.

Regenerative anemia, hyperbilirubinemia, bilirubinuria, hemoglobinuria, thrombocytopenia, metabolic acidosis, azotemia, polyclonal gammopathy, and renal casts are common in dogs infected with babesiosis. IFA tests for *B. canis* and *B. gibsoni* are available commercially. Demonstration of increasing titers over 2 to 3 weeks are consistent with recent or active infection. Currently no standardization exists between laboratories; therefore suggested positive "cutoff" titers vary. False-negative serologic test results can occur in peracute conditions or in dogs with concurrent immunosuppression. A titer of greater than 1:320 was suggested for *B. gibsoni*, but not all infected dogs achieve titers of this magnitude.[83] A presumptive diagnosis can be based on historical findings, physical examination findings, test results, and positive serology. Many dogs are seropositive but clinically normal; therefore serology alone cannot be used to make a definitive diagnosis.[89,90] Definitive diagnosis is based on organism demonstration in RBCs using Wright's or Giemsa stains on thin blood smears. *B. canis* is typically found as paired, piriform bodies measuring 2.4 × 5.0 μm. *B. gibsoni* is typically found as single, annular bodies measuring 1.0 × 3.2 μm. PCR is now available commercially and can be used to document organism presence, but positive results do not always correlate to clinical illness.[91]

Supportive care should be administered as indicated. Phenamidine isethionate and imidocarb dipropionate may be effective for the treatment of babesiosis.[83-88,92] Adverse effects include transient salivation, diarrhea, dyspnea, lacrimation, and depression. Metronidazole or clindamycin hydrochloride may lessen clinical disease if other drugs are not available. Diminazene aceturate, pentamidine isethionate, parvaquoine, and niridazone have also been used. No drugs are available to eliminate infection; therefore it is unknown whether it is beneficial to treat healthy, seropositive dogs.

Ticks should be controlled if possible. Administration of immunosuppressive drugs and splenectomy should be avoided in previously infected dogs. Dogs used as blood donors should be assessed for infection by PCR or serologic screening. Currently no evidence exists to suggest that *Babesia* spp. infecting dogs and cats can cause human disease.

CYTAUXZOONOSIS

Cytauxzoon felis infects cats in the southeastern and south central United States. Bobcats are usually subclinically affected and are the likely natural host of the organism. The organism can be passed experimentally from infected bobcats to domestic cats by *Dermacentor variabilis*; clinical illness occurs after an incubation period of 5 to 20 days.[93] Infected macrophages line the lumen of veins throughout the body and merozoites released from the infected macrophages infect erythrocytes. Clinical disease results from obstruction of blood flow through tissues by mononuclear infiltrates and from hemolytic anemia.

Most cases of cytauxzoonosis are in cats allowed to go outdoors. Fever, anorexia, dyspnea, depression, icterus, pale

mucous membranes, and death are the most common clinical findings.[94-96] A primary differential diagnosis is haemobartonellosis. Ticks are generally not identified on affected cats. Recently, cytauxzoonosis was described in cats of Oklahoma and Arkansas that did not result in death suggesting that variants that are less virulent to cats exist.[97,98]

Cytauxzoonosis is suspected in cats with regenerative anemia and neutrophilic leukocytosis; thrombocytopenia occurs in some cats. Hemoglobinemia, hemoglobinuria, bilirubinemia, and bilirubinuria are uncommon. Antemortem diagnosis is based on demonstration of the erythrocytic phase on thin blood smears stained with Wright's or Giemsa stains. Infected macrophages can be detected cytologically in bone marrow, spleen, liver, or lymph node aspirates. The organism is easily identified on histologic evaluation of most organs. Serologic testing is not commercially available. PCR can be used to amplify organismal DNA from blood.[98]

Supportive care should be administered as indicated. Treatment with diminazene or imidocarb were used in cats that survived infection.[95] Historically, paraquone, buparvaquone, thiacetarsemide therapies have been attempted. However, paraquone and buparvaquone are not routinely available, and thiacetarsemide is toxic for cats and should not be used for the treatment of this parasite. Ticks should be controlled, and cats in endemic areas should be housed during periods of peak tick activity. *Cytauxzoon felis* is not known to be zoonotic.

FLAGGELATES

Leishmaniasis

Leishmania spp. are flagellates that cause cutaneous, mucocutaneous, and visceral diseases in dogs, humans, and other mammals.[99,100] Rodents and dogs are primary reservoirs of *Leishmania* spp., people and cats are probably incidental hosts, and sandflies are the vectors. Leishmaniasis was considered unimportant in the United States until recently, with cases only reported occasionally.[101-103] In 2000, *Leishmania donovani* infection was confirmed in multiple dogs in a foxhound kennel in New York State.[104] Further investigation documented *L. donovani* or *Leishmania* spp. infection in 30 other foxhound kennels in 20 states and Ontario, Canada, suggesting a competent vector exists in North America. The organism has been transmitted by blood transfusion.[105] A clinically affected cat in Texas was infected by *L. mexicana mexicana*.[102] Flagellated promastigotes develop in the sandfly and are injected into the vertebrate host when the sandfly feeds. Promastigotes are engulfed by macrophages and disseminate through the body. After an incubation period of 1 month to 7 years, amastigotes (nonflagellate) form and cutaneous lesions develop; sandflies are infected during feeding. The intracellular organism induces extreme immune responses; polyclonal gammopathies (and occasionally monoclonal), proliferation of macrophages, histiocytes, and lymphocytes in lymphoreticular organs and immune complex formation resulting in glomerulonephritis and polyarthritis are common.

Dogs generally develop visceral leishmaniasis. Subclinical infection may persist for months or years. Weight loss, normal to increased appetite, polyuria, polydipsia, muscle wasting, depression, vomiting, diarrhea, cough, epistaxis, sneezing, and melena are common presenting complaints. Splenomegaly, lymphadenopathy, facial alopecia, fever, rhinitis, dermatitis, increased lung sounds, icterus, swollen painful joints, uveitis, and conjunctivitis are commonly identified on physical examination.[99,100,106] Cutaneous lesions are characterized by hyperkeratosis, scaling, thickening, mucocutaneous ulcers, and intradermal nodules on the muzzle, pinnae, ears, and footpads. Cats are usually subclinically infected. One cat had cutaneous nodules on the ear pinna.[102]

Hyperglobulinemia, hypoalbuminemia, proteinuria, increased liver enzyme activities, thrombocytopenia, azotemia, lymphopenia, and leukocytosis with left shift are common. Hyperglobulinemia is usually polyclonal, but an IgG monoclonal gammopathy was reported in a dog.[107] Neutrophilic polyarthritis occurs in some dogs as a manifestation of a Type III hypersensitivity reaction. Antibodies against *Leishmania* can be detected in serum[108-110]; IgG titers develop 14 to 28 days after infection and decline 45 to 80 days after treatment. Because dogs are unlikely to eliminate infection spontaneously, a true positive antibody test indicates infection. Demonstration of amastigotes (2.5 to 5.0 μm × 1.5 to 2.0 μm) in lymph node aspirates, bone marrow aspirates, or skin imprints stained with Wright's or Giemsa stain gives a definitive diagnosis. The organism can also be identified by histopathologic or immunoperoxidase evaluation of skin or organ biopsy, culture, inoculation of hamsters, or PCR. PCR can be performed on EDTA anticoagulated blood, bone marrow, or lymph node aspirates.[109,110]

Leishmania cannot be eliminated from the body with drugs.[108,111,112] The combination of antimony and allopurinol was superior to treatment with either drug alone in one study.[112] Liposomal amphotericin B has also been prescribed.[113] The prognosis is variable; most cases are recurrent. Dogs with renal insufficiency have a poor prognosis.

Avoidance of infected sandflies is the only means of prevention.[114] If in endemic areas, pet owners should house animals during nighttime hours and control breeding places of sandflies. Potential blood donors from endemic areas should be serologically screened.[105] The primary zoonotic risk for canine leishmaniasis is from dogs acting as a reservoir host for the organism. Direct contact with amastigotes in draining lesions is unlikely to result in human infection.

AMERICAN TRYPANOSOMIASIS

Trypanosoma cruzi infection of mammals is diagnosed primarily in South America, but several cases have been detected in dogs of North America.[115-123] Infected reservoir mammals (dogs, cats, raccoons, opossums, armadillos) and vectors (reduviid bugs, kissing bugs) are found in the United States, but infection in dogs or people is rare; this may relate to differences in vector behavior and sanitation standards in the United States. In one study in Texas, the number of serologically positive dogs increased between 1987 and 1996.[116] The organism has three life stages: (1) trypomastigotes (flagellated stage found free in blood), (2) amastigotes (nonflagellated intracellular form), and (3) epimastigotes (flagellated form found in the vector). When infected kissing bugs defecate during feeding, epimastigotes enter the vertebrate host, are engulfed by macrophages and myocytes, and transform into amastigotes. Amastigotes divide by binary fission until the host cell ruptures, releasing trypomastigotes into circulation. The vector is then infected by ingesting trypomastigotes during a blood meal. Transmission can also occur by ingesting the vector, by blood transfusions, by ingestion of infected tissues or milk, or transplacentally.

Disease in dogs is primarily a cardiomyopathy that develops from parasite-induced damage to myocardial cells or immune-mediated reactions. Exercise intolerance and weakness are nonspecific presenting complaints that relate to myocarditis or heart failure during acute infection. Generalized lymphadenopathy, pale mucous membranes, tachycardia, pulse deficits, hepatomegaly, and abdominal distension can be detected on physical examination. Anorexia, diarrhea, and neurologic signs occasionally occur. Dogs that survive acute infection can present for evaluation of chronic dilative cardiomyopathy. In one study of 11 dogs with chronic infection, right-sided cardiac disease, conduction disturbances,

ventricular arrhythmias, and supraventricular arrhythmias were most common.[116]

Common clinicopathologic abnormalities include lymphocytosis and increased activities of liver enzymes and creatine kinase. Thoracic radiographic, abdominal radiographic, and echocardiographic findings are consistent with cardiac disease and failure, but they are not specific for trypanosomiasis. The primary ECG findings are ventricular premature contractions, heart block, and T-wave inversion. Definitive diagnosis is based on organism demonstration. Tryptomastigotes (1 flagellum, 15 to 20 µm long) can be identified during acute disease on thick blood film or buffy coat smears stained with Giemsa or Wright's stain. The organism is sometimes detected in lymph node aspirates or in abdominal effusions. Histopathologic evaluation of cardiac tissue may reveal amastigotes (1.5 to 4.0 µm). Tryptomastigotes can also be cultured from blood or grown by bioassay in mice. In North American cases, positive serologic test results correlate with infection. PCR can also be used to detect infection.

Nifurtimox administered at 2 to 7 mg/kg orally every 6 hours for 3 to 5 months has been prescribed most frequently but is not routinely available. Glucocorticoid therapy may improve survival of infected dogs. Therapy for arrhythmias or heart failure should be instituted as needed. Most dogs that survive acute infection will develop dilative cardiomyopathy. Survival time in 11 dogs varied from 0 to 60 months.[116]

Dogs should be kept from other reservoir hosts such as opossums and should not be fed raw meat. Potential blood donors from endemic areas should be serologically screened. Infected dogs can serve as a reservoir of *T. cruzi* for vectors, and blood from infected dogs can be infectious to humans. Vector control is the primary means of prevention.

AMOEBA

Acanthamoeba Spp.

Acanthamoeba castellanii and *A. culbertsoni* are free-living amoeba rarely associated with disease in dogs.[124-126] Several cases have been reported in greyhounds. Young dogs seem to be affected most often. Clinical signs resemble CDV infection and consist primarily of oculonasal discharge, fever, anorexia, lethargy, dyspnea, and CNS disease. No pathognomic laboratory or radiographic abnormalities exist, but leukopenia is common. The organism can be demonstrated histologically or cultured; antemortem diagnosis is not usually made. No known effective treatment or zoonotic risk exists.

MICROSPORA

Encephalitozoon Cuniculi

Dogs and cats can develop clinical illness after exposure to *Encephalitozoon cuniculi*.[127-129] Schizonts and sporonts are found intracellularly in many cell types including renal tubular epithelial cells, endothelial cells, tissue macrophages, and hepatocytes. Spores are the extracellular stage of the organism that is passed in urine. Infection is probably from oronasal exposure to spores passed in urine. In utero infection can also occur; infected puppies are weak, have stunted growth, and develop renal failure and CNS disease. Muscle spasms, depression, paralysis, and death have been reported in naturally infected cats. No pathognomonic laboratory abnormalities exist; however, azotemia, increased activities of hepatic enzymes, and increased CSF cell counts (neutrophils) and protein concentrations commonly occur. Diagnosis is based on demonstration of spores in urine sediment stained with Gram or Ziehl-Neelsen stains. Serologic testing is available but is not specific for *E. cuniculi*. Although no drug has been shown to be effective for treatment of *E. cuniculi* in infected dogs or cats, fumigillin and albendazole were effective in vitro.[130] Although the zoonotic risk is considered minimally important, a 10-year-old girl in a home with two infected puppies seroconverted to *E. cuniculi*.[129] Sanitation is the best form of control.

MISCELLANEOUS INFECTIOUS AGENTS

Pneumocystosis

Pneumocystis carinii is a saprophytic organism with worldwide distribution that has characteristics of protozoans, yeast, and fungi that has been detected in diseased dogs.[131-136] The organism is found in the alveoli of some normal animals. Disease only occurs in immune-suppressed individuals. Replication of the organism in the alveoli induces infiltrates of lymphocytes, plasma cells, and macrophages that induces an alveolar-capillary blockage. Disseminated infection is rare in dogs and people. Disease has been detected in cats given corticosteroids.[137] Pneumocystosis in animals is extremely rare and only associated with concurrent immune deficiency. Miniature dachshunds with common variable immunodeficiency syndrome are affected most frequently.[131-132]

Most affected dogs have been less than 1 year of age. Predominant findings are dry cough, dyspnea, and progressive weight loss. Dermatopathies such as demodicosis and pyoderma that likely reflect the immune deficiency occur with most.

Neutrophilic leukocytosis, polycythemia, eosinophilia, and monocytosis occur in some dogs but are nonspecific findings. Common blood gas abnormalities include hypoxemia, hypocapnia, and an increased arterial-alveolar gradient. On thoracic radiographs, interstitial to alveolar patterns predominate.[138] Cor pulmonale can develop. Cytologic demonstration of the organism in transthoracic aspirates, transtracheal wash specimens, or lung biopsies is used to make the final diagnosis. Immune function deficits have been documented in affected dachshunds. Diffuse interstitial pneumonia characterized by free and phagocytosed organism in the alveolar spaces is found on histopathologic examination.

Administration of potentiated sulfas give the best results.[131,132] Pentamidine, carbutamide, trimetrexate, the combination of clindamycin and primaquine, and the combination of dapsone and trimethoprim have been used to treat pneumocystosis in some dogs. Supportive care, including oxygen therapy, bronchodilators, nebulization, and mucolytic agents, should be administered as indicated. For most cases, death occurs or euthanasia is chosen within days to months after diagnosis. Infected dogs are not considered zoonotic risks for people.

PROTOTHECOSIS

Prototheca zopfii and *P. wickerhamii* are the two species in this genus of green algae incriminated as pathogens; protothecosis is a disseminated disease in the dog *(P. zopfii)* and a cutaneous disease in the dog and cat *(P. wickerhamii)*.[139-142] The organism is found in sewage and animal wastes and is transmitted by ingestion of contaminated food, water, or soil. Disease generally only occurs in individuals with decreased cell-mediated immune responses. There may be strain differences in virulence and genetic predispositions.

The disseminated disease is most common in dogs that present for evaluation of weight loss, large-bowel diarrhea, CNS disease, or uveitis. The cutaneous disease occurs in dogs and cats and appears as draining ulcers and crusts of the trunk, extremities, and mucous membranes in dogs and as firm cutaneous nodules on the limbs, feet, and head of cats.

CSF abnormalities include pleocytosis with either lymphocytes or granulocytes as the predominate cell type and increased total protein. Diagnosis is confirmed by cytologic, histologic, or culture documentation of the organism in CSF, rectal scrapings, or rectal biopsies. Cutaneous lesions should be excised if possible. Liposomal amphotericin B, ketoconazole, itraconazole, tetracyclines, and fluconazole may be effective treatments. CNS and ocular manifestations have a poor prognosis; fluconazole may be the drug of choice for disease of these systems. Topical clotrimazole may be effective for treatment of cutaneous *P. wickerhamii* infections. *Prototheca* spp. are not thought to be transmitted between hosts; therefore zoonotic risk is minimal.

CHAPTER 169

Canine Viral Diseases

Rance K. Sellon

CANINE PARVOVIRUS

Cause and Epidemiology

Parvovirus of dogs is caused by type 2 canine parvovirus (CPV-2), a nonenveloped single-stranded DNA virus, of which two pathogenic variants, types 2a and 2b are recognized. Evidence suggests an evolution of the type 2a variant to the type 2b, with the 2b variant the most common isolate infecting dogs in the United States. Both variants can be found in other parts of the world. A third variant, type 2c, has recently been found in cats in Southeast Asia.[1]

Wild and domestic canids are susceptible to infection with CPV-2. Canine parvovirus (CPV) infection has been described in minks and ferrets, and all variants are known to infect cats. The virus is transmitted primarily by the fecal-oral route after exposure of susceptible animals to contaminated feces. CPV is quite stable under many environmental and hospital conditions, contributing to maintenance of the virus in natural settings and creating the potential for transmission in veterinary clinics. CPV is resistant to many detergents and disinfectants, although it is inactivated by bleach solutions (1 part bleach to 29 parts water), formalin, and sunlight.

Pathogenesis

After exposure, CPV replicates in lymphoid cells in the oropharynx, mesenteric lymph nodes, and thymus, then within 3 to 5 days it spreads hematogenously to crypt cells of the small intestine and epithelial cells of the oral cavity, tongue, and esophagus. Lymphoid organs, lungs, liver, kidneys, bone marrow and (in very young animals) myocardial cells may also become infected. Virus excretion begins shortly after infection of intestinal epithelial cells and can occur as soon as 3 to 4 days after exposure; virus excretion typically occurs for 1 to 2 weeks. In the intestinal tract, necrosis of infected crypt cells leads to villus collapse and loss of intestinal epithelial integrity. The hemorrhagic diarrhea that is characteristic of the clinical disease results from a combination of increased intestinal permeability and malassimilation from abnormal mucosal function. Breakdowns in the intestinal epithelial barrier predispose to translocation of intestinal bacteria and absorption of bacterial endotoxins into the systemic circulation (common events in parvoviral-infected dogs).[2,3] Translocation of bacteria and endotoxins can lead to systemic bacteremia and the systemic inflammatory response syndrome, disseminated intravascular coagulation (DIC), and death. Activation of systemic immune responses increases the risk of thromboembolic complications of CPV infection.[4]

Clinical Signs

Clinical features in infected dogs range from asymptomatic infection to fulminant disease and rapid death. The majority of dogs will not develop obvious clinical signs, but in very young animals, immune-suppressed, heavily parasitized or stressed animals, or animals at risk of disease because of breed-related susceptibility, clinical signs often start with anorexia, lethargy, and fever that progresses within 1 to 2 days to vomiting and diarrhea, which is often hemorrhagic. More severe gastrointestinal (GI) signs can be expected in puppies with intestinal parasites or other intestinal disease.

Uncommonly, clinical signs of myocarditis may be observed in very young puppies, typically those less than 8 weeks of age that have not benefited from receipt of maternal antibodies. Puppies may die acutely with no warning, or they may die after signs of enteric disease. Puppies that survive acute myocardial infection may succumb at later times to congestive heart failure (CHF).

Diagnosis

The development of characteristic clinical signs in a dog at risk of infection often provides the first suspicion of CPV. Assays based on enzyme-linked immunosorbent assay (ELISA) techniques to detect CPV antigen in stool samples are commonly used for suspect animals as a first-line diagnostic tool and represent a quick, relatively accurate, and inexpensive means of supporting the diagnosis. Limitations of fecal ELISA testing include brief periods of antigen shedding, varying levels of antigen shedding, and the inability of current tests to discriminate modified-live viral (MLV) vaccine isolates, which can be present in feces for around 1 week starting about 5 days after vaccination, from pathogenic isolates. Thus false negatives and false positives are possible. The development of polymerase chain reaction (PCR)-based assays may prove valuable in the future for discrimination of vaccine from field isolates.

Laboratory abnormalities are common in dogs with clinical CPV infection. Leukopenia and neutropenia can reflect either marrow infection or sepsis and generally parallel the severity of clinical infection; recovery of circulating neutrophil counts often precedes clinical improvement. Anemia and hypoproteinemia, which can be a consequence of hypoalbuminemia, hypoglobulinemia, or both can develop from enteric blood loss.

Vomiting and diarrhea can contribute to electrolyte abnormalities and dehydration leading to prerenal azotemia.

Intestinal intussusceptions are a recognized complication of CPV infection.[5] Puppies with refractory vomiting and diarrhea may need abdominal radiographs to rule out such obstructions.

Treatment

No treatment directed at the virus itself exists, so therapy revolves around supporting effective circulating volume, controlling secondary bacterial infections, and resting the GI tract.[6] Administration of replacement type crystalloid fluids such as lactated Ringer's or 0.9% saline at volumes sufficient to restore and maintain hydration in the face of ongoing fluid losses is a key element of therapy. Supplementation of fluids with potassium and dextrose may be needed to maintain normal serum potassium and glucose concentrations in ill puppies. Administration of crystalloid fluids may contribute to the development of anemia and hypoproteinemia as a consequence of rehydration in conjunction with previous and ongoing enteric blood loss. Puppies that become severely anemic are candidates for blood transfusions, with whole blood preferred for animals that are both anemic and hypoproteinemic. Colloid administration may be indicated in puppies that are hypoproteinemic but not anemic enough to require erythrocyte support.

Puppies with vomiting and diarrhea are typically maintained NPO (nothing by mouth) until such signs have resolved; partial parenteral nutrition may be considered for nutritional support of these animals.[6] Parenteral administration of broad-spectrum antimicrobials with good gram-negative spectra is considered a key aspect of treatment. Good combinations include an aminoglycoside or fluoroquinolone with a beta lactam in the penicillin (amoxicillin, ampicillin) or first-generation cephalosporin families. Fluaroquinolones may cause cartilage abnormalities if administered to puppies.

Other considerations in the supportive care of affected dogs include control of persistent vomiting with antiemetic drugs such as metoclopramide, phenothiazine derivatives (e.g., chlorpromazine), or serotonin antagonists (e.g., ondansetron), although the latter category of drugs is comparatively expensive. Administration of hyperimmune or antiendotoxin serum has also been advocated.[6] Use of recombinant human granulocyte colony–stimulating factor (rHuG-CSF) has been suggested as an adjunctive treatment of neutropenic dogs to improve neutrophil counts. However, one study of a small number of dogs suggested no clinical benefits in recipients of rHuG-CSF as compared with a control group, and an additional study found that peak endogenous granulocyte colony–stimulating factor (G-CSF) concentrations in CPV-infected dogs occurred at the peak of neutropenia, raising the question as to whether higher concentrations of G-CSF would be of any additional benefit.[7,8] Given the expense of rHuG-CSF, its use is not easily justified. Glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDS) may be considered for use in puppies suspected of endotoxemia or sepsis, although their benefits need to be carefully weighed against their potential risks.

Once vomiting has stopped, patients may be offered water. If no more vomiting occurs, food may then be offered. Diets in the initial feeding period should be easily digestible, low-fat foods because villus structure and function may require a number of days to return to normal. A number of diets are commercially available for the benefit of patients recovering from gastroenteritis. Administration of anthelmintics is appropriate at this time as well.

Given adequate supportive care, many affected puppies survive infection. Once recovered, puppies are considered immune to reinfection for long periods—possibly for life.

Prevention

The cornerstone of prevention of CPV infection is vaccination. CPV vaccines are available in live or killed forms, with the latter sometimes used in breeds considered at greater risk of clinical CPV infection, in pregnant animals in need of vaccination, or animals with diminished immune function. Live-virus vaccines produce an asymptomatic infection with a longer duration of immunity than is considered achievable with inactivated vaccines. The use of low-passage (increased antigenicity), high-titer (larger viral inoculum) vaccines incorporating highly immunogenic CPV-2 strains is advised for most dogs to provoke a protective immune response in the presence of maternal antibodies. Recommended schedules are to begin vaccinations at 6 weeks of age with boosters at 9 and 12 weeks of age. For breeds such as Doberman pinschers, Rottweilers, or others that are considered to be at greater risk of infection, an additional booster vaccination around 15 to 16 weeks of age or measurement of serum neutralization or hemagglutination inhibition (HI) antibody concentrations has been recommended. All dogs should receive a booster vaccine 1 year after completion of the initial series. The frequency of vaccination recommended in adult dogs is a subject of some controversy, and support for extending vaccine intervals beyond 1 year exists.[9] Recent recommendations from a canine vaccine advisory board are for adult dogs to receive boosters to CPV every 3 years.[10] The interval chosen should reflect assessment of the risks and benefits of vaccination for each patient. Measurement of serum neutralization or HI titers may be considered as a guide to dictate the need for vaccination because, in general, higher serum titers tend to correlate with protection from infection.

CANINE CORONAVIRUS

Cause and Epidemiology

Canine coronavirus (CCV) is an enveloped single-stranded RNA virus in the family Coronaviridae. CCV can infect many species of canids. The virus is relatively stable in the environment but can be disinfected by many compounds. The virus is spread primarily by the fecal-oral route to susceptible dogs.

Pathophysiology

CCV infects epithelial cells in the villus tips of the small intestine. A malabsorptive diarrhea results as a consequence of loss of villus surface area. After infection, CCV is shed in the feces for 6 to 9 days, but the duration of shedding can be longer in some animals. The development of a local intestinal immune response terminates clinical signs and ultimately viral shedding.

Clinical Signs

Diarrhea is the principle clinical sign in clinically affected dogs; blood in the feces is an infrequent finding. Vomiting may be seen before or after diarrhea in some animals. Anorexia and lethargy are common features, and if vomiting and diarrhea are severe, dehydration may ensue. Clinical disease from CCV is considered infrequent compared with other viral enteropathies and is usually more severe in neonatal animals, with diminishing severity of clinical disease in older animals. Clinical signs abate after 7 to 10 days in most dogs, but the clinical course may be longer in dogs that develop secondary complications or infection.

Diagnosis

The definitive diagnosis of CCV historically has required the demonstration of virus in the stool, usually by electron microscopy. PCR-based techniques, although not yet commercially available, have been developed as a means to detect viral nucleic acid in the stool.[11]

Treatment
Treatment of CCV is primarily supportive during the time needed for the disease to run its natural course. Dehydrated animals may require parenteral fluids. The role of antibiotics in the treatment of CCV has not been assessed. The use of antibiotics in dogs with diarrhea, though not universally accepted, has been supported, because bacteria may be primary or secondary pathogens and attempts to define viral causes may not always be made.[12]

Prevention
CCV vaccines are available, but efficacy of protection is questioned.[10] CCV vaccines are not considered core vaccines, but tend to be reserved for animals going into situations where the risk of exposure may be higher (kennels, shows).

CANINE ROTAVIRUS

Cause and Epidemiology
Canine rotavirus enteritis is most often caused by a group A rotavirus in the family Reoviridae, which are nonenveloped double-stranded RNA viruses. Recently, group C rotaviruses, which are more commonly found in other species such as pigs, have been documented in diarrheic dogs.[13] Infection usually occurs via the fecal-oral route, and causes subclinical or mild gastroenteritis in young animals, especially puppies less than 14 days of age. A high seroprevalence is found in adult dogs. Compared with other enteric viruses, clinical disease caused by rotavirus appears to be uncommon.[12,14]

Pathogenesis
After exposure, rotavirus infects epithelial cells of the villus tip of the jejunum and ileum. Loss of villus epithelial cells ensues with development of villus atrophy. Virus is shed early as infected, necrotic epithelial cells are sloughed from the villus.

Clinical Signs
Anorexia, vomiting, and mild diarrhea, which can occasionally be bloody, are the typical clinical signs of rotaviral gastroenteritis. Recovery is expected in most animals within 5 to 7 days of onset of clinical signs.

Diagnosis
A variety of tests to detect rotaviral antigens are commercially available but are not commonly used in small animal practice. Other methods to obtain a definitive diagnosis include demonstration of virus in stool samples by electron microscopy or PCR.

Treatment
Therapy of rotavirus gastroenteritis is supportive care, with attention to maintenance of hydration status the key element in puppies with anorexia and vomiting.

Prevention
No vaccine is currently available for prevention of rotaviral infection.

CANINE ADENOVIRUS

Cause and Epidemiology
Canine adenovirus type 1 (CAV-1), a nonenveloped double-stranded DNA virus in the Adenoviridae family, is the cause of infectious canine hepatitis (ICH) and causes disease in domestic and wild canids and bears. The virus is relatively hardy, surviving in the environment for days to months, and is resistant to most disinfectants except quaternary ammonium compounds. Infection occurs after oronasal exposure to infectious secretions.

Pathogenesis
After exposure, CAV-1 replicates in lymphoid tissue of the tonsils and area lymph nodes. A viremia follows, leading to infection of other tissues. Direct cytopathic effects of the virus in the liver, eyes, and kidney contribute to early clinical signs, which can become apparent in naïve dogs 4 to 7 days after exposure. The extent of hepatic necrosis is a function of the level of antiviral antibody present at the time of infection: animals with minimal antibody exhibit extensive necrosis that is often fatal; dogs with high levels of antibody exhibit minimal clinical signs; and animals with intermediate antibody levels are susceptible to persistent hepatic inflammation. Clinical signs of anterior uveitis initially develop as a consequence of infection of corneal endothelial cells, then by inflammation provoked by deposition of immune complexes as antibody responses to the virus increase. Virus is shed during the acute infection in all body secretions including saliva, stool, and urine; excretion of virus in urine can persist for months after infection, but urinary virus is not thought to contribute greatly to transmission.

Clinical Signs
Initial clinical signs include fever, depression, and lethargy, with later development of abdominal discomfort, mucous membrane pallor, and inflammation of the tonsils and pharynx with tonsillar and cervical lymph node enlargement. Abdominal discomfort and hepatomegaly will be detected in some dogs, and coughing may be seen in cases of respiratory disease. Vomiting and diarrhea can also occur. In severe cases, petechial and ecchymotic hemorrhages may develop from coagulation abnormalities secondary to hepatic dysfunction and DIC. Icterus is uncommon despite the presence of hepatic necrosis. Neurologic signs may be seen as a consequence of hepatic encephalopathy or central nervous system (CNS) infection; measurement of bile acids or plasma ammonia concentrations, if elevated, would support a contribution of hepatic encephalopathy to observed neurologic signs. Dogs with severe disease may die within hours after showing clinical signs, whereas dogs with less severe disease may exhibit clinical improvement 5 to 7 days after onset of clinical signs.

Diagnosis
The diagnosis of CAV infection is usually based on finding evidence of acute hepatic disease in a dog with a poor vaccination history. No specific laboratory abnormalities pathognomonic for CAV infection are seen. There may be leukopenia or leukocytosis depending on whether the patient is seen early or later in the course of disease. Thrombocytopenia is possible and could contribute to coagulopathies in the setting of DIC or abnormal platelet function. Increases in alanine aminotransferase (ALT) and alkaline phosphate (ALP) activity are expected, but the magnitude of activity will depend on the extent of hepatic necrosis and the timing of sample collection. Prolongations of OSPT and APTT are common as a result of decreased hepatic synthesis of coagulation factors, DIC, or both. Proteinuria is also expected as a sequel to renal injury during viremia or immune complex injury later in the course of disease.

Definitive diagnosis of CAV infection can be established if needed through serological, viral isolation, or immunohistochemical techniques. Inclusion bodies observed during cytologic or histologic examination of tissue, particularly the liver, can be strongly supportive of the diagnosis.

Therapy
No specific treatments exist that address the virus, and therapy is directed at provision of supportive care and managing clinical signs and complications. Intravenous fluid therapy to

replace losses from vomiting or diarrhea is important, as is administration of blood products (whole blood, fresh or fresh frozen plasma) to manage the complications of hemorrhage and DIC. In patients with neurologic signs from hepatic encephalopathy, administration of lactulose via enema (or orally if the patient is not vomiting and can tolerate oral medications) can help reduce circulating concentrations of encephalotoxins.

Prevention

As with other important canine viral diseases, vaccination is the foundation of prevention of CAV-1 infection. Most commonly used vaccines to CAV-1 use CAV-2 isolates which, through the production of cross-reactive antibodies, will elicit a protective immune response without the complications, such as corneal edema, seen more often after vaccination with vaccines using CAV-1 isolates. The duration of immunity after immunization with CAV-2 MLV vaccines is likely long, and revaccination every 3 years after a routine initial series and booster at 1 year of age has been recommended.[10]

CANINE DISTEMPER VIRUS

Cause and Epidemiology

Canine distemper virus (CDV) is caused by an enveloped single-stranded RNA *Morbillivirus* in the Paramyxoviridae family and is closely related to viruses that cause measles, rinderpest, and distemper in other animals. CDV is capable of infecting a large variety of species including dogs, mustelids (e.g., ferrets, skunks), and procyonids (e.g., raccoons). The virus does not survive for long periods outside of the host and is susceptible to inactivation with a number of disinfectants such as phenolic or quaternary ammonium compounds. CDV is most often spread by inhalation of virus particles in respiratory aerosols or aerosols of other infected secretions such as urine.

Pathogenesis

After exposure, virus infects and replicates in macrophages, which spread virus to regional lymph nodes and tonsils, with virus reaching a peak in these tissues by 2 to 4 days after inoculation. By around 4 to 6 days postinfection (PI), virus has spread to, and is multiplying in, the stomach, small intestine, spleen, and hepatic macrophages. The widespread increase in virus production is associated with initial fever and lymphopenia.

After about 9 to 14 days PI, the outcome of infection is dictated by the strength and type of the host's immune response. Dogs with poor immune responses develop viral infection of several additional tissues including skin, CNS, and glandular and epithelial organs. Such animals generally exhibit severe clinical signs and are likely to die as a result of infection. Those animals that recover from the initial clinical signs maintain virus in tissues and are likely to subsequently develop clinical signs of CNS disease.

In animals that mount an intermediate level of immune response, mild or clinically silent infection may develop, with virus persisting in the lungs, skin, or CNS. Such animals may undergo a complete recovery or may develop signs of CNS disease. Animals that mount strong immune responses are unlikely to develop signs of systemic infection but may still develop signs of CNS disease.

The pathogenesis of neurologic disease in CDV-infected dogs is complex. Dogs, especially those that are very young or immune-suppressed, may develop acute encephalitis, which is attributed to direct viral injury. Chronic encephalitis appears to be a consequence of inflammatory responses to viral antigens in CNS cells, with macrophage activation and release of cytotoxic mediators playing a role in destruction and demyelinization of CNS cells.

Clinical Signs

The severity of the clinical course is a function of the age of the animal at the time of infection, the viral strain, and immune responses. Affected dogs may be lethargic, anorexic, and febrile. Animals with respiratory infection may exhibit serous or mucopurulent oculonasal discharge and cough. More severely affected animals can show an initial conjunctivitis followed by cough, vomiting, and diarrhea that can be bloody or mucoid.

Neurologic signs may develop starting 1 to 3 weeks after recovery from systemic signs or can develop many more weeks to months later. Curiously, certain features of clinical disease tend to correlate with the likelihood of developing neurologic disease. Dogs that develop pustular skin lesions are less likely to develop CNS disease than dogs that exhibit hyperkeratosis of the nasal planum and digital footpads, which is frequently associated with the development of neurologic signs. Neurologic abnormalities can reflect lesions in any CNS site and include seizures, ataxia, hypermetria, and paraparesis or tetraparesis. Myoclonus, either generalized or focal, is a common clinical sign and is strongly suggestive of CDV infection.

Other clinical signs that can be seen include anterior uveitis and chorioretinitis; recovered animals may have hyper-reflective retinal lesions that develop from retinal atrophy and scarring. Optic neuritis may cause blindness or mydriasis; blindness can also result from serous retinal detachments. Some dogs, especially young large breed dogs, are susceptible to metaphyseal osteosclerosis of long bones, which is typically not associated with lameness. Puppies infected in utero or as neonates can develop CNS signs early in life, or have enamel hypoplasia if infected before the eruption of permanent teeth. Abortions or neonatal death may also be appreciated.

Diagnosis

Diagnosis of CDV is usually a clinical one, relying on compatible clinical signs in a young animal with a poor vaccination history. However, CDV should not be excluded as a differential in a dog with compatible clinical signs if the animal has a vaccination history.[15] No pathognomonic laboratory abnormalities are seen. Lymphopenia is the most consistent CBC abnormality. There may be CDV inclusions in monocytes, lymphocytes, neutrophils, or erythrocytes seen during examination of a stained blood smear. Biochemical profile abnormalities can include hypoalbuminemia and hypoglobulinemia. The CSF may have (1) increased numbers of lymphocytes and monocytes and increased protein, (2) increased protein only, or (3) may be normal.[15]

Dogs with respiratory disease may have interstitial or alveolar patterns on thoracic radiographs. Radiographs of long bones in lame animals may have metaphyseal lesions consistent with hypertrophic osteodystrophy.

Animals with CDV neurologic disease can be diagnostic challenges if no history of systemic signs exist. Definitive diagnosis of CDV can be made by demonstration of higher concentration of CDV antibody in the CNS as compared with the serum, although not all animals will have CSF antibodies.[15] Demonstration of viral antigen in cells or tissues by immunohistochemical methods such as fluorescent antibody (FA) testing of conjunctival swabs or blood smears also confirms the diagnosis. Recently, reverse-transcriptase polymerase chain reaction (RT-PCR) assays have proven sensitive and specific for detection of CDV in experimental settings and can be performed on virtually any tissue type.[16] Such assays performed on whole blood, serum, or CSF may be more sensitive for detection of CDV than antigen or antibody demonstration techniques. The RT-PCR is not commercially available but holds future promise as diagnostic tool.

Treatment
Treatment of dogs with CDV is largely supportive. Parenteral administration of fluids may be needed in dogs with vomiting or severe diarrhea. Animals with secondary bacterial bronchopneumonia or other infections are candidates for antibiotics. Seizure control with diazepam, pentobarbital, or potassium bromide may be needed. The prognosis for dogs with neurologic disease is considered guarded to poor.

Prevention
The key to CDV prevention is vaccination. Current MLV or recombinant vaccines are effective at inducing immunity. Distemper-measles vaccines may be given to high-risk puppies 4 to 12 weeks of age to provide protection in the face of maternal CDV antibodies. The duration of immunity after immunization with MLV CDV products is considered long lasting, and vaccination intervals of 3 years have been supported.[10]

Immunization of dogs with MLV CDV vaccine has been associated with postvaccinal complications, the most common of which is encephalitis, which can produce clinical signs of neurologic disease and variable neurologic abnormalities 7 to 14 days after vaccination. Though not widely available, molecular techniques such as restriction fragment length polymorphism analysis may help distinguish clinical disease caused by vaccine isolates from that caused by field isolates.[17]

RABIES VIRUS

Cause and Epidemiology
Rabies virus is an enveloped single-stranded RNA virus in the family Rhabdoviridae. Rabies virus is capable of infecting all mammals, although differences exist in susceptibility to infection. Skunks, wild dogs, bats, raccoons, and cattle are most susceptible, whereas domestic dogs, cats, horses, sheep, and goats are considered to have moderate susceptibility. In the United States the principle reservoirs of rabies virus for domestic dogs are skunks, raccoons, and foxes.[18] The virus is not stable in the environment and is inactivated by most common disinfectants. Rabies virus is spread primarily by inoculation of a naïve animal with infected saliva, thus bite wounds are the most common mode of rabies virus transmission. Transmission by ingestion of infected tissue, inhalation of airborne virus, and transplacental transmission have been described but are considered rare.

Pathogenesis
After inoculation, virus replicates in local tissue then enters nerve endings through neuromuscular junctions or breaches in the axonal sheath of injured nerve fibers. Virus spreads along axons in the peripheral nerves to the CNS. Once the CNS has been entered, virus spreads among adjacent axons to involve more neurons and spreads more rapidly to the brain stem and then forebrain. The virus replicates in the CNS and moves out of the CNS to other tissues along peripheral nerve fibers. Infection of salivary glands occurs during this time, and thus virus in the saliva is a reflection of CNS infection. Virus can be shed in the saliva up to almost 2 weeks before neurologic signs develop. In rare instances documented in experimentally infected dogs, virus excretion may persist for several months after resolution of neurologic signs.

Clinical Signs
Rabies can be variable in its clinical presentation, and suspicion can be delayed because of atypical signs. Clinical suspicion may be further delayed because of variable incubation periods after inoculation of virus; incubation periods reflect the size of the viral inoculum, the extent of nerve supply to injured tissue, the distance from the site of inoculation to the spinal cord, and host factors such as age and immune responses. Clinical signs often start with a prodromal phase of 2 to 3 days that is characterized by nervousness, anxiety, or other behavior changes. There may be paresthesia at the site of inoculation. As clinical signs progress, forebrain signs of irritability, restlessness, pica, as well as photophobia and hyperesthesia may be apparent. These clinical signs, often referred to as the *furious form of rabies*, can progress to incoordination, seizures, and death. Paralytic or dumb forms of rabies are characterized by lower motor neuron disease beginning in the area of initial injury and eventually involving the entire CNS. Dysphagia from paralysis of the muscles of deglutition causes accumulation of saliva in the oral cavity, which can be a source of infection to owners and veterinarians attending to such patients. Death follows as the animal develops coma and respiratory paralysis.

Diagnosis
Rabies should be suspected in any animal with an uncertain vaccination history exhibiting neurologic or behavioral abnormalities. Definitive diagnosis hinges on demonstration of virus in the brain, with direct FA testing considered the preferred method in many laboratories. Heads or bodies of suspect animals should be submitted to appropriate diagnostic laboratories without freezing to avoid damage to brain tissue associated with thawing. Detection of intracellular inclusions (Negri bodies) or direct FA testing of sensory vibrissae in the maxillary area is considered insensitive as compared with direct FA of nervous tissue. The application of molecular techniques such as the PCR may be of benefit in situations where brain tissue is not available or is not suitable for FA testing and offers potential advantages in detecting low levels of virus or virus in saliva.

Treatment
Treatment of animals suspected of having rabies is not recommended because of the human health hazard posed by such animals. Asymptomatic animals that are considered suspects should be isolated according to local laws and regulations or euthanized for collection and submission of brain tissue to diagnostic laboratories.

Prevention
Vaccination is an effective measure in the prevention of rabies in dogs and cats. Most commonly used vaccines contain inactivated virus given initially to animals older than 3 months of age with a booster at 1 year of age. The need for subsequent boosters either annually or every 3 years is predicated upon the product used and local laws regarding rabies prophylaxis. Recent epidemiologic studies have suggested that unvaccinated, owned animals represent the largest population of rabid dogs and cats.[18] Such findings emphasize the importance of client education, especially in areas in which rabies is endemic.

PSEUDORABIES

Cause and Epidemiology
Pseudorabies is caused by an enveloped double-stranded DNA virus in the alpha-herpesvirus family. Despite the presence of an envelope, pseudorabies virus is relatively stable in the environment. Affected dogs usually have a history of having been in contact with pigs, which are the main reservoirs of the virus. Most cases in dogs are believed to result from the ingestion of infected raw pork.

Pathogenesis
After ingestion, the virus enters nerve endings in the mucosa and spreads to the brain along nerve axons. Inflammation and

functional abnormalities in brain cells result in neurologic signs after an incubation period of around 3 to 6 days.

Clinical Signs
Signs of neurologic dysfunction are common features of the disease.[19] Neurologic abnormalities can be variable and have included ataxia, abnormal pupillary light responses, restlessness, trismus, and cervical rigidity. Ptyalism, tachypnea, and hyperpnea are common. Pruritus of the head and neck area can lead to self-induced excoriation. In some dogs, vomiting and diarrhea are the predominant signs. The clinical course of pseudorabies infection in dogs is usually swift, with most dogs dying within 48 hours after onset of clinical signs of acute neurologic disease.

Diagnosis
The diagnosis is suspected based on history of exposure to pigs or pork products and on clinical signs. Definitive diagnosis can be established by demonstration of virus by FA or PCR in the brain and tonsil.

Treatment
Treatment is supportive, although the fulminant nature of the clinical disease and poor prognosis have not seen many animals survive the infection.

Prevention
No approved pseudorabies vaccine exists for dogs, so prevention relies on limiting exposure of dogs to pigs or preventing ingestion of contaminated raw pork products.

CANINE PARAINFLUENZA VIRUS AND ADENOVIRUS-2

Cause and Epidemiology
Canine parainfluenza virus is a single-stranded RNA virus in the Paramyxoviridae family, and canine adenovirus-2 (CAV-2) is in the family Adenoviridae. The viruses are transmitted primarily from inhalation of aerosolized droplets from infected dogs and are part of a complex of pathogens causing infectious tracheobronchitis in dogs. Dense populations such as in kennels or shelters facilitate viral spread to naïve dogs.

Pathogenesis
Clinical signs develop after an incubation period of 3 to 10 days, during which time virus is replicating in epithelial cells of the upper respiratory tract of infected dogs, causing epithelial destruction. Damage to the epithelial barrier and disruption of normal respiratory defenses afforded by an intact epithelium predispose to infection with other respiratory tract pathogens such as mycoplasma or various bacteria. Viral shedding can occur for approximately 1 week after infection.

Clinical Signs
A hacking cough with a terminal retch and serous nasal discharge are the typical clinical signs of viral infection. Coughing bouts are often easily elicited with tracheal palpation or manipulation, and can be paroxysmal in nature. Coughing may produce foamy white mucus. Clinical signs are typically of short duration and often subside by 7 days after onset, although occasional dogs may exhibit clinical signs for up to 9 to 10 days.

Diagnosis
The diagnosis is typically established by the presence of clinical signs in an otherwise healthy animal with a history of risk factors for infection. No pathognomonic laboratory abnormalities are seen in affected dogs; thoracic radiographs should be normal unless severe infection creates a secondary bronchopneumonia from other respiratory pathogens or the animal has pre-existing respiratory disease. Isolation of virus from nasopharyngeal or tracheal swabs can establish a definitive diagnosis but is rarely performed in clinical practice.

Treatment
No specific treatment is effective for reducing viral loads, so treatment is largely supportive. Administration of antimicrobials such as amoxicillin, ampicillin, or trimethoprim-sulfa may limit the development of secondary bacterial infections that can prolong the clinical course. Antimicrobials are frequently used empirically because of the clinical difficulty in distinguishing clinical signs of viral infection from clinical signs caused by other upper respiratory pathogens such as *Bordetella bronchiseptica*. Judicious short-term use of anti-inflammatory doses of glucocorticoids or administration of cough suppressants, such as hydrocodone or butorphanol tartrate, may help ameliorate cough and improve patient comfort but are unlikely to shorten the clinical course.

Prevention
Vaccination is the mainstay of prevention of viral respiratory infection. Greater protection is afforded animals that receive MLV parainfluenza vaccines intranasally as compared with parenterally administered vaccines. CAV-2 vaccines are usually part of core vaccine programs because they provide cross protection to CAV-1.

CANINE HERPESVIRUS

Cause and Epidemiology
Canine herpesvirus (CH) is an enveloped, double-stranded DNA virus that infects domestic or wild canids. The virus is transmitted primarily during birth as a puppy passes through the birth canal, contacting infectious secretions of an infected bitch; transmission may also occur transplacentally, and via oronasal secretions from the infected mother. The virus is susceptible to inactivation with most common disinfectants and is not stable at usual environmental temperatures.

Pathogenesis
After oronasal exposure of neonatal puppies, CH first replicates in the epithelial cells of the oropharnyx and in the mucosa of the tonsils. Virus subsequently enters macrophages, which spread virus hematogenously to other tissues including the lymph nodes, spleen, adrenal glands, kidneys, lungs, liver, and CNS. The lower body temperature of neonates, in conjunction with a limited capacity to mount a febrile response, facilitates systemic spread of the virus, which replicates well at lower body temperatures but poorly at higher temperatures.

In older animals, infection tends to be confined to the respiratory and genital tracts, and signs of systemic infection do not develop. Viral DNA persists in neurons of the trigeminal ganglia and lymphocytes in the retropharyngeal lymph nodes.[20]

Clinical Signs
Abortions, or litters of stillborn puppies, may be seen after transplacental infections. Puppies less than 2 to 3 weeks of age are most likely to develop clinical disease. After an incubation period of 3 to 6 days, infected puppies become ill with signs of persistent crying, hypothermia, soft stool, and petechial hemorrhages in mucous membranes. Petechial hemorrhages in abdominal organs and lungs are also typical lesions observed on necropsy of infected puppies. Nursing stops and death usually follows 24 to 72 hours after the onset of clinical signs. Older puppies develop mild signs of respiratory disease with

spontaneous recovery and latent infections that may emerge later as a cause of neurologic disease, with signs of ataxia, blindness, or central vestibular disease most common. Infection in adult dogs is usually associated with vaginal or preputial hyperemia, hyperplasia of vaginal mucosal lymphoid follicles, and sometimes submucosal hemorrhages.

Diagnosis
Diagnosis is made by observation of clinical signs in puppies of susceptible age in conjunction with necropsy lesions. Viral inclusion bodies may be observed in cells surrounding areas of necrosis and hemorrhage. Definitive diagnosis of CH infection centers on demonstration of virus, viral antigen, or nucleic acids by electron microscopy, immunohistochemical techniques, or PCR of tissues or cell cultures inoculated with infected tissue. Serologic testing for neutralizing antibodies confirms exposure but does not necessarily indicate active infection.

Treatment
Treatment is supportive but often ineffective at preventing neonatal losses. Injection of immune sera pooled from bitches that have had recent losses of litters may help reduce mortality during outbreaks. Keeping puppies warm and hydrated may lessen mortality in affected litters, primarily by limiting the spread of infection amongst uninvolved puppies.

Prevention
Currently no vaccine is available for CH. Spread of infection may be limited by not breeding infected dogs, although discrimination of infected versus exposed dogs is not easily achieved. Females that have previously lost litters to CH infection may raise healthy litters; thus caesarian sections or artificial insemination are not considered useful approaches to limit the spread of infection.

CANINE ORAL PAPILLOMA VIRUS

Cause and Epidemiology
Canine oral papillomavirus (COPV) is a nonenveloped double-stranded DNA virus in the family Papillomaviridae and is related to papillomaviruses affecting other species, including people. The virus is relatively stable in the environment.

Pathogenesis
The virus primarily infects cells in the basal layer of the epithelium of the oral cavity, penis, vulva, conjunctiva, and skin, and it is likely that different papillomaviruses account for differences in lesion distribution.[21] Once infected, basal cells increase mitotic activity to produce the characteristic warts.

Clinical Signs
The primary clinical sign of COPV infection is the appearance of papillomas, or warts, in the oral cavity or other epithelial sites. Young dogs are clinically affected more frequently than older animals. Papillomas develop 4 to 8 weeks after infection, and they typically regress within 4 to 8 weeks (and occasionally longer) after appearance when cell-mediated immune responses cause T-cell infiltration into the wart.[22] Humoral immune responses, although capable of preventing infection, do not seem to play a role in regression of lesions. Although lesions can become quite extensive, especially in the oral cavity, in a given dog, the functional impact of papillomas to the affected animal is usually minimal unless warts develop in locations that lead to dysphagia or respiratory obstruction.

Diagnosis
Diagnosis of COPV is usually based on the observation of characteristic lesions. Viral antigen in lesions can be documented by immunohistochemical techniques, electron microscopy, or PCR-based assays.

Treatment
Because the disease usually regresses spontaneously in the majority of dogs, treatment is not usually needed unless, as noted previously, warts compromise eating or respiration. In such cases, warts can be removed by surgical excision, cryosurgery, or electrosurgery. Refractory cases may benefit from autogenous vaccination in which a wart is removed, a crude vaccine is made, and then injected into the same dog.[22]

Prevention
No preventive vaccine is available for dogs. Dogs that have recovered from COPV are generally immune to reinfection, although occasional dogs, presumably dogs with immune defects, may be susceptible to repeated bouts of clinical disease.

EMERGING VIRUSES OF INTEREST

West Nile Virus
The West Nile virus (WNV) is a nonenveloped single-stranded RNA virus in the family Flaviviridae. WNV is found worldwide and is maintained in natural settings via transmission from infected to naïve birds via mosquitoes.[23] WNV has emerged recently in the United States as a cause of meningoencephalitis in people and horses, although occasionally other species, including dogs, can develop clinical disease. Epidemiologic studies have demonstrated that seropositive dogs can be found in areas where human infection is endemic.[24] It is currently suspected that nonavian species that become infected from the bite of an infected mosquito do not readily support viral replication leading to a dead-end infection. The pathogenesis of the infection in dogs is unknown. Although to date there have been no published reports describing canine infections, anecdotal reports suggest that clinically affected dogs develop an acute neurologic disease. Definitive diagnosis requires demonstration of viral antigen or nucleic acid in brain tissues. No specific treatments exist beyond supportive therapy, and no approved vaccine is available to prevent infection in dogs.

Bornavirus
The bornavirus (BV) is a enveloped single-stranded RNA virus in the family Bornaviridae. BV causes a fatal disease of the CNS in horses and other animals. Clinical disease in dogs appears to be relatively uncommon. However, reports documenting cases in Europe and Japan are relatively recent, and more cases may emerge as knowledge of the infection increases. The pathogenesis of the disease in dogs is unknown, but clinical signs in dogs have included tremors, salivation, mydriasis, and circling.[25,26] The infection is suspected based on the histopathologic observation of nonsuppurative encephalomyelitis predominantly in gray matter of the brain. Demonstration of viral RNA by in situ hybridization or PCR-based assays has provided definitive diagnosis.

CHAPTER 170

Feline Leukemia Virus

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VIROLOGY

Household clusters of lymphoma and lymphocytic leukemia were observed among young cats for many years, but it was not until the discovery of retrovirus particles in a leukemic cat in 1964 that an infectious cause was considered likely. Subsequently, feline leukemia virus (FeLV) was isolated and shown to be capable of transmitting lymphocytic neoplasia among cats. An indirect fluorescent antibody (IFA) test, developed in 1973 to detect antigenemia, made the clinical screening of privately owned cats possible. The mass testing that followed demonstrated that the virus was present at low levels throughout the world's domestic cat population, that it appeared to be spread both vertically (from queen to fetus) and horizontally (from cat to cat), and that infection was associated with a variety of illnesses in addition to neoplasia, including bone marrow suppression and immunodeficiency.

FeLV is a retrovirus; its genetic material is transmitted from host to host as RNA. In infected cells, DNA copies of the virus are transcribed, and it is these copies that are inserted randomly into the host genome. Once this DNA provirus is integrated, cell divisions will result in daughter cells that also contain the viral DNA. The virus encodes several major protein groups: *gag* (group-specific antigens), *pol* (reverse transcriptase), and *env* (envelope). One of the *gag* proteins, p27, is abundant in the plasma of infected cats and in the cytoplasm of individual infected cells. This protein is the basis for most currently used diagnostic tests. The envelope protein gp70 defines the virus subgroup and appears to be important for inducing immunity.

EPIDEMIOLOGY

The FeLV infection rate of cats is similar throughout the world, ranging from 1% to 8% of healthy cats. Prevalence in feral cats in the southeastern United States is 4%. To date, no large serosurveys have been performed on healthy pet cats in the United States. An infection rate of 21% among symptomatic cats was reported in a survey of 27,976 clinically ill and "at risk" cats, compared with 7% of asymptomatic cats; overall prevalence in this high-risk population was 13%. The study also found that males (15%) were more likely to be infected than females (11%) and that risk of infection was higher in mixed breed (13%) than purebred cats (10%) and outdoor (20%) compared with indoor cats (8%). The prevalence of FeLV was highest in cats aged 1 to 6 years and higher in cats from multicat households than single cat households. Similar results were reported in a survey of cases referred to veterinary medical teaching hospitals from 1972 to 1998. Of 409,417 cats seen at the teaching hospitals, 8756 (2.1%) were diagnosed with FeLV. Prevalence was greatest in male cats, mixed breed cats, and cats aged 2 to 7 years.

Susceptibility to FeLV infection is highest in young kittens, and resistance develops with age. After experimental inoculation with FeLV, 70% to 100% of neonatal kittens remain persistently infected, compared with 30% to 50% of 8- to 12-week-old kittens and 10% to 20% of adolescent and adult cats. This age resistance can be abolished by corticosteroid administration. When susceptible kittens were introduced into households with endemic FeLV, 70% became infected within 5 months, whereas only 18% of adult cats became infected within 5 years under the same circumstances. In nature, the prevalence of anti-FeLV antibodies increases with age, indicating continuous risk of exposure to FeLV throughout life. However, most cases of FeLV are diagnosed in cats less than 4 years of age. Taken together with the antibody serosurveys, this suggests that exposure to FeLV accumulates with age but that susceptibility to infection simultaneously decreases.

The prevalence of FeLV has been decreasing since the mid-1980s. Widespread test and removal programs have eliminated FeLV from most breeding facilities. Testing of cats at animal shelters prior to adoption and separating infected cats are now common practices. Several FeLV vaccines are available and may also be contributing to the decline of FeLV prevalence. Concurrent with the decline in FeLV is a decline in FeLV-associated diseases, particularly lymphoma.

FeLV infection is slightly more common among male cats than females. Unlike FIV, which is spread primarily by biting during fights, FeLV is passed vertically from infected queens to kittens and horizontally among communal cats with prolonged close contact. The virus is shed in high amounts in the saliva and milk and to a lesser extent in urine and other secretions. Sharing food and water dishes, mutual grooming, and using common litter areas all contribute to virus spread. The wandering and fighting behavior of unneutered males is an additional risk factor for infection among this group.

Infected queens can pass the virus to their offspring in utero. Reproductive failure, taking the form of fetal resorptions, abortions, and neonatal deaths, is common in this situation, although up to 20% of vertically infected kittens may survive the neonatal period to become persistently infected adults. Queens may also infect their kittens after birth via their milk or during grooming. The distinction between vertical transmission from queen to kitten and horizontal transmission among a family group is a somewhat arbitrary one from a clinical perspective. It is common, however, to observe that newborn kittens from persistently or latently infected queens may test negative at birth, only to seroconvert one by one over the following weeks to months. Thus if the queen or any one of her litter tests positive, the entire family should be treated as suspect and isolated from other uninfected cats until their status is resolved.

DIAGNOSIS

Routine screening for FeLV infection became available when the IFA was developed in 1973. With enzyme-linked immunosorbent assay (ELISA) tests developed several years later, clinicians gained the ability to perform rapid and reliable in-house testing. Later, other immunochromatic lateral flow

tests were developed for in-house use. These tests detect the FeLV core protein p27, which is produced abundantly in most infected cats, and are the mainstay of clinical FeLV testing. Immunochromatic tests are performed on serum, plasma, and whole blood samples. In some studies, higher rates of false positives were recorded when whole blood samples were used, particularly when the samples were hemolyzed. User error contributes to false-positive results and is most likely to occur during the washing steps of kits using a micro-well or wand format. The use of membrane-based tests offers the advantage of eliminating separate washing steps and of including both positive and negative controls for each test sample. Some test systems have been developed for use with tears or saliva samples in place of blood. In general, these tests are not as accurate, and, because the consequences of both false-positive and false-negative test results can be disastrous for individual cats or for multiple cat populations, tears and saliva are not recommended for routine screening.

The IFA detects p27 antigen within the cytoplasm of infected blood cells. Because it requires special processing and fluorescent microscopy, a qualified reference laboratory must perform the IFA. Generally, two or more quality blood or bone marrow smears are air-dried and mailed, unfixed, to the laboratory. The antigen is present at highest concentrations in neutrophils and platelets, and false negatives may result when these two cell lines are deficient. False-positive results may occur when smears are too thick, when background fluorescence is high, and when the test is prepared and interpreted by inexperienced personnel.

Immunochromatic tests, such as ELISA, detect viral antigens circulating freely in the plasma. Because FeLV generally replicates in lymphoid tissue and other sites before the bone marrow, immunochromatic tests may detect infection a few weeks earlier than the IFA. Some cats are apparently able to clear the infection at this stage and may revert to negative status within a few weeks to months. IFA-positive tests indicate that the bone marrow is infected with FeLV. In this case, most cats remain persistently infected for life. In general, immunochromatic tests are considered to be slightly more sensitive, and the IFA is slightly more specific. With either test, however, the reliability (predictive value) of the test is dependent on the prevalence of infection within different populations of cats. For example, FeLV is present in most cats with thymic lymphoma, so a positive test is likely to be accurate in this situation. In a lower-risk population, such as a closed cattery known to be free of FeLV, a positive test should be viewed with more suspicion and additional confirmatory tests should be performed.

Recently the polymerase chain reaction (PCR) test has been used for the diagnosis of FeLV infection. This test differs from earlier screening tests in that it detects viral nucleic acid sequences (RNA or DNA) instead of protein antigens. PCR may be useful in helping to determine the true status of cats with discordant results from other testing techniques and may be the most sensitive test available. Well-equipped and trained laboratories must perform PCR, because inappropriate sample handling can destroy the delicate nucleic acid material or introduce minute amounts of cross-contamination, leading to either false-negative or false-positive results. PCR is capable of detecting FeLV infection in blood, solid tissues, tissue cultures, and fixed specimens. Commercial FeLV PCR tests detect proviral DNA. FeLV provirus sequences have been detected in both transiently and latently infected cats, as well as in apparently uninfected cats that reside with FeLV-infected cats. This indicates that detectable viral fragments are not always associated with productive infection or clinical disease.

Because no test is accurate 100% of the time, and because various testing modalities target somewhat different specimens and disease stages, it is possible to have discordant test results. The challenge for the clinician is to determine which most likely reflects the true status of the cat. For example, it is possible for infected cats to be antigenemic (viral proteins circulating in the blood) but to have negative virus blood cultures or PCR if the active infection is sequestered in different tissue compartments such as the bone marrow or lymphoid system. In one study of cats positive by ELISA but negative by culture, viral DNA was detected by PCR in 13 of 39 samples, indicating that the cats were most likely infected with FeLV.

Immunochromatic tests are preferred for screening, with the IFA recommended for confirmation of positive results. The combination of routine screening and confirmatory tests will accurately determine the FeLV infection status of most cats. Some animals, however, will have repeatedly discordant test results or occult infections that remain undetected. Rarely, some cats that test negative for viremia have been shown to secrete infectious virus in body fluids such as milk and urine. These cats are infectious to other cats but test negative on routine screening tests. It is particularly difficult to know the true status of cats that have been "transiently" infected and have apparently recovered. In surveys conducted prior to the development of FeLV vaccines, most free-roaming cats acquired anti-FeLV antibodies (evidence of at least transient exposure and infection with the virus). Although almost all of these antibody-positive cats were seronegative for viral antigens, it is not possible to know whether they were truly clear of infection, resistant to further exposure, or latently infected.

The American Association of Feline Practitioners (AAFP) has developed recommendations for testing cats for FeLV. It states that the FeLV status of all cats should be known. Identifying infected cats provides an opportunity to prevent the spread of the disease and to institute appropriate health care for infected cats. The AAFP further recommends testing prior to vaccination for FeLV and retesting cats that become ill. Screening tests detect viral antigens (not antibodies), so neither vaccination nor maternal immunity has an effect on test results. Because cats may be in the early stage of infection at the time of the first test, it is further recommended that a follow-up test be performed at least 1 month after the initial test or after a potential exposure to FeLV. Although this interval is adequate for detection of most infections, periods of up to 6 months between exposure to FeLV and positive test results have been reported.

PATHOGENESIS

Horizontal transmission of FeLV among susceptible cats occurs most commonly via the oronasal route and by bite wounds. After mucosal or percutaneous inoculation of FeLV, the virus replicates in local lymphoid tissues. From there, infected cells carry the virus to other target tissues, such as thymus, spleen, and lymph nodes. At this stage of acute viral replication, fever, malaise, diarrhea, and leukopenia are common. In addition, generalized lymphadenopathy may be so marked as to be mistaken for lymphoma. The virus later infects the salivary glands and the mucosal glandular epithelium. These sites of infection may secrete most of the infectious virus that is responsible for horizontal transmission. About the same time, bone marrow cells become involved, producing infected leukocytes and platelets that circulate in the blood. In early infection, viral antigens may be detected in the circulation before the bone marrow is infected. This results in discordant test results (immunochromatic tests positive, IFA negative) and explains the slightly higher sensitivity of the immunochromatic tests. Acute infection may follow one of three courses: (1) a vigorous immune response may eliminate the virus, (2) the virus may be sequestered in an inactive latent form, or (3) persistent viremia may develop. It is difficult to differentiate cats that have cleared infection from those that have latent virus. PCR tests on bone marrow may be more

sensitive than peripheral blood. Initially, latent infections can reactivate naturally or in response to immune suppression. As time passes, latent infections become more difficult to reactivate, even with the administration of high doses of corticosteroids. By 1 year after infection, reactivation of the virus is considered unlikely. If viremia persists more than 16 weeks, or if the bone marrow is infected, as indicated by a positive IFA test result, chances are high that the cat will remain persistently infected, viremic, and infectious to other cats for the remainder of its life. The ability of FeLV to integrate into the host's own genome is one of the most important factors in persistent infection. Once the pool of stem cells becomes infected, true elimination of the virus becomes unlikely.

PREVENTION

When FeLV was first described in the mid-1960s, the highest rates of infection were found in large multicat households and catteries. In contrast, free-roaming cats had lower rates of infection, and cats housed singly indoors were rarely infected. The development of reliable tests allowed cat breeders to implement control programs. A dramatic example was a mandatory test and removal program imposed on all members of a cat breeding society in the Netherlands in 1974. When testing was first implemented, the prevalence of FeLV in purebred catteries was 11%. The rate was reduced to less than 2% within 4 years, and no infected cats have been reported since 1984. Cat fanciers in other countries responded similarly, although on a more voluntary basis, so FeLV is now considered an anomaly in well-run catteries.

The control of FeLV is facilitated by the fragility of the virus outside of the host's body. The virus begins losing viability immediately on dry surfaces and is completely inactivated within a few hours. Environmental contamination from infected cats is easily neutralized by routine disinfectants (detergent, quaternary ammonium, dilute bleach). Indirect exposure between cats at shows or veterinary clinics is not a risk for transmission as long as the cats are not allowed direct contact. FeLV-infected cats do not need to be housed in special isolation rooms at veterinary clinics as long as cats are kept in separate cages. Veterinarians and handlers, however, should take precautions to avoid inadvertent transmission of the virus via contaminated body fluids such as blood, urine, and saliva. Clinical practices that risk nosocomial transmission include serial surgeries performed with the same instruments, reuse of inadequately sterilized needles, reuse of saliva-contaminated endotracheal tubes and dentistry equipment, use of unscreened or latently infected blood donors, and fluid bags shared between patients. The same universal precautions used in human health facilities to prevent the spread of HIV should be incorporated into veterinary practices to prevent the transmission of FeLV and other infectious agents.

FeLV infection is primarily a concern for cats that are social with other cats, because close, intimate contact between cats is optimal for transmission. This type of contact occurs among cats as a result of mutual grooming and sharing of dishes and litter pans. If an FeLV-positive cat is identified in a household, the best method of preventing spread to other cats in the household is to isolate the infected cat in a separate room to prevent the infected cat from interacting with its housemates. Kittens less than 1 year of age are at a greater risk of infection than are adults. If owners choose not to separate housemates, uninfected cats should be vaccinated against FeLV in an attempt to enhance their natural level of immunity. However, it should be understood that FeLV vaccines do not necessarily protect all cats against FeLV infection, and vaccination is not as effective as isolation.

The simplest protection against infection is to keep susceptible cats confined indoors. For cats that are allowed to wander outdoors or that reside with infected cats, vaccination against FeLV may offer protection. Because no standard method exists to evaluate the efficacy of FeLV vaccines in challenge studies, the relative protection offered by the available products is subject to debate. Transient viremia is commonly observed in cats deemed to be protected against persistent viremia in challenge studies, and latent infection can be identified in some of these cats. All FeLV vaccines are inactivated, most contain adjuvants, and they are based on a variety of different virus strains. Vaccines may contain whole virus particles, viral subunits, or recombinants. The emergence of injection-site sarcomas and other problems associated with widespread annual vaccination has led the AAFP to develop revised vaccination guidelines for cats and recommends tailoring vaccine protocols for each patient. The AAFP recommends immunizing only those cats with potential risk of exposure to FeLV (i.e., cats allowed outdoors and cats residing in households with infected cats or with cats of unknown FeLV infection status). Furthermore, it is recommended that all cats be tested for FeLV prior to immunization, because FeLV vaccination of infected cats is not believed to be of benefit. Prevaccination screening also avoids the situation in which an undetected infected cat later develops FeLV-related disease, leading the client to suspect vaccine failure. The AAFP further recommends administering any vaccine with FeLV antigen in the lower left hind leg. This is to aid both the treatment of subsequent sarcomas (by amputation) and to help identify the offending product. It is important to keep detailed medical records of vaccine administration (including date, injection site and route, product, and lot number). The use of peel-off vaccine labels that are placed in the permanent medical record are helpful in this regard. It is also important to report adverse vaccine reactions (please contact the manufacturer).

CLINICAL DISEASE SYNDROMES

Many cats carry FeLV infections in an asymptomatic state. Clinical signs, when they occur, are varied and nonspecific, depending on the organ system involved and the presence of secondary diseases. In one study of 3712 FeLV-infected cats, 29% were free of clinical signs. This study may underestimate the proportion of asymptomatic cats, because cases were selected based on the presence of illness or a life style at high risk for FeLV infection. Weight loss was the most common clinical sign reported in symptomatic cats (63%), followed by fever (42%), dehydration (35%), rhinitis (18%), diarrhea (17%), conjunctivitis (17%), oral infections (15%), lymphadenopathy (13%), and abscesses (12%). FeLV infection increases the risk for a wide variety of conditions, but it is not always possible to determine whether concurrent diseases are a consequence of FeLV infection or are independent events. Anemia was the most common finding in a study of 8756 FeLV-infected cats seen at veterinary medical teaching hospitals and was diagnosed in 18% of infected cats. Other findings included upper respiratory infections (11%), lymphoma (10%), myeloproliferative diseases (6%), stomatitis (5%), leukopenia (3%), haemotrophic mycoplasmas (3%), lymphadenopathy (3%), and uveitis (2%).

Bone Marrow Disorders

Bone marrow suppression is the most common clinical syndrome associated with FeLV infection and results from primary viral infection of hematopoietic stem cells and from viral infection of stromal cells that constitute the supporting environment for hematopoietic cells. The most common form of FeLV-induced anemia is pure red cell aplasia, a severe nonregenerative anemia associated with marked depletion and maturation arrest of erythroid precursors in the bone marrow. Serum erythropoietin levels are markedly increased, and few cats with FeLV-associated anemia respond to exogenous

erythropoietin therapy. A rarely encountered form of FeLV-induced anemia is associated with red blood cell (RBC) macrocytosis. This is believed to represent a virus-induced defect in cell division during RBC maturation.

Regenerative anemia in FeLV-infected cats, indicated by increased reticulocytes and, in some cases, nucleated RBCs, is less common than nonregenerative anemia and usually occurs in the presence of *Mycoplasma haemofelis* and *Mycoplasma haemominutum* (formerly *Haemobartonella felis*). Approximately one third of cats with immune-mediated hemolytic anemia are FeLV-positive; in some cases, hemolysis precedes the emergence of myeloproliferative disease or lymphoma. Erythemic myelosis is a myeloproliferative disease characterized by high numbers of nucleated RBCs (sometimes exceeding 500 nRBC/100 white blood cells [WBCs]). Although the high number of nucleated RBCs may suggest a regenerative process, the absence of reticulocytes indicates that it is actually a nonregenerative anemia. Erythemic myelosis is resistant to chemotherapy and is virtually always fatal, although affected cats may survive while supported with blood transfusions. Diagnostic evaluation of anemic FeLV-infected cats should include a complete blood count (CBC), reticulocyte count, serum chemistry panel, Coombs' test, and bone marrow evaluation. Examination of blood smears for *Mycoplasma haemofelis* or *M. haemominutum* may be performed, but PCR is more sensitive. If a specific cause for anemia is not determined, treatment should include a course of doxycycline (10 mg/kg orally for a minimum of 21 days) to rule out occult *Mycoplasma* spp. infection. Prednisone at antiinflammatory or immunosuppressive doses or erythropoietin therapy may improve nonregenerative anemia in some cats, but many become transfusion-dependent. Regenerative anemia, which is less common, should be treated as an immune-mediated disease once infectious causes such as *Mycoplasma* spp. and *Babesia* spp. have been ruled out.

FeLV is the most common cause of thrombocytopenia and granulocytopenia in cats. FeLV and myeloproliferative diseases accounted for 44% of cases of feline thrombocytopenia in one report. Cyclic and persistent neutropenia have been observed. The cycles are regular, ranging from 8 to 14 days. In one such cat, platelet count and reticulocyte count also cycled. An immune-mediated mechanism may be involved, because some cats respond to treatment with prednisone. Various cytopenias may wax and wane in FeLV-infected cats, seemingly responding to a variety of therapeutic interventions. Some persistent cytopenias are associated with myelodysplasia and may eventually evolve into a terminal myelodysplastic syndrome or leukemia. In addition to the direct bone marrow suppressive effects of FeLV, nonregenerative anemia, leukopenia, and thrombocytopenia may also be due to secondary effects of the virus, including bone marrow infiltration with lymphoma, leukemia, infectious agents, myelofibrosis, and osteosclerosis.

If cytopenia is severe, or if treatable underlying causes are not identified, therapy may be attempted with hematologic growth factors. Erythropoietin (Epogen, Amgen; 35 to 100 IU/kg subcutaneously every other day to correct anemia, then weekly to sustain PCV) has been of benefit to some cats with FeLV-associated anemia, although most do not respond. Reasons for resistance to erythropoietin include iron deficiency, concurrent infections, FeLV infection of bone marrow stromal cells, and the development of antierythropoietin antibodies. In some nonresponsive cats, repeated blood transfusions may be the only treatment possible. Recombinant human granulocyte colony–stimulating factor (rhG-CSF; Neupogen, Amgen; 5 μg/kg subcutaneously each day) was developed for neutropenia associated with aggressive human chemotherapy protocols. In cats, rhG-CSF has been used successfully to treat neutropenia due to drug toxicity, infectious diseases, FeLV-associated cyclic neutropenia, and idiopathic causes. Long-term use of the drug in cats is limited by its high cost and the development of neutralizing antibodies against the human protein within a few weeks, but it is often effective for acute or life-threatening neutropenia. Whether antibodies develop in cats that are immune suppressed by FeLV infection or with concurrent use of prednisone is unknown. No growth factor is currently available to stimulate platelet production, and recovery depends on identifying and correcting the underlying cause.

Neoplasia

FeLV-infected cats have sixtyfold increased risk of developing lymphoma compared with FeLV-negative cats. Lymphoma is expected to occur in approximately 25% of cats infected with FeLV, usually within 2 years after diagnosis of the viral infection. Multicentric and mediastinal lymphoma are the most common forms to occur in FeLV-positive cats. Although less common, spinal, renal, ocular and other forms of lymphoma are also reported in young FeLV-infected cats. As the prevalence of FeLV decreased since its discovery, so did its association with lymphoma. Currently, alimentary lymphoma is the most common form diagnosed and a majority of affected cats are now middle-aged or geriatric and FeLV negative. FeLV may also have a role in lymphoma development in some cats that test negative for infection. FeLV genetic sequences and antigens have been identified in the tumors of some cats with negative FeLV blood tests. FeLV-negative housemates of infected cats have a fortyfold increased risk of lymphoma compared with cats that do not reside with infected cats. Although some reports suggest that concurrent FeLV infection is associated with reduced rate or duration of remission in cats treated for lymphoma with chemotherapy, other reports found no such effect.

Myelodysplasia (preleukemia) is characterized by nonregenerative anemia accompanied by abnormalities in cellular maturation in the bone marrow. Granulocytopenia and thrombocytopenia may also occur. Most cats are positive for FeLV. Bone marrow is usually hypercellular, and many samples also exhibit myelofibrosis. Blast cells comprise less than 30% of the marrow elements, distinguishing myelodysplasia from leukemia. Progression to acute leukemia is common and may occur within weeks to months after the diagnosis of myelodysplasia. Treatment with immunosuppressive doses of corticosteroids and blood transfusions may palliate clinical signs, but the prognosis is poor for most cats that have cytopenias due to myelodysplasia. Nearly all cats with acute nonlymphoid leukemia (ANLL or acute myeloid leukemia) are FeLV positive. These leukemias can involve erythroid elements (erythemic myelosis, erythroleukemia, reticuloendotheliosis), myeloid elements (granulocytic, monocytic, or myelomonocytic leukemia), or megakaryocytes. Stem cell involvement may result in a sequential expression of leukemia of various cell lines. Prognosis is grave for ANLL because chemotherapy does not appear to alter the course. Most cats are euthanized within days to weeks of diagnosis. Heavy infiltration of bone marrow (and frequently other organs) with lymphoblasts characterizes acute lymphocytic leukemia (ALL). ALL is often accompanied by anemia and circulating blasts. Most cats with ALL are FeLV-positive. Differentiating ALL from advanced lymphoma can be difficult, although the treatment for both forms of lymproliferative disease are similar. Chronic lymphocytic leukemia is uncommon in the cat, tends to occur in older FeLV-negative cats, and carries a better prognosis than ALL. Hypereosinophilic syndrome, polycythemia vera, and multiple myeloma are proliferative hematologic disorders that are not associated with FeLV infection.

Although lymphoid and hematologic malignancies are the most common forms of neoplasia associated with FeLV, viral infection is also associated with specific tumors of other organ systems. Osteochondromatosis is a syndrome usually observed in young FeLV-infected cats in which multiple lesions affect the skeleton; solitary lesions in older cats are usually not associated with FeLV. Olfactory neuroblastoma is a rare FeLV-associated tumor involving the nasal cavity with frequent

invasion through the cribriform plate. Multiple subcutaneous fibrosarcomas require coinfection of FeLV and feline sarcoma virus, which arises as a recombination between FeLV and cellular oncogenes. Similar to the reduction in observed cases of lymphoma, the decreasing prevalence of FeLV has paralleled a decrease in cats diagnosed with ANLL and other FeLV-associated malignancies. Diagnosis and treatment of FeLV-associated neoplasms are discussed in detail in Chapter 181.

Secondary Infections

Diseases associated with immune suppression account for much of the morbidity and mortality in FeLV-infected cats. Thymic atrophy and depletion of lymph node paracortical zones are common findings, particularly in cats infected as kittens. Neutropenia and lymphopenia may further exacerbate immune suppression. Several immune function tests have been reported to be abnormal in FeLV-infected cats, including poor response to T-cell mitogens, prolonged allograft rejection, reduced immunoglobulin production, depressed neutrophil function, complement depletion, and cytokine dysregulation.

Many reports exist of FeLV-infected cats having concurrent bacterial, viral, protozoal, and fungal infections; however, few studies prove these cats have a higher rate of infection than FeLV-negative cats or that they have a less favorable response to therapy. Thus, although FeLV is well known to suppress immune function, it should not be assumed that all concurrent infections are a result of FeLV infection. The most common secondary infections associated with FeLV are respiratory viruses that persist longer and cause greater illness than observed in immune competent cats. *Mycoplasma* spp. infections (haemobartonellosis), which may be clinically silent in healthy cats, are more likely to be associated with severe hemolytic anemia in FeLV-coinfected cats. Cats residing in households endemic for both FeLV and coronavirus are more likely to develop fatal FIP if they are infected with FeLV. Treatment-resistant dermatophytosis and acute generalized toxoplasmosis are also associated with FeLV infection.

Miscellaneous Disorders

A variety of other disorders are associated with FeLV infection. Reproductive failures have been associated with abortion due to transplacental infection of fetuses and endometritis. Glomerulonephritis has been a histologic finding in FeLV-infected cats, but is not usually clinically significant. Generalized lymphadenopathy has been observed in several young cats and may be mistaken for lymphoma. The lymph node enlargement usually resolves after several months without treatment. A "panleukopenia-like syndrome" of FeLV mimics feline parvovirus infection and is characterized by panleukopenia, crypt necrosis, and high mortality. In some cats, parvovirus is identified as a coinfection, suggesting that FeLV may enhance the susceptibility of adult cats to parvoviral enteritis. Neurologic infection has been reported to cause urinary incontinence and papillary spasm leading to *D*-shaped pupils and anisocoria. FeLV-associated myelopathy results in vocalization, hyperesthesia, and paresis progressing to paralysis. Lymphocytic-plasmacytic stomatitis, although more common in cats infected with FIV, is also increased in FeLV-infected cats.

TREATMENT OF FeLV-INFECTED CATS

Adherence to the AAFP guidelines to test all cats for FeLV is likely to result in the identification of many asymptomatic cats. Early identification allows steps to prevent the spread of infection and to optimize the health of infected cats. The AAFP recommends that cats infected with FeLV be confined indoors to prevent spread to other cats in the neighborhood and exposure of affected cats to infectious agents carried by other animals. As for all cats, good nutrition and husbandry are essential to maintaining health. Cats should be fed a nutritionally balanced and complete feline diet. Raw meat and eggs and unpasteurized dairy products should be avoided, because the risk of food-borne bacterial and parasitic infections is greater in immune-suppressed individuals. A program for routine control of gastrointestinal parasites, ectoparasites, and heartworms, where applicable, should be implemented.

Cats infected with FeLV should receive wellness visits at least semiannually to promptly detect changes in their health status. Veterinarians should obtain a detailed history to help identify problems requiring more intensive investigation and perform a thorough physical examination at each visit. Special attention should be paid to the oral cavity, because dental and gum diseases are common in affected cats. Lymph nodes should be identified and carefully evaluated for changes in size and shape. The skin should be examined closely for evidence of external parasitic infestations and fungal diseases. The body weight should be recorded, because weight loss is often the first sign of deterioration in a cat's condition. A CBC should be performed semiannually for FeLV-infected cats, because of the high risk of hematologic disorders. Serum biochemical analyses and urinalyses should be performed yearly; urine samples should be collected by means of cystocentesis so that bacterial cultures can be performed, if necessary. Fecal examinations should be considered for cats with a history of possible exposure to internal parasites or with a history of GI tract disease.

Vaccination programs to prevent common, serious infectious diseases should be maintained. In general, vaccination programs for infected cats are similar to those for uninfected cats. Rabies vaccines should be given in accordance with state and local regulations. Feline viral rhinotracheitis-calicivirus-panleukopenia vaccines should be given in accordance with the AAFP guidelines (i.e., routine primary vaccination, followed by a booster vaccination 1 year later and every 3 years thereafter). Some clinicians recommend that only inactivated vaccines be used in infected cats. However, little evidence indicates that such cats are at increased risk of adverse effects with modified-live virus (MLV) vaccines. FeLV vaccines are of no benefit in and should not be given to FeLV-infected cats. Other vaccines should be evaluated carefully before being administered. Sexually intact cats should be sterilized to reduce stress associated with aggression, estrus, and mating behaviors. Neutered animals are also less likely to roam outside the house or to interact aggressively with their housemates. Surgery is generally well tolerated by infected cats that are not showing clinical signs of disease. Perioperative antibiotic administration may be considered for cats undergoing dental procedures and invasive surgeries.

Illnesses in cats infected with FeLV are often secondary diseases acquired because of immune dysregulation and not the direct effects of the FeLV infection. Prompt and accurate identification of secondary illnesses is essential to allow early therapeutic intervention and a successful outcome. Therefore intensive diagnostic testing may proceed earlier in the course of illness for infected cats than might be recommended for uninfected cats. Many cats infected with FeLV respond as well as their uninfected counterparts to appropriate treatment strategies, although a longer or more aggressive course of treatment may be needed. Owners should be forewarned and clinicians should not be discouraged if a response to treatment takes longer than expected. As in the case of asymptomatic cats, corticosteroids and other immunosuppressive drugs should be administered only to those patients with a clear indication for their use.

IMMUNE-MODULATOR AND ANTIVIRAL THERAPY

The evaluation of anti-FeLV therapies is hampered by the lack of well-controlled clinical trials in which new treatments are compared against standard care or placebo. Host factors, such

as the age of the cat at the time of infection, genetics, immune function, and concurrent diseases interact with viral factors, including virus strain, dose, and route of infection in determining the clinical outcome of infection. The marked natural variation in disease expression among infected cats makes it risky to predict which cats will have rapid progression of disease and which will be long-term survivors. In addition to host and viral factors that affect infected cats, the attitude and motivation of both the owners and the treating veterinarians can have a profound influence on the clinical outcomes. Immune modulators are suggested to benefit FeLV-infected cats by restoring compromised immune function, thereby allowing the patient to control the virus and recover from associated clinical syndromes. Antiviral agents directly inhibit virus infection and replication.

Immune-Modulating Agents

Acemannan (Carrisyn, Carrington Laboratories) is a complex carbohydrate (mannan) polymer derived from the aloe vera plant. In one uncontrolled open-label trial, 50 cats with natural FeLV infection were treated with acemannan (2 mg/kg intraperitoneally every week for 6 weeks). Whether concurrent supportive care was permitted was not described. At the end of the 12-week study period, nine cats had been excluded from evaluation. Of the remaining 41 cats, 29 (71%) were known to be alive. All cats remained ELISA-positive for FeLV antigen, and there were no significant changes in clinical or hematologic scores. Because the study did not include a control group, and because clinical and laboratory evaluations failed to document improvement from pretreatment evaluations, it is difficult to determine whether the use of acemannan improved the outcome of infection in treated cats.

Propionibacterium acnes (ImmunoRegulin, ImmunoVet) is a killed bacterial product. No prospective studies have been reported for use in FeLV-infected cats, but veterinarians have described their clinical experiences in anecdotal reports. In one discussion, 76 clinically ill cats with natural FeLV infections were treated with ImmunoRegulin (0.25 to 0.5 mL intravenously twice weekly, then every other week for 16 weeks) and supportive care, including prednisone, antibiotics, and vitamins. Although no specific clinical and laboratory evaluations were discussed, 55 (72%) of the cats reportedly became seronegative for FeLV antigens and survived for an unspecified period of time.

Interferons (IFNs) have been used as antiviral agents (at high doses) and as immune modulators (at low doses). Anecdotal reports of beneficial responses in cats with FeLV infection treated with low doses administered orally (0.5 to 30 U orally each day) have been described. The most positive responses are reported with recombinant (rhIFN) human IFNα in contrast to bovine or feline products. In a review of more than 100 FeLV-infected cats treated with various protocols for low-dose rhIFNα in combination with antibiotics, blood transfusions, fluids, and other supportive care, it was recommended to treat cats with 15 to 30 U orally each day for 7 days on alternate weeks. The mechanism by which oral rhIFNα acts is unknown, but it is not believed to be present in the blood or oral cavity in concentrations high enough to exert a direct antiviral effect. In one study, rhIFNα failed to improve hematologic or lymphocyte subset abnormalities in cats with chronic FeLV infection. rhIFNα (Roferon, Hoffman LaRoche; Intron A, Schering-Plough) is supplied in 3,000,000 U vials. The protocol for diluting the drug for oral use is (1) mix 3,000,000 U in 1 liter sterile saline; (2) freeze in 1 or 10 mL aliquots; (3) as needed, thaw aliquots and mix into the working solution by further diluting into 100 mL (1 mL aliquot) or 1000 mL (10 mL aliquot); (4) the final working concentration of 30 U/mL is considered an appropriate cat dose. This working solution is reportedly stable in the refrigerator for 2 months.

Staphylococcus protein A (SPA, Sigma) is a bacterial polypeptide product purified from the cell wall of *Staphylococcus aureus* Cowan I. A variety of SPA sources and treatments have been used in FeLV-infected cats. In some studies, a high rate of tumor remission and conversion to FeLV-negative status was observed, whereas in others, responses were less dramatic and short-lived. In a study of kittens with experimental FeLV infection, treatment (20 μg/2.75 kg intraperitoneally twice weekly for 8 weeks) neither reversed viremia nor improved humoral immune function. A recent double-blind controlled trial compared treatment of naturally infected cats with SPA, rhIFNα, SPA+rhIFNα, or placebo. There were no significant differences in survival, hematology, or clinical findings.

PIND-ORF (Baypamune, Bayer) is derived from an inactivated *Parapox ovis* virus and is proposed to induce nonspecific or "para" immunity. After reports of curing infection and disease in hundreds of FeLV-infected cats, Baypamune (1.0 mL subcutaneously 1 to 3 times weekly for 4 to 30 weeks) quickly became the most commonly used treatment for FeLV infections in Europe. In one of the only large-scale double-blind, placebo-controlled clinical trials of an immune modulator reported to date, 150 cats with natural FeLV infection were randomized to receive Baypamun (1.0 mL subcutaneously twice for 1 week, then weekly for 6 weeks) or placebo. There were no significant differences in clinical score, hematology score, lymphocyte subsets, FeLV p27 concentration, pterin concentration, reversion to negative status, or survival between the groups. Overall, between 7% and 12% of the cats in both groups became negative for FeLV p27 antigen. This study demonstrates the marked differences that can be observed in uncontrolled or retrospective studies compared with randomized, controlled clinical trials.

Specific Antiviral Agents

AZT/Zidovudine (Retrovir, GlaxoSmithKline) is the most widely used antiviral agent for both human and feline retroviral infections. It is a nucleoside analog inhibitor of the viral reverse transcriptase enzyme, preventing conversion of viral RNA into DNA, which would then enter the host genome. Only 1 controlled clinical trial has been reported in which cats with natural FeLV infections were treated with AZT. In this study, 32 FeLV-infected cats, all with chronic oral inflammation (stomatitis), were treated with AZT (5 mg/kg subcutaneously twice a day) or placebo for 3 weeks in a double-blind design. No other treatments were permitted. AZT-treated cats had improved stomatitis score and decreased FeLV p27 antigenemia compared with placebo. Previously, AZT was recommended at 15 mg/kg twice a day. The dose of 5 mg/kg twice a day used in this study was associated with decreased hematologic toxicity and cost.

Recombinant human interferon alpha (rhIFNα IntronA, Schering-Plough; Roferon, Hoffman LaRoche) has potent antiviral activity, preventing final virion assembly and budding. When administered to cats with experimental FeLV infection, rhIFNα (10^4 to 10^6 U/kg subcutaneously each day) effectively reduced FeLV p27 antigenemia. The effect was most rapid and complete in the high-dose treatment group. However, neutralizing antibodies developed against the human protein and appeared earliest in the high-dose group. Thus, the authors concluded that the intermediate dose of 10^5 U/kg provided the most beneficial balance of efficacy and duration of action, which persisted approximately 50 days until antibodies inhibited activity. Interestingly, the addition of AZT to a rhIFNα treatment did not enhance the antiviral effect in this study of chronically infected cats as it did in a study of FeLV prophylaxis. The cats in this study were healthy, so a clinical benefit could not be assessed. Theoretically, the observed suppression of virus load could benefit FeLV-infected cats because the immune system may achieve some level of reconstitution during this period. A recombinant feline rhIFNα

omega product (10^3 to 10^6 U/kg subcutaneously each day) from Japan (INTERCAT, Toray) failed to decrease FeLV p27 levels or prevent lymphoma in experimentally infected cats. Recently, rfaIFN omega became available in Europe (Virbagen Omega, Virbac) and is approved for the treatment of parvoviral enteritis in dogs. The manufacturer reports that clinical condition and the proportion of cats surviving ±1 year are increased in FeLV-infected cats treated with IFN omega (10^6 U/kg subcutaneously each day for 5 days on day 0, day 14, and day 60) compared with cats treated with placebo.

CHAPTER 171

Feline Immunodeficiency Virus Infection and Related Diseases

Katrin Hartmann

In 1986, feline immunodeficiency virus (FIV), a T-lymphotropic lentivirus causing an acquired immunodeficiency syndrome (AIDS) in domestic cats, was isolated in Davis, California. FIV shares many morphologic and biochemical properties with human immunodeficiency virus (HIV) but is antigenetically distinct. The pathogenesis of both virus infections is characterized by a long period of clinical latency during which immune function gradually deteriorates. Triggered by factors as coinfections, ultimately the immunodeficiency syndrome develops and is accompanied by opportunistic infections, myelosuppression, tumors, or neurologic disease. No evidence links FIV infection to any human disease, including AIDS. Investigations have failed to identify antibodies in people that have been bitten by infected cats or who have inadvertently injected themselves with virus-containing material.

FIV has been detected worldwide in domestic cats. In the United States, antibody prevalence ranges from 1% to 24%; prevalence is higher in cats at high risk of exposure and in sick cats. In large surveys of stray and feral cats in the United States, overall percentage rates of 2% to 4% are reported. There seem to be no regional difference in the United States; in Europe, however, infection rates vary significantly (e.g., from 2% in Germany and The Netherlands to over 30% in Italy). Cats that are free roaming in areas of high cat density have an increased opportunity for exposure, largely because bite wounds are the most important mode of transmission. Male cats are infected 2 to 4 times more frequently than females, and the prevalence is higher in adult cats. In a survey study of 826 naturally FIV-infected cats examined at North American Veterinary Teaching Hospitals, 80% were male and 78% were at least 2 years old at the time of presentation. Adult male cats living outdoors consistently compose the majority of FIV-infected cats, and the risk is highest for sexually intact males.[1,2]

PATHOGENESIS

The pathogenesis of FIV infection is not completely understood. Despite the generation of antibodies and a strong cellular immune response, a latent infection arises and infection cannot be cleared. The hallmark of FIV pathogenesis is the progressive disruption of normal immune function. FIV replicates in $CD4^+$ and $CD8^+$ lymphocytes, B lymphocytes, macrophages, astrocytes, and microglia cells. Ability to replication in different cell types is thought to be associated with use of different cellular receptors and to be responsible for different clinical manifestations of FIV infection. Virus replication in cells of the monocyte and macrophage lineage can result in central nervous system (CNS) disease.[3]

FIV can be isolated from lymphocytes, at the earliest, 10 to 14 days after infection. Viremia rapidly increases until day 21, peaks between weeks 7 and 8, and then decreases gradually until the virus load increases in the terminal stage. Conversely, when the virus peaks, the number of $CD4^+$ cells decreases. In the first few weeks of infection, numbers of both $CD4^+$ and $CD8^+$ cells decline. The initial lymphopenia is followed by a strong immune response characterized by the production of anti-FIV antibodies and a rebound in $CD8^+$ cells above pre-infection levels. This results in a persistent inversion of the CD4/CD8 ratio. Over time, numbers of both $CD4^+$ and $CD8^+$ cells gradually decline. Decrease of $CD4^+$ cells is caused by a shortened life span in infected lymphocytes and apoptosis of uninfected cells. In HIV, distinctive clinical stages can be defined based on absolute $CD4^+$ cell count. A $CD4^+$ cell count of 200/μL or less is considered an AIDS-defining condition. It is more difficult to assign clinical stages of disease to cats based on $CD4^+$ cell counts, mainly because FIV appears to be less pathogenic than HIV. Although chronic inflammatory conditions and opportunistic infections are more common in cats with low $CD4^+$ cells, other cats with low counts appear to remain healthy.

In addition to the quantitative decrease in $CD4^+$ cells, FIV-infected cats show dysfunction of immune cells (e.g., loss of ability of lymphocytes to proliferate in response to stimulation) and a significant perturbation of cytokine production. Cell-mediated immunity is more profoundly affected than humoral immunity. Despite being target cells of viral infection, no changes in number or proportions of B cells occur after FIV infection.[2] Consequently, chronic inflammatory conditions, neoplasia, and infections with intracellular organisms are more common than infections controlled by antibodies. FIV-infected cats respond adequately to vaccinations and frequently develop a polyclonal hypergammaglobulinemia characteristic of nonspecific stimulation of humoral immunity.

CLINICAL SIGNS

FIV infection progresses through several stages, much like HIV infection in humans. Clinical stages in cats include an acute phase, a clinically asymptomatic phase of variable duration, and a terminal phase. Attempts have been made to define the clinical course in different stages analogous to those of HIV infection; however, often no sharp distinction is seen

between the phases in cats, and not all stages will always be apparent. The clinical disease caused by FIV is dependent on age and health at the time of infection, dose and route of virus inoculation, virus strain, and immunologic competence of the cat. Experimental infections of cats in different environments have helped to differentiate between primary viral effects and syndromes that develop only in the presence of cofactors. During a 4-year follow-up period, both SPF and random source FIV-infected cats experienced immunodeficiency with progressive inversion of the CD4/CD8 ratio. The random source cats went on to an AIDS-like syndrome characterized by stomatitis, recurrent respiratory disease, diarrhea, and weight loss. In contrast, SPF cats developed lymphoma or neurologic disease believed to be caused by direct viral effects and not to be the consequence of immunodeficiency.[2]

Many FIV-infected cats are healthy; others have a history of recurrent illnesses. In a follow-up study of naturally FIV-infected cats, 18% of infected cats died within the first 2 years of observation (5 years after the estimated time of infection) and 18% developed increasingly severe disease. However, more than 50% of infected cats remained asymptomatic during the 2 years.[1] In a survey study of 826 naturally FIV-infected cats examined at North American Veterinary Teaching Hospitals, the most common disease syndromes were stomatitis, neoplasia (especially lymphoma and cutaneous squamous cell carcinoma), ocular inflammation (uveitis and chorioretinitis), anemia and leukopenia, opportunistic infections, renal insufficiency, lower urinary tract disease, and endocrinopathies such as hyperthyroidism and diabetes mellitus.[2] Some of these symptoms are most likely associated with the older age at which these cats presented (e.g., endocrinopathies, renal insufficiency) than with their FIV infection.

Stomatitis

Chronic ulceroproliferative stomatitis is the most common disease syndrome found in cats naturally infected with FIV, affecting up to 50% of infected cats. It characteristically originates in the fauces and spreads rostrally, especially along the maxillary teeth. Lesions are often painful and tooth loss is common. Severe stomatitis can lead to anorexia and emaciation. Histologically, the mucosa is invaded by plasma cells and lymphocytes, accompanied by variable degrees of neutrophilic and eosinophilic inflammation. The cause of the syndrome is uncertain, but the histologic findings suggest an immune response to chronic antigenic stimulation or immune dysregulation. Circulating lymphocytes of cats with stomatitis have greater than normal expression of inflammatory cytokines,[2] further implicating immune activation in the pathogenesis of this condition. Concurrent calicivirus infection is often identified in the oral cavity of cats with FIV-associated stomatitis and may be one of the infectious cofactors. Other infectious agents, including *Trichomonas*, *Candida*, or *Bartonella* infections, may also play a role.

Neurologic Disease

Both central and peripheral neurologic disease are common in HIV-infected humans, and the same is true of FIV. Dementia of human AIDS is often characterized by a slight decline in cognitive ability or behavior, changes that may be too subtle to recognize in cats. About 5% of clinically affected FIV-infected cats have neurologic disease as a predominant clinical feature. Although the majority of FIV-infected cats do not show clinically observable neurologic signs, a much higher proportion of infected cats exhibit microscopic CNS lesions. Brain lesions may occur in the absence of massive infection, and abnormal neurologic function has been documented in FIV-infected cats with only mild to moderate histologic evidence of inflammation.[1]

Uncommonly, neurologic signs may be caused by opportunistic infections such as toxoplasmosis, cryptococcosis, or feline infectious peritonitis (FIP). Mostly abnormal neurologic function is the result from a direct effect of the virus on CNS cells. Neurologic expression of FIV infection is highly strain dependant. The virus infects the brain early, with virus-induced CNS lesions sometimes developing within 2 months of experimental infection.[1] Neurologic abnormalities seen in naturally infected cats tend to be more behavioral than motor. Twitching movements of the face and tongue, psychotic behavior, compulsive roaming, dementia, loss of bladder and bladder control, and disturbed sleep patterns have been observed. Other signs described include nystagmus, ataxia, seizures, and intention tremors. In addition, sensitive electrodiagnostic tests such as nerve conduction velocity and brain stem auditory evoked potentials have detected abnormalities in clinically normal FIV-infected cats. Pathologic findings include the presence of perivascular infiltrates of mononuclear cells, diffuse gliosis, glial nodules, and white matter pallor. These lesions are usually located in the caudate nucleus, midbrain, and rostral brain stem.[1] Microglia and astrocytes are infected by FIV. The virus does not infect neurons; however, neuronal death has been associated with FIV infection. In particular, forebrain signs are often a result of direct neuronal injury from the virus. The mechanism of neuronal damage by FIV is unclear but may include neuronal apoptosis, effects on the neuron-supportive functions of astrocytes, toxic products released from infected microglia, or cytokines produced in response to viral infection. In vitro studies support the hypothesis that FIV infection may impair normal metabolism in CNS cells, particularly astrocytes.[1] Documented abnormalities of astrocyte function include altered intercellular communication, abnormal glutathione reductase activity that could render cells more susceptible to oxidative injury, and alterations in mitochondrial membrane potential that disrupt energy-producing capacities of the cell.[4] Astrocytes are by far the most common cell type of the brain and are important in maintaining CNS neuronal microvascular microenvironment. One of the most important functions of astrocyes is to regulate the level of extracellular glutamate, a major excitatory neurotransmitter that accumulates as a consequence of neuronal activity. Excessive extracellular glutamate often results in neuronal toxicity and death. FIV infection of feline astrocytes can significantly inhibit their glutamate-scavenging ability, potentially resulting in neuronal damage.[4,5]

Tumors

FIV-infected cats have a higher incidence of certain types of tumors and are five times more likely to develop lymphoma or leukemia than noninfected cats, compared with sixty-twofold increase in cats infected with feline leukemia virus (FeLV).[4] In contrast to lymphoma in FeLV-infected cats that is primarily of T cell origin, the phenotype of FIV-associated lymphoma is mainly B cell. Other neoplastic diseases in FIV-infected cats include squamous cell carcinoma, fibrosarcoma, mast cell tumor, myeloid tumor, and leukemia. It is not known exactly how FIV is associated with these cancers. Lentiviruses are not directly oncogenic. Because increasing age is a risk factor both for FIV infection and development of neoplasia, it is difficult to determine the exact role of FIV in carcinogenesis. Infection with immunosuppressive lentiviruses is associated with increased cancer risk, but most studies suggest indirect mechanisms. With the exception of one recently published case,[5] integrated FIV sequences cannot been detected in lymphoma cells, suggesting that, unlike FeLV, the role of FIV in lymphoma development is generally indirect. Several theories exist concerning the association of tumors with FIV infection. FIV might increase cancer incidence by decreasing tumor immunosurveillance mechanisms. It might promote tumor development through the immunostimulatory effects of replicating in lymphocytes. Finally, it might impair immunologic control of FeLV infection and accelerate the proliferation of transformed lymphoid cells.

DIAGNOSIS

Currently available tests for FIV infection rely on the detection of antibodies to FIV (Figure 171-1). In contrast to FeLV, FIV antigen concentration in blood is too low to be detected. FIV-infected cats do, however, usually develop high levels of FIV-specific antibodies, and FIV produces a persistent infection from which cats do not recover. Therefore FIV-specific antibody detection was effectively used for diagnosis, and the presence of antibodies was predictive of infection in cats older than 6 months of age. In kittens less than 6 months of age, antibody tests must be interpreted carefully because kittens acquire anti-FIV antibodies by passive transfer in colostrum from infected or vaccinated mothers. It is very rare for kittens to become infected from their mothers under natural circumstances, so most kittens (that are truly uninfected) initially testing positive will eventually test negative when their maternal antibodies wane.

Antibodies to FIV can be detected by immunochromatographic tests like enzyme-linked immunosorbent assay (ELISA). These tests can produce false-positive results for a number of reasons, a fact that is of major importance in areas with low FIV prevalence (e.g., United States, Northern European countries). Therefore positive results should be confirmed with a Western blot or at least with a second immunochromatographic test.

Interpretation of positive FIV tests is unfortunately confounded by a recently approved vaccine (on the U.S. market) that interferes with all tests relying on antibody detection, including the confirmatory Western blot. This vaccine induces broad spectrum antibody production to FIV proteins and results in long-lasting titers. These antibodies are indistinguishable from those detected in infected cats. After vaccination a cat will test positive for at least 12 months and will transfer antibodies to kittens through colostrum. Polymerase chain reaction (PCR) and virus isolation have been suggested as alternative testing methodologies. Virus isolation is possible over the whole infection period, but is time-consuming, expensive, and requires expertise; therefore it is not practical for routine diagnosis. PCR is a very sensitive and specific method when used in experimental conditions. If appropriately inactivated the current vaccine should not result in viral genome production and should not interfere with PCR assays. PCR requires specialized equipment, is not available for patient-side testing, and is performed only by specialized laboratories. Current PCR tests in the field are not standardized, and information about sensitivity, specificity, and overall diagnostic performance in naturally infected cats is not available. Due to the marked variability of the viral genome in the field, failure rates to detect FIV infection by PCR of up to 50% have been reported. Another concern is that the high sensitivity of PCR may lead to false positive results if even minor contaminations occur during handling of samples.[3,5]

PREVENTION

FIV infection can be best prevented by keeping cats out of environments that encourage high-risk behavior. Cats should be neutered and not be exposed to untested homeless, feral, abandoned, or stray cats.

Development of an effective vaccine is difficult because of the nature of the retrovirus-host interaction and the relatively poor immunogenicity of lentiviral antigens in inducing

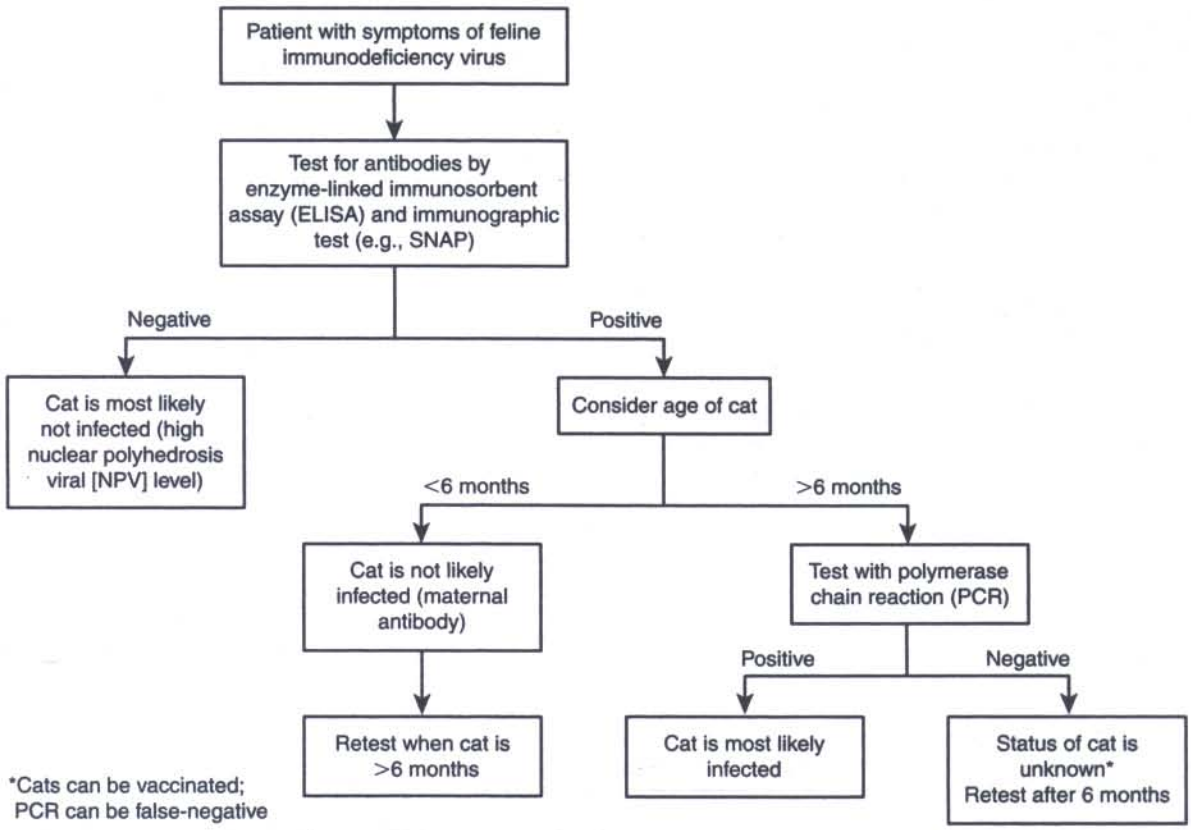


Figure 171-1 Algorithm for feline immunodeficiency virus.

vaccinal immunity. Cats typically mount a marked antibody response after exposure to FIV, but these antibodies are unable to clear infection. Many approaches have been taken toward the development of an effective vaccine against FIV, but the same hurdles facing HIV prevention also apply to FIV. Both viruses have an error-prone RT, which enhances the mutation rate of replicating virus and increases the opportunity for escape from immune surveillance. The viruses can even take advantage of specific antibody formation, using antibodies to enhance pathogenicity or to enter cells via immune complexes. To date, no vaccine approach has been completely successful in preventing infection, and in some cases immunization paradoxically enhanced viral replication and disease expression. One major obstacle in designing an effective vaccine against FIV infection is the large genetic diversity among viral isolates. Five known subtypes of FIV exist, and sequence divergence ranges from 2% to 15% within a subtype (between subtypes it ranges up to 26%). The new vaccine (Fel-O-Vax FIV®) is a dual-subtype vaccine containing inactivated FIV subtype A and subtype D with an adjuvant. The combination of two genetically distinct subtypes elicits strong anti-FIV cellular immunity and broad-spectrum virus-neutralizing antibodies, but the range of protection is still unknown. This vaccine has not yet been field tested against natural FIV infection, and protection against the frequently found subtype B viruses (in USA and in Europe) is uncertain.[3,5]

TREATMENT

In most naturally infected cats, FIV infection does not cause a severe clinical syndrome. With proper care, FIV-infected cats can live many years and, in fact, may die in older age from causes unrelated to their FIV infection. Survival time is long and quality of life is usually good. The most important life-prolonging advice is to keep FIV-infected cats strictly indoors, not only to prevent spread to other cats but also to prevent exposure of the immunosuppressed cat to infectious agents carried by other animals. Secondary infections not only cause clinical signs in FIV-infected cats but also lead to progression of FIV infection.

Antiviral Chemotherapy

Clinical use of antiviral drugs is still not very common in veterinary medicine. With the exception of feline interferon-ω now on the market in Japan and some European countries, no antiviral drugs are licensed for veterinary use; therefore human drugs must be used in animals. Most antivirals are specifically intended for treatment of HIV infection, and many of those can be used to treat FIV infection because most enzymes of FIV and HIV have similar sensitivities to various inhibitors. In cell culture and experimental studies, several compounds have been shown to be active against FIV. However, many of these studies used FIV as a model for screening new compounds for HIV, and most of these drugs will never be accessible to veterinarians. Unfortunately, to date the drugs available to cats are limited, and only few controlled studies have been performed to support their use.

Licensed antiviral compounds that have been used in FIV-infected cats include zidovudin (3′-azido-2′,3′-dideoxythymidine, AZT), phosphonoformate (foscarnet), ribavirin, and interferons (human interferon-α, feline interferon-ω). Phosphonoformate and ribavirin are relatively toxic in cats, and their use is limited in feline medicine. AZT is the most thoroughly studied anti-FIV drug. It is a nucleoside analogue (thymidine derivative) that blocks the RT of retroviruses. It is integrated in the developing DNA strand and thus inhibits new infection of cells but not replication of viruses already present in infected cells. AZT reduces plasma virus load and improves the immunologic and clinical status of FIV-infected cats resulting in increased survival time. In a placebo-controlled trial, AZT improved stomatitis in naturally infected cats. It is used at a dose of 5 to 10 mg/kg every 12 hours (orally or subcutaneously). During treatment, regular blood cell counts are necessary because nonregenerative anemia is a common side effect, especially if the higher dose is used. Cats with myelosuppression should not be treated. Studies in which cats were treated with AZT for 2 years demonstrated that AZT is well tolerated in most FIV-infected cats. Some cats developed a mild decrease in hematocrit initially in the first 3 weeks that resolved even if treatment is continued. If hematocrit drops below 20%, discontinuation of AZT is recommended and anemia usually resolves within a few days. Unfortunately, as in HIV, AZT-resistant mutants of FIV can arise as early as 6 months of treatment.

Interferons have an immunomodulatory effect and a direct antiviral effect by inducing an antiviral state of cells that protects against virus replication. Human interferon-α used in cats with FIV infection can be given parenterally for a maximum of 6 to 7 weeks in high doses (10^5 to 10^6 IU/kg), leading to measurable serum levels. After 6 to 7 weeks, cats develop antibodies against the human interferon-α. If given orally, interferons are destroyed in the gastrointestinal (GI) tract and no measurable serum levels develop. The only potential effect that oral interferon could have is stimulation of the lymphoid tissue in the oral cavity with subsequent systemic immunomodulation. No placebo-controlled studies prove a positive effect of low-dose oral human interferon-α in FIV-infected cats. Interferons are species-specific and feline interferon-ω (recently licensed in some countries) is more effective in feline cells than human interferon. So far only one study has been performed with feline interferon-ω in FIV-infected field cats at 10^6 IU/kg every 24 hours subcutaneously for 5 consecutive days. This study failed to show a significant difference in survival rate when compared with a placebo group; virus load or $CD4^+$ cell counts were not measured.[3] Other trials are needed to assess the efficacy of feline interferon-ω against FIV infection.

Immune Modulatory Therapy

Nonspecific immunostimulatory agents (e.g., Acemannan, *Staphylococcus* protein A (SPA), *Propionibacterium acnes*, paramunity inducer) are probably the most widely used medications in FIV-infected cats. It has been suggested that these agents restore compromised immune function, allowing the patient to control viral burden and recover from associated clinical syndromes. Although reports of uncontrolled studies frequently suggest clinical improvement, these effects have not been observed when followed by controlled studies. No conclusive evidence from controlled studies shows that immunomodulators or alternative drugs have any beneficial effects on health or survival of asymptomatic or symptomatic FIV-infected cats. A nonspecific stimulation of the immune system might even be contraindicated. In HIV infection, nonspecific stimulation can lead to increased virus replication by activating latently infected lymphocytes and macrophages. Consequently this therapy can actually promote progression of disease. This is why unspecific immunomodulators with unknown effects should not be used in FIV-infected cats.

CHAPTER 172

Feline Infectious Peritonitis and Feline Enteric Coronavirus

Janet E. Foley

FELINE CORONAVIRUSES

Feline enteric coronavirus (FECV) and feline infectious peritonitis (FIP) virus are two feline coronavirus phenotypes of positive-stranded RNA virus. Like transmissible gastroenteritis virus of pigs, murine hepatitis virus, and others, the FEVC and FIP virus are in the family Coronaviridae. FECV is a fecal-orally transmitted virus that can infect intestinal epithelium of all Felidae but is not infectious to nonfelids or humans. FECV produces moderate villus pathology with no clinically detectable disease; the major clinical importance is that frequent RNA mutations confer a novel phenotype that allows the virus (now an FIP virus) to enter and replicate within feline macrophages.[1,2] If a cat fails to eliminate FIP virus–infected cells early in infection, the presence of FIP virus within macrophages may initiate an ultimately fatal Arthus-type immune-mediated vasculitis, which defines FIP. Affected cats may develop signs due to lesions in a sensitive target organ (central nervous system [CNS], kidney, or liver) or it may die due to fluid redistribution into second spaces, disseminated intravascular coagulopathy, or secondary sepsis.

DIAGNOSIS OF FELINE INFECTIOUS PERITONITIS

FIP is diagnosed on histopathologic examination of lesions, supported by signalment, history, physical examination, and laboratory findings (Figure 172-1). Cats with FIP may be any breed or either sex, with a peak age distribution from 6 months to 3 years (although FIP occurs in all ages). Commonly, affected cats come from a multiple-cat household (more than five cats), even though the cat may have been in a single-cat household for months or years. Often, cats with FIP have a history of failure to thrive or grow. On physical examination, affected cats may have antibiotic-unresponsive or cycling fever, lethargy, icterus, abdominal masses (especially associated with kidneys, liver, spleen, and mesenteric lymph nodes), and neurologic abnormalities. Diarrhea is not a sign of either FIP or FECV infection. Cats with ocular FIP may have keratic precipitates, anterior uveitis, hypopyon, hyphema, or retinal hemorrhage or detachment. Cats with effusive or "wet" FIP develop a yellow-tinged, high-protein, inflammatory exudate in their abdominal, pleural, pericardial, or scrotal cavities. Pleural effusion may cause dyspnea, and abdominal fluid may cause obvious ascites. Clinical pathologic examination of the fluid indicates either exudate (possibly turbid, specific gravity >1.017, 5 to 12 g/dL protein, moderate numbers of nondegenerate neutrophils, macrophages, plasma cells, and lymphocytes) or occasionally modified transudate. There may be bacteria present, reflecting the cat's immunosuppressed state. Synovial fluid may appear inflamed due to immune complex deposition. Blood testing for coagulopathy may demonstrate increases in prothrombin time (PT) and partial thromboplastin time (PTT) and increased fibrin degradation products.

Several hematologic changes occur in cats with FIP, although many affected cats have patterns differing from "classic." Cats with FIP often have a mild neutrophilia and lymphopenia. Anemia secondary to red cell destruction or to chronic disease is common. Serum biochemistry results frequently demonstrate increases in serum protein concentration (>8.0 g/dL) consisting of hypergammaglobulinemia. Less commonly, abnormal liver enzyme activities occur due to hepatitis, hepatic lipidosis, or prehepatic sequelae of vasculitis, erythrocyte destruction, and hypoxia. Hyperbilirubinemia is common and secondary to vasculitis within the liver. Affected cats have severe liver disease.

Serology can be helpful as part of the diagnostic profile but is so often misinterpreted that results need to be evaluated carefully. Serology does not differentiate the FIP virus from FECV, is not correlated with severity of disease, and is not indicative of active infection.[3-6] Most commonly, serology for anti-FECV and FIP virus IgG is an indirect immunofluorescent antibody (IFA) test using FIP virus–infected feline cell lines; enzyme-linked immunosorbent assay (ELISA) is available in some commercial laboratories. Dilution should start at 1:25; if a cat is negative at 1:25, one can assume that the cat is truly negative (or was only exposed within the last 10 days). Unfortunately, many laboratories only report high titers (≥1:400) as positive, despite the fact that FIP can occur in cats with titers lower than 400. Rising titers are not very helpful because cats with FIP and FECV can both have fluctuating titers. Titers greater than 16,000 are suggestive of FIP. In multiple-cat facilities, virtually all cats are seropositive. Kittens in catteries often have high titers (400 to 6400), but most do not develop FIP. Positive titers wane slowly, but cats held in single-cat households with no further exposure to coronavirus eventually become seronegative after months to years if they are not FECV carriers and do not have FIP. Rare cases occur in which cats appear to be seronegative and yet have FIP. In almost all such instances, the problem is with testing: low titers are not detected. Other reported, rare causes of seronegativity in cats with FIP include immune complex consumption of free antibodies, exhaustion of antibody-producing plasma cells, or acute fulminant disease less than 10 days after first exposure to coronavirus. It is technologically possible to generate antibodies to mutant FIP viruses. However, so many potentially different mutations exist that any single antimutant FIP virus antibody becomes useless for routine diagnostic purposes. Commercially available anti-7b antibody tests anecdotally suffer from poor positive and negative predictive values.

Reverse-transcription polymerase chain reaction (RT-PCR) can be performed to reverse-transcribe coronavirus RNA to cDNA and then make visually detectable large quantities of DNA. Although FIP viruses are genetic mutants of FECVs, numerous sites exist in the S, 3c, or 7b genes of FECV that can be mutated or deleted and confer on the virus the capability to infect and replicate within macrophages. Sometimes the change can be a single RNA base. As a result, PCR primers to discriminate between FECV and FIP virus cannot be designed. RT-PCR is sensitive and useful for documenting FECV or FIP virus RNA to confirm that a suspect lesion is due to FIP or that a cat is shedding FECV in feces. All samples for

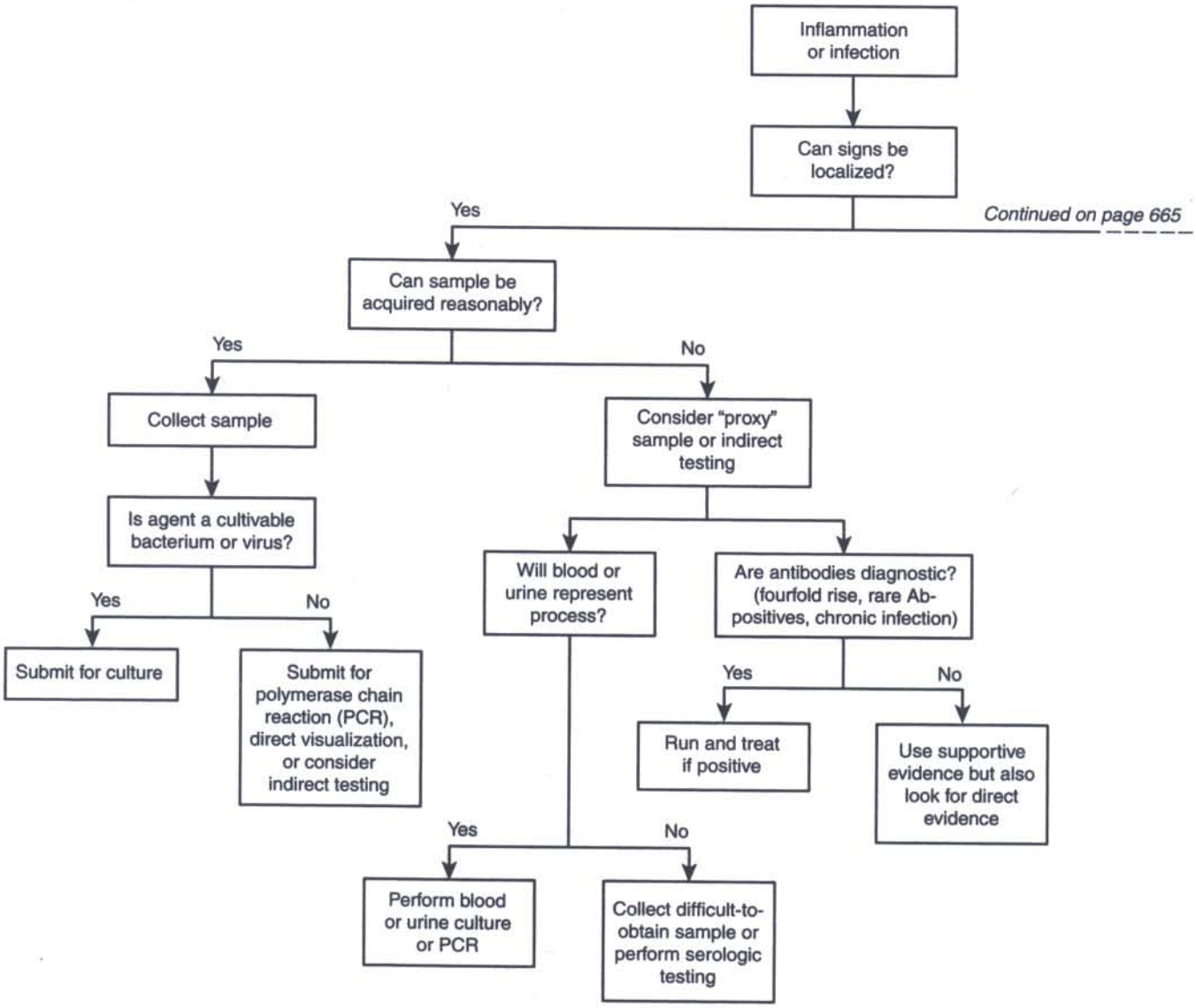
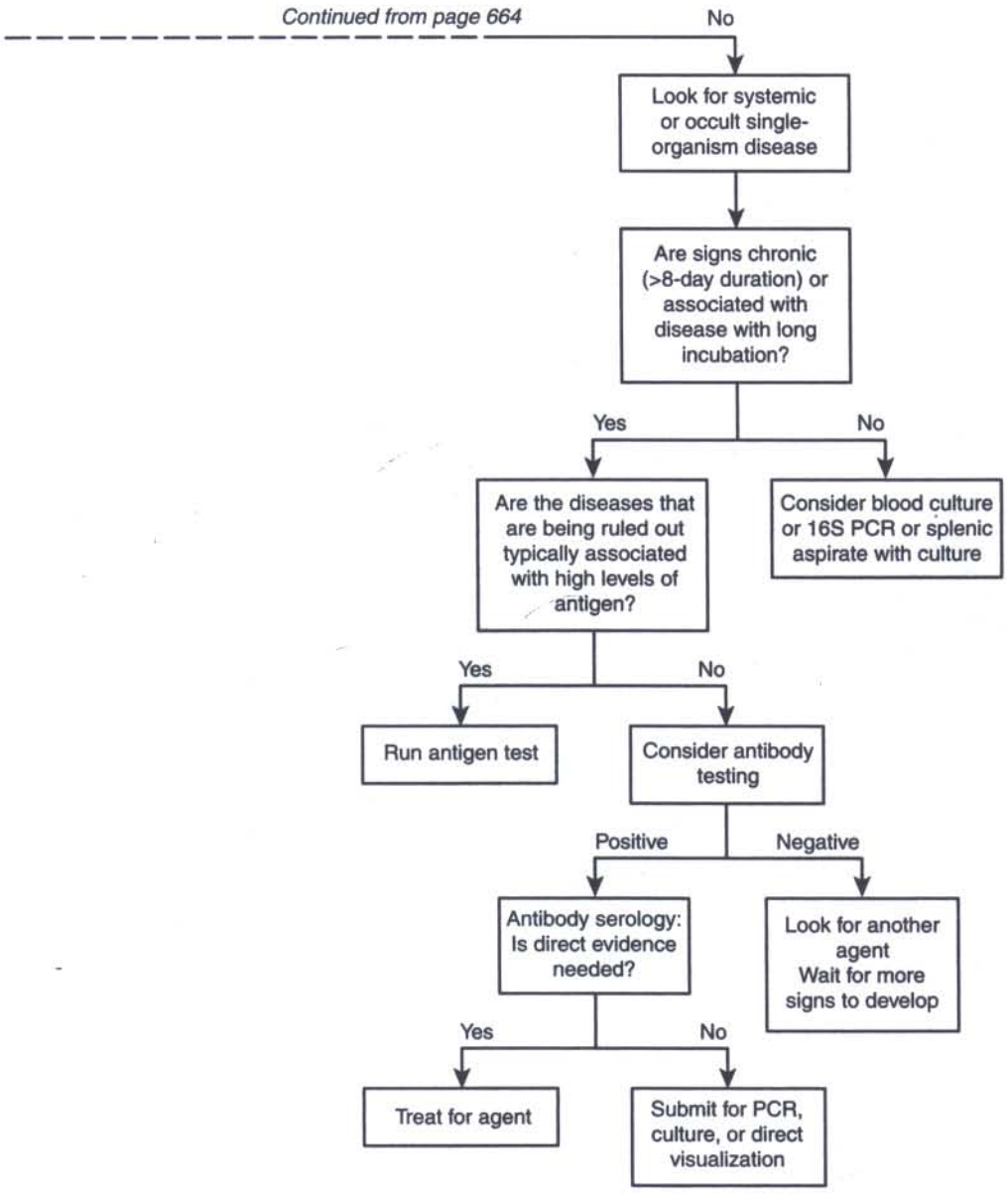


Figure 172-1 Algorithm for inflammation or infection.

coronavirus PCR must be carefully handled, kept frozen, and protected from RNA-degrading enzymes (which are ubiquitous in most environments). PCR should be performed as quickly as possible after collection, even if samples are frozen; delays in testing may result in false-negative results. In feces, PCR-positive tests document FECV infection. The strength of the PCR signal in feces correlates with the level of infection.[7,8] Because cats with FECV vary in how much FECV is shed in feces, repeated PCR should be performed daily over 4 to 5 days to accurately detect whether a given cat sheds FECV.

Urine and cerebrospinal fluid (CSF) are not recommended for FIP PCR, because these fluids contain low numbers of virus. Ascites may be false negative because of PCR inhibitors. Blood and mesenteric lymph nodes may be false positive for FIP (small amounts of FECV). In other lesions, positive PCR can be interpreted as positive for FIP virus.

Confirmation of FIP is made by histopathology of biopsy or necropsy samples with pyogranulomas, coronavirus antigen, or nucleic acids. Hematoxylin and eosin-stained samples contain localized perivascular mixed inflammation with macrophages,



neutrophils, lymphocytes, and plasma cells (or any combination of these). Pyogranulomas may be large and consolidated, sometimes with tissue necrosis, or numerous and small. To confirm coronavirus within the lesions, PCR may be performed or formalin-fixed, paraffin-embedded tissues may be stained with a chromagen-tagged monoclonal antibody such as 5.2D5 against the FIP N protein, then lightly counter stained with hematoxylin and eosin.[9]

In the less commonly encountered cats with the neurologic form of FIP, several ante-mortem tests have a high probability of successfully ruling in or out a diagnosis of FIP. Clinical signs indicate disease in various parts of the spinal cord, cerebrum, and cerebellum and may include seizures, ataxia, paresis, paralysis, vestibular disease, peripheral neuropathy, hyperesthesia, urinary incontinence, and behavior changes. Cats with neurologic FIP are seropositive in blood and in CSF (and often in anterior chamber fluid), with a ratio of CSF:serum antibodies generally much higher than the ratio of CSF protein:serum total protein. The CSF often appears normal, or there may be mild increases in protein concentration and cell number.

CNS inflammation often results in hydrocephalus. On magnetic resonance imaging (MRI), hydrocephalus may be observed, as well as contrast enhancement in ependyma, meninges, and other sites.

TREATMENT AND PREVENTION OF FELINE INFECTIOUS PERITONITIS

Virtually every cat with confirmed FIP dies. Some veterinarians prescribe immunomodulators (*Propionobacterium acnes* (immunoregulin), interferon, acemannan) to treat cats with FIP with no documented, controlled evidence of efficacy. Immunosuppressive drugs such as prednisone (4 mg/kg, orally once a day) or cyclophosphamide (2 to 4 mg/kg, orally four times a week) may slow disease progression but do not produce a cure. Cats with FIP should also be treated with broad-spectrum antibiotics and supportive therapy (subcutaneous fluids, rest, good nutrition, lack of stress) for as long as they are comfortable. Once disease signs become debilitating and weight and appetite decline, the owner must be prepared for the reality that their cat is dying.

Unfortunately, preventing FIP is extremely difficult. Three prevention targets will be discussed: (1) preventing FIP in cats that were in contact with cats with FIP, (2) preventing FIP in cats harboring FECV, and (3) preventing FECV. After a cat in a household develops FIP, one can do virtually nothing to prevent FIP in other in-contact cats. All cats will have already been exposed to the same coronaviruses, although this is usually an FECV. Few healthy cats in the household will develop FIP, although the stress of being locked in a bathroom in the misguided attempt to prevent exposure would not help remaining cats fight infection. After a diagnosis of FIP, the probability of any other cat dying of FIP is no higher than in any other cattery with endemic FECV (which is all catteries). Exceptions exist to this rule. The first is full-sib littermates of cats with FIP, which have a 0.25 to 0.5 probability of dying of FIP as well. The second exception is during rare epidemics that may be associated with spread of FIP (in contrast to the typical scenario of spread of FECV and periodic mutations to FIP virus).[3] This type of spread of FIP virus has not been documented in natural epidemics and is unlikely, because FIP lesions are not in epithelial surfaces where the virus could be shed.

The second target is to prevent FIP in catteries with endemic FECV. This includes virtually all multiple-cat households, breeding catteries, shelters, foster homes, and other homes with more than five cats. Various tactics have been used. To be successful, they should focus on supporting cats' natural resistance to FIP virus phenotypes and reducing FECV challenge in these cats. In catteries, the major risk factor for FIP is the overall prevalence of FECV. Reducing the number of cats (especially kittens less than 12 months old) and keeping possibly FECV-contaminated surfaces clean can minimize population loads of FECV.

Vaccination is supposed to help cats fight FIP but has not proven to do so. Often cats do not seroconvert after vaccination, and study results are mixed as to whether vaccination has no effect versus a small effect. Although marginally if at all efficacious, the vaccine is safe and does not induce antibody-dependent enhanced FIP.

It is reasonable in breeding catteries to maximize heritable resistance to FIP. If a cat has two or more litters that develop FIP (at any age), then that cat should not be bred again. It would be rare for such a cat to have FIP, so it should be screened (complete blood count [CBC], serology, abdominal palpation, and possibly ultrasound). If no abnormalities are found, the animal should be neutered and placed for adoption. Particular attention should be paid to pedigrees of toms where FIP is over-represented. Because line breeding often uses valuable toms extensively, eliminating such toms may have a small but important effect on improving overall resistance.

Concurrently with palliative efforts, cattery managers should use education and communication to minimize adverse effects of FIP on cat populations. For example, if a shelter has a reputation for having FIP, adoptions may be reduced and cats may be euthanized for space. Cattery managers should have written information sheets or contracts informing buyers or adopters about FECV and FIP. They should understand that FECV is unavoidable in multiple-cat environments and that FIP is an unavoidable consequence of endemic FECV. It is particularly important that cats associated with the cattery be diagnosed accurately. For example, cats from shelters may have moderately high FECV titers *not* due to FIP and yet be euthanized inappropriately because of a history of having been at a shelter.

The last FIP-prevention scenario is to prevent or eliminate FECV, which is difficult. Isolation is not effective because of the ease with which FECV is transported on things such as clothes, shoes, dust, and cats' fur. As long as five or more cats live in a home, FECV infection maintains itself by infecting and reinfecting the same cats, whether or not the cats are separated. When the number of cats drops to five or fewer, it is much more difficult for the virus to sustain itself.

If depopulation is possible, a chance exists that endemic FECV can be induced to become extinct in the cat population. It is important to determine whether any cats are chronic FECV carriers so that they can be removed. Forty to 60% of cats in large multiple cat environments shed virus in their feces at any given time. About 20% will shed virus persistently, whereas 20% will be immune and not shed virus. Repeated PCR testing of feces should be performed at weekly intervals for 2 months or more to document carriers: if the cats remain persistently PCR-positive more than 6 weeks, they should be placed for adoption (only in very small catteries attempting to eradicate FECV).

Early weaning has been proposed as a means to interrupt transmission from adult cats to kittens. Unfortunately, queens may infect kittens as early as 5 to 6 weeks. This is prohibitively young to be removing kittens from the nurturing of the queen, particularly when the kittens likely will be exposed within a few weeks anyway. For early weaning to be effective, kittens should be taken to a new home (with no other cats) at 5 weeks of age. Even then, early weaning is not always successful.

To conclude, management of FIP should be directed at minimizing the population impact and accurately diagnosing and supporting individually affected cats. Vaccination neither prevents FIP nor FECV; testing and removing is ineffective. Thus cattery managers have few effective management tools. However, veterinarians need to be knowledgeable regarding both successful and unsuccessful strategies to provide useful counsel to their clients with multiple-cat households.

CHAPTER 173

Other Feline Virus Diseases

Rosalind M. Gaskell
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FELINE VIRAL RESPIRATORY DISEASE

Feline viral respiratory disease (Table 173-1) is most commonly seen where cats are grouped together, such as in breeding and boarding catteries and in rescue shelters. The two main causes of viral respiratory disease in cats are (1) feline herpesvirus 1 (FHV-1) (feline rhinotracheitis virus) and (2) feline calicivirus (FCV). FHV-1 generally induces a more severe disease than FCV, but FCV appears to be relatively more common.[1] Other viruses implicated in the syndrome include feline reovirus and cowpox virus (see following). Bacterial pathogens such as *Bordetella bronchiseptica* and *Chlamydophila felis* may also be involved in infectious respiratory disease in cats.

Causative Agents

FHV-1 is an alphaherpesvirus affecting both domestic cats and other members of the Felidae. Only one serotype of the virus exists, and genetically all isolates are very similar. The virus contains double-stranded DNA and is enveloped, making it relatively labile.

FCV is a small nonenveloped RNA virus. Only one genotype and one serotype of the virus exist, although a large degree of variability exists within both of these.[2,3] However, most strains of FCV are closely related enough antigenically to induce some degree of cross-protection, and this has been used in developing vaccines.

FCV affects both domestic cats and some nondomestic Felidae. Although dogs have their own genetically distinct calicivirus, some canine calicivirus isolates appear to be closely related to FCV and some epidemiologic evidence indicates of a link between the two.[4,5]

FCV is slightly more resistant than FHV-1 and is less susceptible to some disinfectants. However, a diluted hypochlorite and detergent mixture should be effective for both viruses.

Clinical Signs

FHV-1 causes upper respiratory tract (URT) disease, with oculonasal discharges, conjunctivitis, sneezing, and sometimes hypersalivation and coughing. Occasionally more severe signs including pneumonia and generalized disease may be seen, particularly in young or debilitated animals. Abortion occurs rarely and is probably due to severe systemic disease rather than a direct effect of the virus itself. The role of FHV-1 in ocular disease has been increasingly recognized, with keratitis, corneal sequestration and a possible association with uveitis having been reported.[6] Similarly, involvement of FHV-1 with skin ulcers and dermatitis has also been described.

FCV causes typical URT signs, but the disease is generally milder than that seen with FHV-1. Mouth ulceration is a characteristic feature of the disease, typically on the tongue, but lesions may occur elsewhere in the mouth or on the skin. Lameness and pyrexia may also occur, with or without respiratory or oral disease. In addition, FCV infection is associated with chronic stomatitis, although its precise role in the condition is not clear and other factors are likely to be involved.[1]

There is some strain variation in FCV with respect to pathogenic potential. Some isolates appear to be apathogenic, some may induce an interstitial pneumonia, and more recently very virulent strains have emerged in California that induce a hemorrhagic syndrome. Affected cats had variable signs, such as facial and paw edema, respiratory signs, pyrexia, icterus, and hemorrhages from the nose and in the feces.[7]

Diagnosis

Diagnosis of FHV-1 and FCV infection has classically been confirmed by virus isolation in cell culture from oropharyngeal or conjunctival swabs, although immunofluorescence has also been used (particularly for FHV-1). Increasingly, polymerase chain reaction (PCR) is being used for diagnosis of FHV-1, because it is significantly more sensitive than traditional methods.[8,9] However, the clinical and epidemiologic significance of PCR-positive and virus isolation–negative cats is currently unclear. For FCV, reverse-transcriptase polymerase chain reaction (RT-PCR) is less sensitive than isolation but it is useful for differentiating between strains in investigating the epidemiology of the disease.[10]

Treatment

Treatment involves both broad-spectrum antibacterial cover and supportive therapy. Tetracyclines are indicated if *Bordetella bronchiseptica* or *Chlamydophila felis* are involved. No specific antivirals are licensed for use in either FHV-1 or FCV infection. Some antiherpesvirus drugs used in human medicine, such as acyclovir, are not sufficiently active against FHV-1 or are too toxic for use in cats.[11] However, others have been used with some success in cats with ocular herpesvirus lesions.[12] For FCV, ribivarin has been shown to be effective in cell culture but was too toxic for use in cats. It has been suggested that recombinant interferon may be helpful in cats with viral respiratory or ocular disease.[12] In addition, some evidence reveals that orally administered L-lysine may be useful in treating acutely and latently FHV-1 infected cats.[13]

Epidemiology

Both viruses are primarily transmitted by direct contact between cats, although indirect transmission may also occur in the short term through contact with infectious discharges. Aerosols are not of major importance, although sneezed macrodroplets may transmit infection over a distance of 1 to 2 m.

Acutely infected cats are clearly an important source of virus, but infection also commonly occurs from clinically recovered carrier cats. In FHV-1 carriers, the virus persists in a latent form largely in trigeminal ganglia, although other tissues may also be involved. Periodically, particularly after a stress, virus reactivates in such carriers, and they can then infect other animals. Stresses that may induce virus shedding include a change of housing, kittening and lactation, and corticosteroid treatment. Some cats may show clinical signs during a reactivation episode, which can be a useful indicator that they are likely to be infectious.

Table 173-1

Recognized Virus Infections of Cats

Upper Respiratory Tract (URT) Viruses	Feline herpesvirus type 1 (FHV-1)	URT disease
	Feline calicivirus (FCV)	URT and oral disease; sometimes lameness
	Feline reovirus	Conjunctivitis/respiratory lesions/diarrhea, experimentally; no evidence important in the field
Enteric Viruses	Feline parvovirus (FPV)	Enteritis and panleukopenia; cerebellar hypoplasia; fetal death
	Feline coronavirus	Mild enteritis; feline infectious peritonitis (FIP)
	Feline rotavirus	Mild diarrhea; disease uncommon
	Feline astrovirus	Persistent watery diarrhea; disease uncommon
	Feline torovirus	Putative torovirus detected in cats; possible association with protruding nictitating membrane and diarrhea syndrome in cats
Retroviruses	Feline leukemia virus (FeLV)	See Chapter 170
	Feline immunodeficiency virus (FIV)	See Chapter 170
	Feline foamy virus (FFV)	Previously feline syncytium-forming virus; no definite disease association
Miscellaneous Virus Infectious of Cats	Cowpox virus	Sporadic disease in cats; mainly skin lesions; cowpox virus endemic in small wild rodents
	Hantavirus	Endemic disease in rodents; serologic evidence of infection in cats; zoonotic (but cats are unlikely source)
	Rabies virus	See Chapter 177
	Aujeszky's disease virus/pseudorabies virus	Herpesvirus infection in pigs/swine; cats occasional host; disease signs are severe behavioral changes, pruritus, paralysis, coma, and death
	Feline herpesvirus type 2 (FHV-2)	Possible association with idiopathic feline lower urinary tract disease, now thought to be bovine herpesvirus 4; possible disease association unclear
	Canine distemper virus (CDV)	Evidence from field serology and experimental studies indicate that cats can be infected subclinically; however, severe disease with neurologic signs seen in large Felids
	Paramyxoviruses: hendra and nipah viruses	Newly emerged, fatal zoonotic respiratory disease of horses in Australia (Hendra virus) and pigs in Malaysia (Nipah virus); endemic in certain species of fruit bats; cats can be infected experimentally with both viruses
	Paramyxovirus: unclassified	Report of demyelinating lesions in central nervous system (CNS) of cats
	Influenza virus	Can replicate in cats after experimental inoculation but no disease signs; no evidence of cat-human transmission; may occur in reverse during human influenza outbreaks
	Borna disease virus (BDV)	Rare but fatal neurologic disease that occasionally occurs in cats
	Arthropod-borne viral infections	Cats in some parts of the world may become infected with several arthropod-borne diseases; usually asymptomatic, occasionally cause encephalitis

Unlike FHV-1 carriers, FCV carriers shed virus more or less continuously and are therefore always infectious to other cats. The virus persists in tonsil and other oropharyngeal tissues. In some cats the carrier state appears to be lifelong, but most spontaneously recover at some point and appear to eliminate virus. FCV carriers appear to be very common, with approximately 20% to 30% of cats in the general population shedding FCV.[1]

Prevention and Control

Prevention and control may be achieved through a combination of vaccination and management. Both modified-live virus (MLV) vaccines and inactivated adjuvanted vaccines are marketed for parenteral injection against FHV-1 and FCV. Modified-live intranasal vaccines are also available in some countries but are not widely used. A number of recombinant vaccines have also been created, including FHV-1 deletion

mutants, baculovirus constructs, a myxoma FCV recombinant, and an FCV DNA vaccine.

Both MLV and inactivated FHV-1 and FCV vaccines are reasonably effective at protecting against disease, but none protects against infection or the development of the carrier state. For FCV, various strains are used in commercial vaccines, for example, strains F9 and 255. Most seem to protect against the majority of FCV isolates but not as well against all of them. Some evidence suggests that the percentage of isolates neutralized by such strains is decreasing.

Parenteral MLV vaccines are generally safe, but disease signs may occasionally occur after their use. This may be due to inadvertent oronasal exposure to the vaccine, for example, if the cat licks the injection site, and occasionally vaccine virus may generalize and spread.[10,14,15] Inactivated adjuvanted vaccines may therefore be safer in disease-free colonies. However, adjuvants can sometimes cause local or systemic reactions, and (very rarely) sarcomas may develop at the site of injection.

Intranasal MLV vaccines induce better protection but often at the expense of slight side effects, such as sneezing and oculonasal discharges. They are however useful for rapid onset of protection.

Primary vaccination in young kittens is generally at 8 to 9 weeks of age, with a second dose at 12 weeks. Boosters are traditionally recommended every year, but immunity may last longer in some cases.[16] In view of this and because of concerns over vaccine site reactions, it has been suggested that after the first annual booster, revaccination intervals may be extended to up to 3 years.[17] However, an individual risk-benefit assessment should be carried out to determine the most appropriate vaccination strategy for a particular animal[18] (see Chapter 164).

Management measures are aimed at preventing spread of viruses within a cattery, through both direct and indirect contact between cats. In boarding catteries and rescue shelters, cats should be individually housed with solid partitions between pens, and good hygiene and disinfection procedures should be used. In breeding colonies, young kittens are most at risk when they lose their maternally derived antibodies (MDA). Overcrowding should be avoided and cats kept as stress free as possible. Ideally, queens should kitten in isolation with early weaning of kittens or earlier vaccination schedules implemented if required. Such measures have been described in detail elsewhere.[1]

FELINE PANLEUKOPENIA/FELINE PARVOVIRUS (FPV) INFECTION

Feline panleukopenia is a highly infectious disease affecting members of the Felidae and a number of other species including mink, ferrets, and raccoons. The disease is characterized by enteritis and a panleukopenia and has a high mortality. Vaccination is generally highly effective in controlling the disease.

Feline panleukopenia is caused by a parvovirus, a small nonenveloped DNA virus similar to the canine parvovirus type 2 (CPV-2), which causes a severe hemorrhagic enteritis in dogs. Although feline panleukopenia is a long-established disease of cats, CPV-2 emerged suddenly in 1978 as a host range variant of FPV and spread rapidly within the dog population. The mechanism of its evolution is unknown, but it has been suggested that it may have originated from a wild carnivore intermediate host.[19] CPV-2 has largely been replaced by CPV-2a and CPV-2b, which now coexist in dog populations worldwide.[20] Although CPV-2 isolates did not replicate in cats, both CPV-2a and CPV-2b do so and have been reported to constitute a small proportion of isolates found naturally in cats.[21-23] In addition, some evidence suggests that the percentage of CPV isolates from cats in some parts of the world is increasing and that a potential new variant, CPV-2c, from leopards may also have emerged.[22]

Parvoviruses have an affinity and requirement for actively dividing cells. The main target tissues are the rapidly dividing cells of lymphoid tissue and the bone marrow, leading to panleukopenia, and the crypt epithelium of the intestinal mucosa, leading to enteritis. Infection early in pregnancy may lead to fetal death and resorption. From the middle third of gestation to immediately postnatally, infection results in cerebellar hypoplasia in kittens.

The severity of the disease varies considerably, ranging from a subclinical infection to a peracute syndrome with sudden death. In general, the disease appears to be more severe in young kittens. Other factors, such as a change of food or coinfection with other pathogens, which increase the mitotic rate in the intestinal villi, may increase the severity of disease. In a typical case the first signs of illness are lethargy, fever, and anorexia with apparent thirst but refusal to drink. Affected cats may vomit, particularly in the early stages. Profuse watery diarrhea or dysentery then develops, and cats may become severely dehydrated. Most fatalities occur within 3 to 5 days of the first signs of illness and are probably due to overwhelming bacterial infection, dehydration, and electrolyte imbalance. Experimental infections have suggested that infection with CPV in cats may lead to milder disease with reduced virus shedding compared with FPV, although the situation in the field is unclear.[24,25]

Kittens with cerebellar hypoplasia show ataxia, incoordination, hypermetria, and often intention tremors. These signs persist for life. Nevertheless, affected kittens may learn to compensate and otherwise function normally. Forebrain lesions have been reported and may lead to seizures and behavioral abnormalities.[26] Retinal lesions may also be present but are usually of no clinical significance. A possible role of FPV in myocarditis and idiopathic cardiomyopathy has also been suggested.[27]

A presumptive diagnosis of feline panleukopenia may be made based on history, vaccination status, and clinical signs. Disease is more commonly seen in rescue shelters and in groups of unvaccinated cats. Virus culture from fecal samples is difficult, and fecal shedding only occurs for a short period after infection. Enzyme-linked immunosorbent assays (ELISAs) and rapid immunomigration tests have been used for detection of viral antigen in fecal samples, with variable sensitivity and specificity. More recently, PCR tests for the detection of viral DNA in fecal samples have been used, and these have good sensitivity.[28] Antibody levels, which may reach very high titers after an active infection, may be useful as an aid to diagnosis.

Diagnosis may also be confirmed at necropsy, where characteristic histopathologic changes, including the presence of intranuclear inclusion bodies, may be seen in the crypt epithelium of the small intestine. Specific diagnosis using in situ hybridization and immunohistochemistry has also been reported.

Treatment is largely supportive and is aimed at restoring the fluid and electrolyte imbalance and covering against secondary bacterial infection.

Both MLVs and inactivated parenteral vaccines are available. Only one serotype of the virus exists, and the vaccines are generally highly effective in preventing disease. Protection against CPV-2b has also been shown experimentally,[24] and it is likely that FPV vaccines will protect against such isolates in the field. Primary vaccination usually takes place at 8 to 9 weeks of age, with a second dose at 12 weeks. However, the duration of MDA in kittens can be quite variable, and those born to unvaccinated queens or those who have not suckled colostrum may have no or very low levels of MDA. In contrast, kittens born to recovered queens may have very high levels of MDA

lasting up to 20 weeks. MLV vaccines should not be used in kittens under 4 weeks of age or in pregnant queens because of the risk of the development of cerebellar hypoplasia.

Boosters have typically been administered every 1 to 2 years, although some evidence suggests that immunity may last longer.[16] Consequently, and because of possible safety issues with respect to feline vaccines, three yearly intervals are now being suggested by some.[17]

Although the disease has largely been controlled by vaccination, cases still occur, particularly in rescue shelters and sometimes also in breeding colonies.[29] FPV is a remarkably stable virus and may persist in infected premises for up to 1 year: subclinical infection of susceptible cats can also help maintain the virus within a population. Not all disinfectants are active against FPV, but sodium hypochlorite and glutaraldehyde solutions are effective. Because of the ability of the virus to survive in the environment, thorough disinfection of premises must be carried out after any disease outbreaks and any new cats admitted to such infected premises should be fully vaccinated. Although persistent infections may occasionally occur after in utero or neonatal infection, carriers do not play a significant role in the epidemiology of the disease.

BORNAVIRUS DISEASE (FELINE "STAGGERING DISEASE")

Borna disease (BD) is a rare but fatal neurologic disease caused by a negative-stranded RNA virus, Borna disease virus (BDV). The disease occurs predominantly in horses and sheep; but a number of other species may also be affected, and increasing evidence indicates that cats are also susceptible.[30,31] The disease in cats has been reported mainly in Europe but also occurs in other parts of the world, including Japan.[32] Affected cats show motor dysfunction and behavioral changes including an unsteady "staggering" gait, depression, and progressive hindlimb ataxia and paresis. Other signs include anorexia, increased salivation, hyperesthesia, impaired vision, and seizures. The disease is generally progressive; despite supportive treatment, affected cats die or are euthanized. At necropsy a characteristic non-suppurative meningoencephalomyelitis is seen mainly in the gray matter of the cortex, brain stem, and spinal cord. In some cases, evidence of BDV infection is seen in cats with no neurologic disease. It has been suggested that BDV or a related virus may be involved in psychiatric disorders in humans.[33]

POXVIRUS INFECTION

Cats are susceptible to cowpox virus, a member of the Orthopoxvirus family.[34,35] Occasional cases of parapoxvirus infection in cats have also been reported.[36] Cowpox virus is found only in Eurasia, and the reservoir hosts are small wild mammals such as voles and woodmice. The disease is mostly seen in rural cats that hunt rodents, and most cases are seen in summer and autumn when opportunities for contact with the reservoir hosts are highest. Cat-to-cat transmission rarely occurs and generally causes only subclinical infection.

The disease typically starts with a single primary lesion, generally on the head, neck, or forelimb, which may be ulcerated or scabbed and can become secondarily infected. Although some cats may only have a primary lesion, in many cases widespread secondary skin lesions also develop after 1 to 3 weeks. These appear as randomly distributed, small epidermal nodules that increase in size over a few days to well-circumscribed ulcers about 1 cm diameter. These gradually become scabbed and heal over a period of 4 to 5 weeks, and most animals recover uneventfully. Occasionally, especially in immunosuppressed cats, systemic illness may develop. Some exotic felids (e.g., cheetahs) are particularly susceptible, and a rapidly fatal pneumonia often develops.

Diagnosis is by virus culture, electron microscopy (EM), or PCR of scab material, or by serology.[37,38] Characteristic histopathologic lesions include the presence of intracytoplasmic, eosinophilic inclusion bodies. Immunostaining is a useful aid to diagnosis.

Treatment includes broad-spectrum antibiotics to control secondary bacterial infection and general supportive therapy with fluids where necessary. Glucocorticoids are contraindicated because they can predispose to the development of secondary lesions, more severe disease, or both. Cidofovir has been shown to be active against cowpox virus in cell culture and some animal systems, although its use in cats has not been reported.[39] No vaccines are available, although vaccinia (smallpox vaccine) may be considered for valuable zoo collections.[40] Cowpox is zoonotic and may cause both a localized lesion and sometimes severe systemic illness in infected people, particularly those who are immunosuppressed. However, the risk of cat-human transmission is small if basic hygiene precautions are taken.

FELINE FOAMY VIRUS (FELINE SYNCITIUM-FORMING VIRUS) INFECTION

Feline foamy virus (FFV) is a member of the foamy virus group (spumaviruses) in the retrovirus family. Spumaviruses have been isolated from many species, but they generally do not appear to be pathogenic. Their main importance lies not in clinical medicine but as potential contaminants in research and vaccine production and, more recently, as possible viral vectors in recombinant vaccine technology.

FFV infection is very common in cats, with seroprevalences of up to 90%, depending on the population tested.[35,41] Infected cats harbor virus indefinitely; therefore seropositivity equates with infection. FFV is transmitted horizontally, and in some cases vertically, from infected queens to kittens.

The virus has been isolated from both clinically healthy cats and cats with a variety of diseases, although no clinical signs have been seen after experimental infection. However, FFV may predispose to disease in conjunction with other agents or particular MHC types. Such an association has been suggested for FFV in the feline progressive polyarthritis syndrome.[42]

ASTROVIRUS

Astroviruses have been detected in a number of species including cats, and in humans are a common cause of gastroenteritis. Astroviruses have been detected in the feces of kittens with diarrhea, and in normal cats.[43,44] The diarrhea has been described as persistent (4 to 14 days) and watery and may be accompanied by vomiting, pyrexia and depression. Mild diarrhea has also been reproduced experimentally.[43] It is not clear how commonly astrovirus-induced disease occurs in cats: a limited serologic study has reported that less than 10% of cats in the UK have antibody, although this may be an underestimate as only one serotype was examined.[45]

Serologic cross-reactivity has been reported between feline astrovirus and human sera and a close phylogenetic relationship shown between pig, human, and feline astroviruses. However, no evidence indicates on-going human-animal transmission, although it may have occurred in the past.

FELINE REOVIRUS INFECTION

Reoviruses have been isolated from both healthy and diseased cats with a variety of signs. Serologic surveys suggest infection is widespread, although the clinical importance of reovirus

infection in cats is unknown.[35] Three serotypes of the virus exist. Experimental inoculation of kittens with serotype 3 induced predominantly conjunctivitis, photophobia, and serous ocular discharges; type 2 induced mild diarrhea[46]; and newborn kittens inoculated with type 1 nursed poorly and died 2 days later with respiratory lesions identified at necropsy.[35,47] However, little evidence suggests that these conditions occur in the field.

ROTAVIRUS

Rotaviruses are a major cause of enteritis in humans and in many animal species such as cattle and pigs. Typically rotavirus infections occur in neonatal animals, although older animals may also be affected.

In cats, rotavirus infection is widespread, with between 28% to 100% of cats seropositive depending on the population sampled.[35,48] However, clinical disease appears to be uncommon, and diarrhea, when it occurs, tends to be mild and of only short duration.[35,49,50] Diagnosis of rotavirus infection may be carried out from fecal samples by EM, polyacrylamide gel electrophoresis of viral RNA, or by PCR.[45] Because of serologic differences between strains, ELISAs developed for diagnosis of human rotavirus infections may not necessarily detect all feline rotaviruses.[45]

Cross-species transmission is known to occur with rotaviruses experimentally, although to what extent this happens under natural conditions is not known. A number of recent reports have shown close phylogenetic relationships between some feline and some human rotavirus strains, and it has been suggested that cross-infection between cats and humans may sometimes occur.

HANTAVIRUS INFECTION

Hantaviruses are enzootic worldwide in wild and laboratory rodents, and they are zoonotic.[51] However, strains vary in their pathogenicity to humans. Disease syndromes seen in humans include hemorrhagic fever with renal syndrome in Asia and hantavirus pulmonary syndrome in North America. Only mild or subclinical disease is seen with most European strains.[52]

Hantavirus antibody has been detected in laboratory-housed cats in Belgium and in up to 10% cats from a variety of backgrounds in the United Kingdom, Austria, and Canada.[53-55] In addition, virus has been isolated from a cat in China.[56] However, the clinical significance of Hantavirus infection in cats is not known. There is little evidence to suggest that in most parts of the world cats are likely sources of human infection; however, an increased risk of human infection associated with cat ownership has been reported in China.

TOROVIRUS INFECTION

Toroviruses are a group of viruses similar to coronaviruses, but with a characteristic rod- or doughnut-shaped core. They have been detected in a number of species including cattle (Breda virus), horses (Berne virus), and humans and tend to be associated with enteritis. There is some evidence for a torovirus of cats that may be associated with protruding nictitating membrane and diarrhea syndrome.[48] However, other workers have been unable to substantiate this.[57]

CHAPTER 174

Systemic Mycoses

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Amy M. Grooters

Systemic mycoses are fungal infections that disseminate from a single portal of entry. The respiratory system serves as the portal of entry for most systemic fungi that affect the dog and cat, but the gastrointestinal (GI) system is occasionally implicated.[1]

Systemic mycoses are becoming more worrisome in human medicine because of immune-suppressive diseases such as acquired immunodeficiency syndrome (AIDS) and the expanded use of immune-suppressive therapy for cancer and organ transplantation. Immune suppression does not play as important a role in veterinary patients, but the importance of such diseases in humans has led to tremendous pharmacologic advances in the treatment of fungal infections.

Systemic fungal infections cause disease, the clinical signs of which are dependent on which systems are involved (Table 174-1). Weight loss, lymphadenopathy, and fever are typical of most systemic mycoses. Because the respiratory system is the usual portal of entry, clinical signs such as cough, dyspnea, and exercise intolerance are common. If the GI system is the portal of entry, as may occur with histoplasmosis, malabsorption may lead to severe diarrhea and weight loss.

In most cases, diagnosis of a systemic mycosis is dependent on demonstrating the presence of the organism in tissue. For yeasts such as *Cryptococcus* or *Candida*, or for dimorphic fungi that have a yeast phase in tissue, such as *Blastomyces dermatitidis* or *Histoplasma capsulatum*, the diagnosis can usually be made cytologically. For other fungi that grow as hyphal organisms in infected tissue, the diagnosis is usually dependent on histopathology, culture, or molecular techniques. Serology is used extensively in practice to support the diagnosis of fungal infections, but with the exception of tests for cryptococcal antigen, most commercially available assays determine the presence of antibody and may indicate only previous exposure.

Many treatment regimens have been reported for the management of various systemic mycoses, but few veterinary studies have been performed that have critically evaluated these agents in a prospective manner, and studies comparing treatment regimens are practically nonexistent. A lack of

Table 174-1

Differential Diagnoses for Systemic Manifestations of Systemic Mycoses

Multisystemic granulomatous, neoplastic, and immune-mediated diseases must be differentiated from disseminated systemic mycoses.

Differential Diagnosis for Nodular Skin Disease

Bacterial skin disease
Actinomycosis
Mycobacteriosis
Botryomycosis
Brucellosis
Rhodococcus equi infection
Bartonella vinsonii Subs, *berkhoffi infection*

Mycotic and miscellaneous infectious skin disease
Cryptococcosis
Coccidioidomycosis
Sporotrichosis
Basidiobolomycosis
Conidiobolomycosis
Phaeohyphomycosis
Hyalohyphomycosis
Eumycotic mycetoma
Dermatophytic mycetoma
Protothecosis
Pythiosis
Lagenidiosis
Nodular leishmaniasis

Noninfectious pyogranulomatous skin disease
Foreign body reaction
Idiopathic nodular panniculitis
Sebaceous adenitis (nodular form)
Canine cutaneous sterile pyogranuloma/granuloma syndrome

Neoplasia
Squamous cell carcinoma
Cutaneous lymphoma
Mycosis fungoides (cutaneous T-cell lymphoma)
Cutaneous histiocytosis

Miscellaneous diseases
Systemic lupus erythematosus (SLE)
Systemic vasculitis
Cutaneous embolic disease

Differential Diagnosis for Chorioretinitis, Exudative Retinal Detachment, and Panophthalmitis

Fungal
Cryptococcosis
Coccidioidomycosis
Geotrichosis
Histoplasmosis
Aspergillosis

Neoplasia
Lymphosarcoma
Metastatic neoplasia

Miscellaneous infectious causes
Protothecosis
Brucellosis
Toxoplasmosis
Neosporum caninum infection
Leishmaniasis
Lymphadenopathy must be differentiated from numerous causes, including lymphosarcoma, other fungal infections, rickettsial diseases, brucellosis, mycobacteriosis, protothecosis, and leishmaniasis.
Solitary bone lesions must be differentiated from primary or metastatic bony neoplasia and other fungal or bacterial osteomyelitis.

controlled observations has led to recommendations that are based primarily on anecdotal information, extrapolation from what is done in people, and small retrospective studies. The "best" treatment regimen for any given systemic fungal infection is therefore largely a matter of opinion.

The principal antifungal agents are antibiotics produced by microorganisms (e.g., amphotericin B, griseofulvin) and synthetic agents (e.g., potassium iodide, flucytosine, azole derivatives, allylamine derivatives, chitin synthesis inhibitors). The options for treatment of fungal infections increased substantially during the 1990s with the Food and Drug Administration's approval of the azole derivatives fluconazole and itraconazole. Clinical trials have been performed using itraconazole,[2-4] and case reports and retrospective reviews documenting the use of both drugs are available in the veterinary literature. The high cost of most antifungal agents and the long treatment protocols required affect the number of cases that are treated, both limiting and probably epidemiologically biasing the data that have been generated to date. Adding to the difficulty of assessing the efficacy of antifungal agents are that the pharmacologic principles of antifungal therapy are only partially understood, in vitro testing of fungi for resistance to antifungal agents provides little clinically useful information, susceptibility testing yields variable results, and tissue distribution of antifungal agents correlates variably with the clinical outcome.

ANTIFUNGAL AGENTS

Amphotericin B

Amphotericin B is a polyene macrolide antibiotic produced by the aerobic actinomycete *Streptomyces nodosus*. It was discovered in the 1950s and was one of the first antifungal agents found to be widely useful in treating systemic fungal infections. It has become the gold standard against which the efficacy of new antifungal agents is compared; despite significant toxicity and poor oral bioavailability, it remains the drug of choice for the treatment of many invasive mycoses. The traditional formulation of amphotericin B is a desoxycholate preparation (Fungizone) that, after intravenous administration, is highly protein bound (91% to 95%), primarily to lipoproteins, erythrocytes, and cholesterol in the plasma, and then is redistributed from the blood to the tissues. Penetration into

the cerebrospinal fluid (CSF) is poor. Tissue accumulation accounts for the majority of drug disposition. Only 5% to 10% of amphotericin B is excreted in the urine and bile. Although great care should be used when treating animals in renal or hepatic failure, no modification of the dose is necessary unless the renal or hepatic damage is attributable to the drug. Amphotericin B acts by binding to sterols in cell membranes, especially ergosterol in fungal cell membranes. Binding alters membrane permeability, causing leakage of sodium, potassium, and hydrogen ions and eventually leading to cell death. Amphotericin B probably also has important immunostimulatory effects by oxidation-dependent stimulation of host macrophages.[5] Stimulation of macrophages may play an important role in the treatment of some systemic fungal infections with amphotericin B. Toxic effects are attributable to affinity for sterols such as cholesterol in mammalian cell membranes.

Amphotericin B has been effective in the treatment of blastomycosis, histoplasmosis, coccidioidomycosis, cryptococcosis, systemic candidiasis, zygomycosis, and occasionally pythiosis. It is administered as a series of intravenous infusions (0.22 to 0.5 mg/lb [0.5 to 1 mg/kg] every 48 hours to a cumulative dose of 2 to 4 mg/lb [4 to 8 mg/kg] or until azotemia occurs). Bolus dosing over 5 to 10 minutes is common, but clinicians can reduce renal toxicity by infusing the drug in 5% dextrose over 1 to 5 hours. Nephrotoxicity is the most significant adverse effect and is dose dependent.[6] Generally, renal azotemia is reversible, and renal function returns to normal after cessation of therapy. However, return to pretreatment values may take several months. Irreversible renal dysfunction is more likely in animals with pre-existing azotemia or in those receiving other nephrotoxic agents such as aminoglycosides. Blood urea nitrogen (BUN) should be monitored before each administration of amphotericin B. If the BUN is greater than 50 mg/dL, the drug should be discontinued until the azotemia has resolved. Clinicians believe nephrotoxicity is caused by disruption of renal tubular epithelial cell permeability resulting in increased delivery of chloride ions to the distal tubule, with subsequent decreased glomerular filtration rate (GFR) being the result of tubuloglomerular feedback. This feedback is amplified by sodium depletion and suppressed by sodium loading. Administration of 0.9% sodium chloride (5 to 10 mL/lb) before amphotericin B administration decreases the incidence of nephrotoxicity in people. Other possible mechanisms of nephrotoxicity include decreased renal blood flow and direct renal cellular toxicity. Tumor necrosis factor (TNF) may also play a role in mediating amphotericin B–induced azotemia. Pentoxifylline, a hemorrheologic drug, seems to exert protective effects in people and rats. Mannitol and dopamine have also been shown to decrease nephrotoxicity in experimental situations. Other possible toxic effects include thrombophlebitis, pyrexia (usually ameliorated by pretreatment with nonsteroidal anti-inflammatory drugs or anti-inflammatory doses of glucocorticoids), hypokalemia, distal renal tubular acidosis, hypomagnesemia, cardiac arrhythmias, and nonregenerative anemia. Calcinosis cutis has been reported in dogs with blastomycosis 2 to 4 weeks after beginning treatment with amphotericin B.[7]

Recently the use of novel delivery systems have been effective in reducing nephrotoxicity and improving site-specific delivery of amphotericin B, allowing higher doses to be administered. Currently three new formulations of amphotericin B are available for clinical use in human patients: (1) amphotericin B lipid complex (ABLC) (Abelcet®, Enzon), (2) amphotericin B colloidal dispersion (Amphotec®, Intermune, Inc.), and (3) liposome-encapsulated amphotericin B (AmBisome®, Gilead Sciences).[8] Of these three formulations, ABLC has been the most extensively evaluated in small animal patients and is the least expensive. In dog studies, lipid-complexed amphotericin B was determined to be 8 to 10-fold less nephrotoxic than conventional amphotericin B. The decreased toxicity is due to decreased renal cell uptake, reduced tubular toxicity, reduced free amphotericin in solution in plasma, and a selective transfer of amphotericin directly to fungal cell membranes. The reduced toxicity allows higher cumulative doses to be used, which increases drug efficacy. This increase in efficacy is also thought to be related to rapid uptake of lipid complexes by phagocytic cells of the reticuloendothelial (RE) system, which allows sites of inflammation and organs with high RE system activity such as liver, spleen, and lung to receive higher doses of amphotericin B despite minimal renal uptake.

Clinical trials in people have documented improvement in treatment outcomes for many types of fungal infections. ABLC has been used successfully to treat blastomycosis in dogs without significant nephrotoxicity being noted.[9] ABLC can be used in dogs at a dose of 1 to 1.5 mg/lb (2 to 3 mg/kg) intravenously three times a week to a cumulative dose of 24 to 27 mg/kg. Azotemia is rare.

Oral Azole Antifungal Drugs

The azoles are classified as imidazoles (ketoconazole [Nizoral Janssen]) or triazoles (fluconazole [Diflucan Pfize] and itraconazole [Sporanox Janssen]), according to whether they contain two or three nitrogen atoms, respectively, in the five-member azole ring. Ketoconazole and itraconazole have similar pharmacologic profiles, but fluconazole is unique because of its comparatively small molecular size and low lipophilicity. The azole antifungal agents act by inhibiting ergosterol synthesis through interaction with 14-α-demethylase, a cytochrome P-450 enzyme that is necessary for the conversion of lanosterol to ergosterol. Similar interaction in mammalian cells with enzymes dependent on cytochrome P-450 also mediates some of the major toxic effects. The imidazoles are much more potent inhibitors of mammalian cell cytochrome P-450 than are the triazoles. Other antifungal effects include inhibition of endogenous respiration, toxic interaction with membrane phospholipids, and inhibition of morphogenetic transformation of yeasts to the mycelial forms. Some of the azole antifungal drugs, especially itraconazole and ketoconazole, are potent immune-suppressive agents, suppressing T-lymphocyte proliferation in vitro. Ketoconazole has anti-inflammatory properties that are probably mediated through inhibition of 5-lipoxygenase activity.

Ketoconazole and itraconazole are weak bases that require an acid environment for maximal oral absorption. Antacid administration inhibits oral bioavailability, and the bioavailability of itraconazole is two to three fold higher when taken with food. Recently, itraconazole has been solubilized in cyclodextrins in an effort to increase its absorption after oral dosing and to allow development of a parenteral formulation. Pharmacokinetic studies in both humans and cats have demonstrated increased absorption of itraconazole after administration of the oral solution in comparison to capsules. Both the oral solution (10 mg/mL) and the parenteral formulation (200 mg ampules diluted in 50 mL 0.9% sodium chloride for intravenous administration) are currently available.

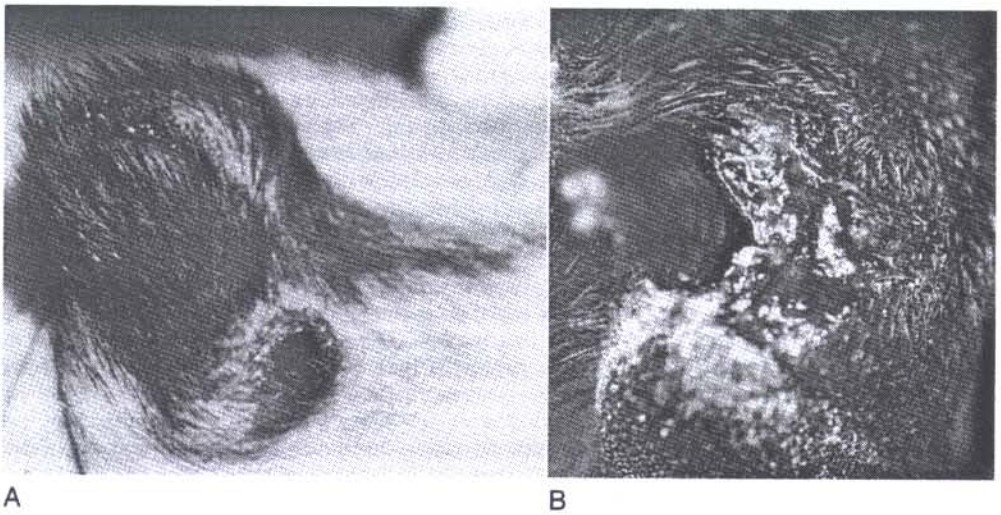
Fluconazole is not affected by gastric pH, and food does not affect its oral bioavailability. Peak plasma concentrations of itraconazole and fluconazole do not occur until 6 to 14 days after treatment is begun. This may account for the clinical lag time often seen between the time the drug is started and the time the patient begins to improve. A loading dose can be given for the first 3 days of treatment to reduce the time until steady-state concentrations are attained. Ketoconazole and itraconazole are extensively bound to plasma proteins (>99%), but because of their lipophilicity, both drugs distribute well throughout most tissues; however, concentrations in urine and CSF are typically very low. Neither drug crosses

the blood-brain, blood-prostate, or blood-ocular barriers well. Despite this, central nervous system (CNS), prostatic, and ocular fungal infections respond well to treatment with itraconazole. Itraconazole is concentrated in the skin, with delivery being via sebum. Sebum concentrations are 5 to 10 times higher than plasma concentrations, and detectable amounts persist for up to 14 days after the drug is discontinued. Detectable concentrations can be found in the hair and stratum corneum for up to 4 weeks. This property makes itraconazole ideal for treating dermatophyte infections and other fungal infections with cutaneous manifestations. Fluconazole is minimally protein bound and highly water soluble and distributes similarly to free water. High concentrations can be found in urine, CSF, and ocular fluids, and the drug crosses the blood-brain, blood-prostate, and blood-ocular barriers well. Ketoconazole and itraconazole are extensively metabolized in the liver and excreted in the bile and, to a lesser extent, in the urine. In contrast, fluconazole is minimally metabolized, and approximately 80% is excreted unchanged in the urine; consequently, the dose of fluconazole should be reduced in animals with decreased GFR.

The azole antifungal agents are widely used in veterinary medicine for treating systemic fungal infections.[2-4,10] Ketoconazole has been effective as a sole therapeutic agent in the management of blastomycosis, histoplasmosis, cryptococcosis, and coccidioidomycosis. However, with the possible exception of coccidioidomycosis, ketoconazole is probably not as effective as amphotericin B. Ketoconazole is primarily used in conjunction with amphotericin B when managing systemic infections, allowing lower doses of amphotericin B to be used and thus limiting nephrotoxicity. Itraconazole and fluconazole are safer and more effective than ketoconazole and can be used as sole agents in the management of most systemic mycoses. Itraconazole appears to be more effective than fluconazole in most situations, but fluconazole may be superior in the management of cryptococcosis and CNS, prostatic, and urinary tract infections. Itraconazole is the treatment of choice for blastomycosis in dogs and probably cats. Itraconazole has proven very effective as a sole treatment agent for histoplasmosis in cats.[3] The authors have found itraconazole to be effective in treating about 15% of dogs with GI pythiosis, despite the fact that *Pythium insidiosum* does not contain significant concentrations of membrane ergosterol. In treating most systemic fungal infections, a lag occurs between the initiation of treatment and clinical improvement. In severely affected animals, amphotericin B should probably be used initially or in conjunction with the triazole during this lag period.

The dose of ketoconazole is 4.5 to 13.6 mg/lb (10 to 30 mg/kg) divided twice a day. Side effects are often limiting, especially at higher doses. Fluconazole (1 to 4.5 mg/lb; 2.5 to 10 mg/kg) and itraconazole (2.2 to 4.5 mg/lb; 5 to 10 mg/kg) are usually better tolerated. Pharmacokinetic studies of itraconazole have been performed in cats.[11] Based on these studies, the oral itraconazole solution is preferred to the capsules, with a 24-hour dosing interval being sufficient at 4.5 mg/lb (10 mg/kg). Steady-state concentrations take up to 3 weeks to achieve. Most adverse effects of itraconazole are related to high serum concentrations, and animals that exhibit adverse effects usually do well on half the original dose. Adverse effects of the azole antifungal agents are similar across the class. Ketoconazole is the least tolerated, and itraconazole appears to be the best. Dose-related GI side effects (anorexia and vomiting) are most common, especially in cats. When these occur, dividing the dose into two treatments or reducing the dose may be of benefit. Azole-induced anorexia in cats is often ameliorated by the use of appetite stimulants such as oxazepam or cyproheptadine. Liver enzymes should be periodically monitored in animals being treated with azole antifungals. Asymptomatic increases in transaminase concentrations are seen in about half of animals treated with itraconazole, but this does not necessitate a change in therapy unless the animal also has anorexia, vomiting, depression, or abdominal pain. Enzyme concentrations often return to normal over time without intervention. Symptomatic hepatotoxicity is occasionally seen with ketoconazole use but is unusual after fluconazole or itraconazole administration. Cutaneous reactions are seen in approximately 7% of dogs receiving itraconazole at a dose of 4.5 mg/lb (10 mg/kg).[2] A local ulcerative dermatitis due to a cutaneous vasculitis (Figure 174-1) usually resolves shortly after the drug is discontinued. More severe reactions such as erythema multiforme or toxic epidermal necrolysis are rare. Thrombocytopenia has been associated with fluconazole use in people but has not been documented in animals. Adrenal insufficiency is possible with ketoconazole use. Azole interference with the activity of hepatic microsomal enzymes can lead to increased concentrations of coadministered drugs such as cyclosporine, digoxin, phenytoin, sulfonylureas, and warfarin.

The emergence in human patients of itraconazole-resistant fungal pathogens has prompted a search for new triazoles with greater potency. One of these newly developed triazoles, voriconazole, has recently gained FDA approval and is available to veterinarians. Voriconazole (Vfend™, Pfizer) is a fluconazole derivative that has potent in vitro and in vivo activity against common endemic and opportunistic fungal pathogens,



A B

Figure 174-1 A, Lesion on the prepuce of a dachshund being treated for blastomycosis with itraconazole. The lesion is caused by an itraconazole-induced cutaneous vasculitis. B, Paronychial lesion caused by an itraconazole-induced cutaneous vasculitis in a Doberman pinscher.

including molds other than the zygomycetes. It has demonstrated efficacy for invasive aspergillosis and oropharyngeal candidiasis in phase III clinical trials and can be administered either orally or intravenously. Its indications in human patients are for the treatment of invasive aspergillosis and other infections caused by molds (such as *Fusarium*) in immunocompromised individuals. Unfortunately, its high cost makes it unlikely to be used extensively in veterinary patients.

Flucytosine

Flucytosine is a synthetic antifungal drug with activity attributed to disruption of protein synthesis by inhibition of DNA and RNA synthesis. The drug is synergistic with amphotericin B and is used almost exclusively as an adjunct to amphotericin B in the treatment of cryptococcosis in cats. Flucytosine has good oral bioavailability. It is widely distributed and crosses the blood-brain barrier. The most common side effects are diarrhea, anorexia, and vomiting. Dose-dependent bone marrow suppression manifesting as neutropenia, thrombocytopenia, or pancytopenia is a less common but more significant toxicity. Cutaneous or mucocutaneous drug eruptions consisting of depigmentation followed by ulceration, exudation, and crust formation (occurring most frequently on the scrotum and nasal planum) have been described in a series of dogs. The dose of flucytosine used in cats is 125 to 250 mg orally divided two to four times a day.

Allylamines

Terbinafine is a synthetic allylamine antifungal drug that interferes with squalene epoxidase and is a potent inhibitor of ergosterol biosynthesis. Squalene accumulation in the fungal cell may account for the drug's fungicidal activity. A keratinophilic compound that is well distributed in skin, it has been used primarily for the treatment of dermatophytosis and onychomycosis in both human and veterinary patients. It may also have efficacy for the treatment of sporotrichosis. The efficacy of terbinafine for invasive or systemic fungal infections has not been well evaluated. However, the authors' clinical observations support the use of this drug in combination with itraconzole for the medical treatment of pythiosis when complete surgical resection of infected tissues is not possible. Potential side effects of terbinafine include GI toxicity, cutaneous reactions, and hepatitis. The drug dose ranges from 2.5 to 9 mg/lb (5 to 20 mg/kg) orally once daily.

Chitin and Glucan Synthesis Inhibitors

Drugs that inhibit the synthesis of chitin or β-glucan, two substances important to the structural and functional integrity of the fungal cell wall, hold promise as antifungal therapeutic agents because their targets are unique to fungi. Chitin synthase inhibitors include lufenuron [program] Novaris (a nonspecific inhibitor of chitin synthase) and drugs in the nikkomycin class, which are competitive inhibitors of chitin synthase. Although one drug in this class (nikkomycin Z) has been highly effective for the treatment of coccidioidomycosis in animal models, the spectrum of activity of nikkomycins for other systemic mycoses is limited and they are no longer being developed. Lufenuron has not been well-evaluated for the treatment of systemic mycoses in animals, but the limited spectrum of the nikkomycins suggest that the usefulness of lufenuron will be limited.

Echinocandins and pneumocandins, which are β-glucan synthase inhibitors in the new lipopeptide class of antifungal agents, hold perhaps the greatest promise for changing the way that clinicians will treat systemic mycoses in the next decade. The most studied of these agents, caspofungin (Cancidas®, Merck) is a potent broad-spectrum parenteral formulation that has potent activity against *Aspergillus* spp. and *Candida* spp. In addition, it is highly effective for the treatment of *Pneumocystis carinii* pneumonia because of its ability to prevent development of the glucan-rich cyst form. The primary limitation of this class of antifungals is its ineffectiveness against *Cryptococcus neoformans*, which contains very little glucan synthase. To date, the use of caspofungin in veterinary patients has not been evaluated, and its extremely high cost will certainly limit its otherwise tremendous potential.

SPECIFIC SYSTEMIC MYCOSES

Blastomycosis

Blastomycosis is a systemic fungal infection that usually originates in the lungs and then disseminates to the lymphatics, skin, eyes, bones, and other organs. The dog is most commonly affected. Young, male, large breed dogs (especially sporting breeds and hounds) living near water are at an increased risk.[12] In endemic areas, blastomycosis usually occurs as a sporadic event, but outbreaks are occasionally observed in both dogs and people.[13-15] Epidemiologically, outbreaks can often be traced back to a common point source of exposure to a focal area in the environment from which infective spores had been aerosolized for a short time. Confirmation of the source is rarely achieved by organism isolation because of the transient nature of the environmental contamination and the difficulties inherent in laboratory isolation.

The dimorphic fungus *Blastomyces dermatitidis* is the causative agent of blastomycosis. In infected tissue or when cultured at 37° C, the organism is a thick-walled yeast that reproduces by budding. Most often, organisms in tissue have a single bud, attached to the mother cell by a broad base. When cultured at 25° C, mold colonies grow slowly and contain branching, septate 1 to 2 μm mycelia that form round to piriform 2 to 10 μm conidia. In nature, *Blastomyces dermatitidis* is probably a soil saprophyte, but the reservoir remains unresolved because the organism can rarely be cultured from the environment. When cultured, it is usually cultured from wet, acidic or sandy soil containing decaying wood, animal feces, or other organic enrichment.[16] Moisture appears to be important to growth and transmission.

Disease occurrence is reported primarily in a geographically restricted distribution that follows the Mississippi, Ohio, Missouri, Tennessee, and St. Lawrence Rivers, the southern Great Lakes, and the southern Mid-Atlantic states (Figure 174-2). Within these geographic regions, infections are generally limited to smaller geographic pockets, with most affected animals living within a quarter of a mile of water.[15,17] It is not unusual for one veterinary practice within an endemic area to diagnose blastomycosis commonly, whereas another practice located within the same county rarely encounters the infection.

Pathophysiology Blastomycosis is not a contagious disease. It follows contact with the organism in the environment. Infection usually occurs via a respiratory route after the host inhales infective conidiophores. Rarely, disease may be seen after direct inoculation.[18] The incubation period varies from 5 to 12 weeks. Rain, dew, fog, or mist may play a critical role in liberating conidiophores from the environment. In addition, activities that disrupt the soil such as digging or construction may play a role in the aerosolization of spores. After inhalation, conidia are phagocytized by alveolar macrophages and transform from the mycelial phase to the yeast phase.

The yeasts stimulate local cell-mediated immunity, which results in a marked suppurative to pyogranulomatous inflammatory response. In some cases the cell-mediated immune response controls the infection locally; in others, phagocytized yeasts are transported into the pulmonary interstitium, where they gain access to both the lymphatics and the vascular system.

Figure 174-2 Areas in the United States endemic for blastomycosis, coccidioidomycosis, and histoplasmosis.

Hematogenous and lymphatic dissemination then results in multisystemic pyogranulomatous disease. Although dissemination can be to any organ system, the lymph nodes, eyes, skin, bones, subcutaneous tissues, and prostate are common organs affected in dogs[2,17,19]; skin, subcutaneous tissues, eyes, CNS, and lymph nodes are most commonly affected in cats.[20]

The immune response determines the severity of clinical disease, but blastomycosis is not considered an opportunistic infection. Antibody production occurs in most but not all cases, with the highest titers usually found in dogs with severe disseminated disease. Antibodies are not considered protective but can be used as a clinical marker of recent exposure or current disease. Recovery from infection is dependent on cell-mediated immunity. An adequate immune response may result in mild respiratory disease that resolves spontaneously. If dissemination has occurred, disease may be obvious in other organ systems, even without apparent pulmonary involvement. A poor immune response may result in severe pulmonary and disseminated disease.

Clinical Signs Bluetick coonhounds, treeing-walker coonhounds, pointers, and Weimaraners have the highest risk of infection.[12] Males are affected more commonly than females, and although any age dog can be affected, those in the 2- to 4-year age group have the highest incidence of disease. Exposure to possible environmental sources of infection, close proximity to water, and the likelihood of being housed in outdoor kennels probably explains the breed association. Clinical findings in animals with blastomycosis vary greatly because of the multisystemic nature of the disease. One or more organ systems may be involved.

Nonspecific signs such as anorexia, depression, weight loss, cachexia, and fever are common. Approximately 40% of dogs are febrile, and dogs with chronic pulmonary disease are most likely to be cachectic. Because the lungs serve as the portal of entry for the *Blastomyces* organism, it is not surprising that pulmonary signs are seen in 65% to 85% of affected dogs. Signs of pulmonary involvement range from mild respiratory distress when exercised to severe dyspnea at rest. Hypoxemia resulting in cyanosis is seen in the most severely affected cases and has a negative prognostic significance.[2] A dry, hacking cough is common. Mildly affected dogs may initially be diagnosed as having kennel cough. Enlarged perihilar lymph nodes compressing primary bronchi, as well as infiltrative bronchointerstitial and alveolar disease, contribute to the cough. Rapid, shallow respiratory efforts may be noted and can be caused by pleural effusion or pleuritic pain. Chylothorax, solid granulomatous masses, and pulmonary thromboembolism are uncommonly reported complications of blastomycosis.

Diffuse lymphadenopathy is seen in about 40% to 60% of dogs with blastomycosis. The lymph node enlargement can be marked and may be mistaken for lymphosarcoma if cytology or histopathology is not performed.

Cutaneous signs are reported in about 30% to 50% of affected dogs and are also commonly noted in affected cats. Reported prevalences of skin disease in cases of blastomycosis may underestimate the actual prevalence, because lesions are sometimes small and easily overlooked unless a thorough dermatologic examination is performed. Single or multiple papules, nodules, or plaques that can ulcerate and drain a serosanguineous to purulent exudate characterize typical skin lesions. The nodular lesions are often quite small in dogs, but large abscesses occasionally occur, especially in cats. Paronychia is common in dogs, so the feet and nail beds should be closely examined.

Ocular involvement is noted in 20% to 50% of cases. Posterior segment disease, characterized by chorioretinitis, retinal separation, subretinal granulomas, and vitreitis, usually occurs initially. Approximately 50% of affected dogs have bilateral ocular involvement. Optic neuritis is occasionally noted and may signify more diffuse CNS involvement and a poorer prognosis. Anterior segment disease is usually, but not always, secondary to the posterior segment involvement. It may be characterized by conjunctivitis, keratitis, iridocyclitis, and eventually anterior uveitis and endophthalmitis. Secondary glaucoma is common in dogs with anterior segment disease.

Dogs that are blind at the time of initial diagnosis rarely regain vision, even with aggressive treatment and good systemic response. Dogs that have vision and only posterior segment disease at the time of diagnosis have a better prognosis for vision.

Lameness caused by fungal osteomyelitis or painful paronychia is noted in about 25% of dogs with blastomycosis, and fungal osteomyelitis is noted in about 10% to 15% of dogs with blastomycosis. The pain and swelling are usually noted over epiphyseal regions below the elbow or stifle. Single lesions are more common than multiple lesions. Fungal mono- or polyarthritis is a rare cause of lameness.

The reproductive system is affected in approximately 5% to 10% of affected dogs. Orchitis was noted in 16% of 61 intact male dogs with blastomycosis seen at Louisiana State University. Fungal prostatitis or mastitis is reported in less than 5% of affected dogs.

The nervous system is affected in less than 5% of canine cases but is commonly affected in feline cases (Figure 174-3). Advanced CNS imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) should be considered in any cat diagnosed with blastomycosis, even if obvious neurologic signs are not apparent. The clinical signs associated with nervous system involvement are dependent on which parts of the CNS are involved, but often neurologic localization indicates diffuse or multifocal disease. Other potential sites of infection include cranial mediastinum, liver, spleen, kidney, and nasal cavity.[21]

Feline blastomycosis is less common than canine blastomycosis. The veterinary literature contains only scattered case reports and small case series.[20] Most of the clinical signs observed in dogs are also noted in cats. The main differences are that large abscesses are more common in cats than in dogs, and neurologic involvement is often noted.

Diagnosis Blastomycosis is usually fairly easy to diagnose because of the large numbers of characteristic yeasts found within lesions, especially within infected skin, eyes, and lymph nodes.[17,22]

Complete blood count (CBC) results are often normal. A mild nonregenerative anemia and mature neutrophilia or neutrophilia with mild left shift may be seen. Clinical chemistry results are also often unremarkable. Hypoalbuminemia is the most consistent abnormality. Mild hypercalcemia is noted in up to 10% of cases.[17] Severe hypercalcemia requiring treatment is occasionally seen.

Radiographic assessment can be very helpful in the diagnostic evaluation of a dog or cat suspected of having blastomycosis

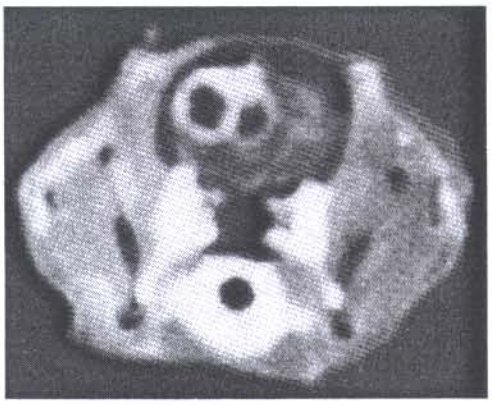


Figure 174-3 Cross-sectional magnetic resonance image (MRI) revealing a contrast-enhancing mixed-intensity lesion in the rostral portion of the right cerebral cortex in a cat with blastomycosis.

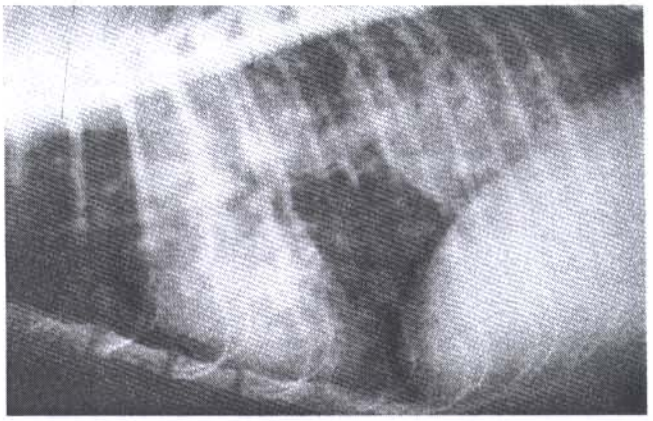


Figure 174-4 Lateral thoracic radiograph revealing a diffuse nodular interstitial pattern in a cat with blastomycosis.

(Figures 174-4, 174-5, and 174-6). Thoracic radiographs reveal an interstitial pattern in about 70% of canine cases. Although a nodular interstitial pattern is classically observed (41% of cases), diffuse interstitial (24%) and bronchointerstitial (5%) patterns may also be prominent findings. An alveolar or mixed interstitial-alveolar pattern is observed in about 20% of canine cases, and tracheobronchial lymphadenopathy is noted in about 30%. Radiographic patterns mimicking other diseases such as mediastinal mass (8%) or solitary pulmonary mass (8%) are not as common. Pleural effusion (7%) is rarely observed and when present may obscure pulmonary parenchymal changes. Pneumothorax induced by pulmonary blastomycosis is rare. Bone lesions may be noted on radiographs of long bones,

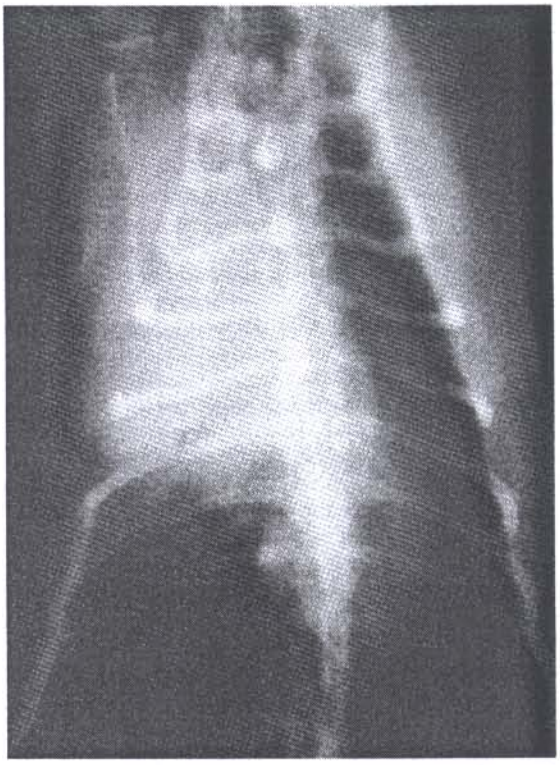


Figure 174-5 Consolidation of the right cranial lung lobe in a cat with blastomycosis. Consolidating and abscessing lesions are often seen in cats with systemic fungal infections.

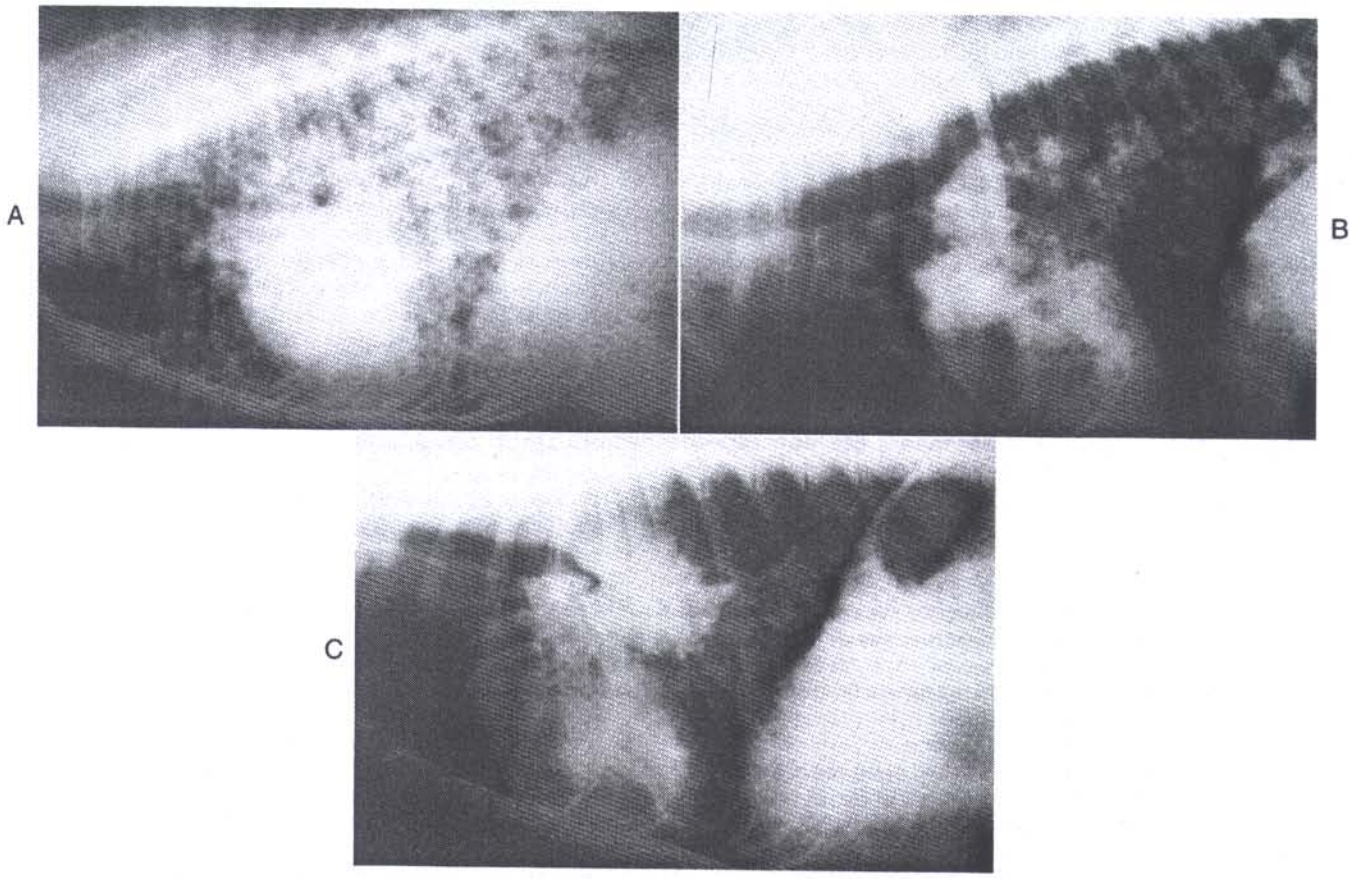


Figure 174-6 A, Lateral thoracic radiograph from a dog with blastomycosis revealing the classic "snowstorm" appearance of the nodular interstitial pattern commonly seen in systemic mycotic infections. B, Lateral thoracic radiograph from a dog with blastomycosis showing multiple large, ill-defined nodules and a bronchointerstitial pattern. C, Lateral thoracic radiograph from a dog with blastomycosis showing perihilar lymphadenopathy and a patchy interstitial pattern. Perihilar lymphadenopathy is common in systemic fungal infections, especially histoplasmosis and coccidioidomycosis.

especially those of the distal limbs. Lesions are osteolytic and typically occur at the ends of the long bones (Figure 174-7). The forelimbs are affected more commonly than the rear limbs, with most extremity lesions being below the elbow or the stifle. Periosteal proliferation and soft tissue swelling are noted in about 50% of lesions.

Definitive diagnosis is made by organism identification. This can be done by cytology, histopathology, or fungal culture. Cytology from affected tissue typically reveals pyogranulomatous or suppurative inflammation, often with thick-walled yeasts (8 to 12 µm in diameter, with 0.5 to 0.75 µm thick walls) that bud to form daughter cells from a broad base (Figure 174-8).[22,23] The yeast cells lack a capsule, helping to differentiate them from *Cryptococcus*. Skin lesions yield organisms about 80% of the time. This is the easiest and most useful site for cytologic diagnosis. Impression smears, skin scrapings, and fine needle aspirate of nodular lesions can be used. Vitreal aspirates yield organisms from almost all affected eyes, and lymph node aspirates yield organisms approximately 60% of the time. Bone and lung aspirates, transtracheal wash cytology, and bronchoalveolar lavage each yield organisms less than 50% of the time.[17,24] Urinalysis or prostatic wash cytology rarely reveals organisms.

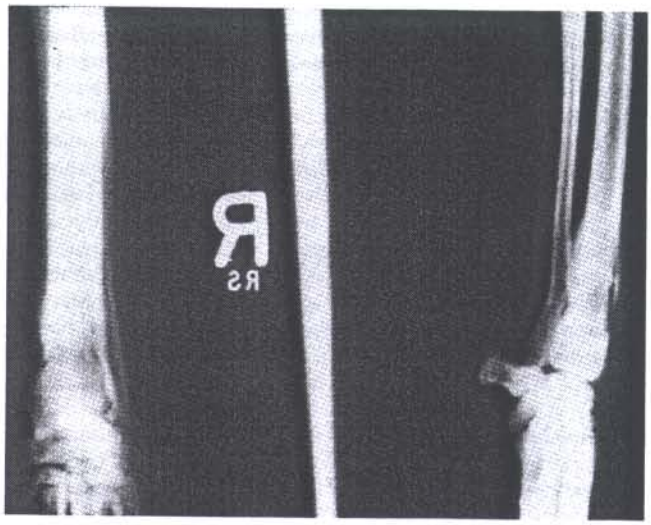


Figure 174-7 Lateral and anteroposterior view of the distal radius, ulna, and carpus from a Brittany spaniel with *Blastomyces* osteomyelitis. The reader should note the bony lysis and periosteal proliferation involving the distal aspect of the proximal radius.

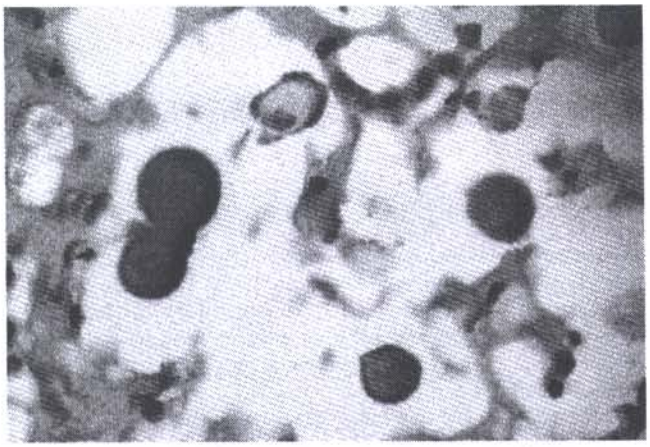


Figure 174-8 Impression smear from a dog with cutaneous lesions revealing thick-walled, budding yeast typical of *Blastomyces dermatitidis*.

Rarely, organisms may be coughed up and swallowed and appear in the stool on fecal examination.[25] Care must be taken when handling samples that may contain yeast cells. Direct inoculation of organisms from needle-stick injury may result in localized cutaneous disease.[26] This is seen as an occupational hazard in laboratory workers who handle infective material and cultures and in veterinary personnel who sample infected tissue via fine needle aspirate or biopsy. Local inoculation is probably rare as a cause of subcutaneous disease in dogs and cats.

Histopathology is generally characterized by purulent to pyogranulomatous inflammation, with broad-based organisms usually being apparent. Special stains such as periodic acid–Schiff (PAS), Gridley's fungal, and Gomori's methenamine silver (GMS) stain are best for demonstrating organisms. PCR has recently been used to identify organisms in tissue.[27]

Culture is not needed for definitive identification in clinical cases. If tissue is cultured, mycelial growth on Sabouraud's dextrose agar may take 1 to 4 weeks at 37° C, whereas yeast will grow on blood or brain-heart infusion agar in 1 to 2 weeks at 25° C. Culturing the organism from the environment is rarely achieved. The microbiology lab should be alerted if blastomycosis is suspected, because viable cultures of *Blastomyces dermatitidis* present a potential danger of infection for laboratory personnel if the plates are handled inappropriately.[28]

Serology should be used only when a high degree of suspicion for blastomycosis exists and repeated attempts have failed to demonstrate the organisms. Several different types of serologic tests have been evaluated, including agar-gel immunodiffusion (AGID), complement fixation, enzyme-linked immunosorbent assay (ELISA), counterimmunoelectrophoresis, and agar-gel precipitin tests. An AGID test is most commonly used. This test detects antibodies directed against the fungal organism and has a sensitivity and specificity of approximately 90%. Serology may be negative early in the disease course, and in some cases it may revert back to negative as the disease progresses. Antibody titers have not proven useful as an assessment tool in following response to therapy.

Treatment Spontaneous recovery from symptomatic blastomycosis has been reported in people but rarely occurs in dogs and has not been reported in cats. Therefore all cases of symptomatic blastomycosis in dogs and cats should be treated. Itraconazole is presently considered the treatment of choice, except in cases of moderate to severe hypoxemia, when amphotericin B should still be considered the drug of first choice.[2] Clinical cures can be expected in 70% to 75% of treated cases. Treatment failure is most likely in dogs that are hypoxemic or have three or more organ systems affected. The dose of itraconazole that has proven effective is 2.2 mg/lb (5 mg/kg) orally once a day or divided twice a day. The drug should be continued for 2 to 3 months or until active disease is not apparent. Response to itraconazole treatment is minimal during the initial 1 to 2 weeks. A loading dose of 4.5 mg/lb (10 mg/kg) daily for the first 3 days of treatment may minimize this lag time. Treatment for an extra month after signs have resolved does not appear to reduce the likelihood of recurrence. Recurrence occurs in approximately 20% of treated dogs from months to years after treatment has been discontinued.[2,17] Thoracic radiographs are an insensitive tool in monitoring recovery, because significant radiographic abnormalities continue to improve for months after itraconazole treatment has been discontinued. Cats require 4.5 mg/lb (10 mg/kg) once a day or divided twice a day, and longer courses of treatment are usually required.

Ketoconazole is effective in less than 50% of cases at an oral dose of 4.5 to 13.6 mg/lb (10 to 30 mg/kg) divided twice daily for a minimum of 3 months. The response rate is much lower, and the relapse rate is higher when compared with treatment with itraconazole; in addition, dogs generally have to be treated longer. Toxicity is more likely with ketoconazole. Fluconazole has not been investigated for the treatment of blastomycosis in dogs and cats. The author's clinical impression is that it is not as effective as itraconazole, and fluconazole is more expensive. Fluconazole has been used successfully at high doses to treat blastomycosis in people.[29] In addition, because fluconazole does not require a low gastric pH for maximal bioavailability and is not affected by the presence or lack of food, it may be a better initial choice in animals that will not eat. Because it is excreted in the urine and crosses the blood-brain, blood-ocular, and blood-prostatic barriers well, it may be a more appropriate treatment choice for urinary tract, prostatic, and CNS infections. Studies evaluating efficacy in these situations in dogs and cats have not been performed, however. Parenteral forms of fluconazole and itraconazole are available and may be useful for treating severely affected or hypoxemic animals in which amphotericin B is not an appropriate option.

Amphotericin B has very good efficacy against *Blastomyces* organisms. It is recommended that amphotericin B be used in combination with itraconazole or ketoconazole for severely affected or hypoxemic animals.

ABLC (Abelcet), a lipid complexed formulation of amphotericin B is recommended. It allows relatively high doses to be used with low toxicity.[9] A dose of 1 to 1.5 mg/lb (2 to 3 mg/kg) intravenously every other day to a total dose of 24 to 27 mg/kg has been recommended for dogs with blastomycosis. ABLC is expensive when compared with the deoxycholate form, but the authors consider it the treatment of choice for severely affected dogs.

The deoxycholate formulation, although much less expensive, carries a higher risk of toxicity. When using this formulation, reconstituted, amphotericin B is mixed with 5% dextrose in water (D5W) and administered as a rapid infusion over 10 minutes or as a longer infusion over 1 to 6 hours. The longer infusion is less likely to cause toxicity. The dose is 0.22 mg/lb (0.5 mg/kg) for dogs, 0.1 mg/lb (0.25 mg/kg) for cats, intravenously every other day to a total dose of 1.8 mg/lb (4 mg/kg) when used in combination with azole antifungal drugs. A higher dose of 0.22 to 0.45 mg/lb (0.5 to 1 mg/kg) to a total dose of 3.6 mg/lb (8 mg/kg) is recommended in dogs if amphotericin B is the sole treatment agent. The BUN or creatinine should be monitored before each treatment, and amphotericin B should be discontinued if the dog or cat becomes azotemic (BUN >50 mg/dL, creatinine >3 mg/dL).

The efficacy of amphotericin B when combined with ketoconazole or itraconazole is equal to that seen with itraconazole alone, but side effects are much more likely.

Ancillary therapy in hypoxemic animals should include oxygen, bronchodilators, and possibly antibiotics. Anterior uveitis should be treated with topical steroids and atropine; secondary glaucoma with dichlorphenamide (0.9 to 1.8 mg/lb [2 to 4 mg/kg], orally two to three times a day). Atropine should not be used in animals with glaucoma.

Approximately 70% to 75% of dogs treated with either itraconazole or ketoconazole-amphotericin B combination respond completely to therapy. Dogs that die are usually those with severe respiratory disease and hypoxemia. Dogs that live through the first 10 days of therapy generally do well. Hypoxemia and the involvement of three or more systems are poor prognostic factors.[2] Relapse occurs in 15% to 20% of treated dogs. It usually occurs in the first 6 months after treatment but can occur after a year or more. Relapses should be treated as new infections and are no less likely to respond.

Public Health Significance Blastomycosis is not likely to be transmitted from animal to animal or from animal to person. Localized *Blastomyces* infections have occurred after needlestick injuries when obtaining fine needle aspirate from infected lesions, and laboratory workers can potentially be infected from fungal cultures. Outbreaks in which both people and dogs are affected are due to exposure to a common environmental source rather than to zoonosis.

Histoplasmosis

Histoplasmosis is a systemic fungal infection that usually originates in the lungs and potentially the GI tract, then disseminates to the lymphatics, liver, spleen, bone marrow, eyes, and other organs. A wide variety of mammalian species can be affected, and cats may be more susceptible to infection than dogs. As with most systemic fungal diseases, animals younger than 4 years old are at an increased risk, but any age can be affected.

Histoplasmosis is caused by the dimorphic fungus *Histoplasma capsulatum*. In infected tissue or when cultured at 30° to 37° C, the organism is a yeast. In the environment, *H. capsulatum* is a soil saprophyte that survives a wide range of moistures and temperatures. Nitrogen-rich soils, especially those containing bird or bat guano, appear ideal for supporting growth. The fungus is endemic throughout most of the temperate and subtropic regions of the world. Most cases of histoplasmosis in the United States occur in the central states, with the geographic distribution following the Mississippi, Ohio, and Missouri Rivers. The geographic distribution is wider than that of blastomycosis.

Pathophysiology Histoplasmosis is not a contagious disease. Infection is probably via inhalation or ingestion of infective conidia from the environment. The respiratory system is likely the primary route of infection in cats, humans, and dogs, but the GI system may also be an important route in the dog.

After inhalation or ingestion, conidia transform from the mycelial phase to the yeast phase and are phagocytized by cells of the macrophage monocyte system, where they grow as facultative intracellular organisms. Hematogenous and lymphatic dissemination results in multisystemic disease. Dissemination can be to any organ system, resulting in a granulomatous inflammatory response. The lungs, GI system, lymph nodes, liver, spleen, bone marrow, eyes, and adrenal glands are common organs affected in dogs; lungs, liver, lymph nodes, eyes, and bone marrow are most commonly affected in cats. The incubation period is 12 to 16 days in dogs and humans.

The cell-mediated immune response determines the severity of clinical disease, with subclinical infection probably being common. Most cases of infection are sporadic events, but point-source outbreaks of disease are occasionally reported in both dogs and humans. Epidemiologically, these outbreaks are usually associated with exposure to areas heavily contaminated with *Histoplasma* organisms such as chicken coops, bat habitats, or starling roosts.

Clinical Signs Feline histoplasmosis occurs most commonly in cats younger than 4 years of age. No breed or sex predilection exists. Disease in cats is usually insidious in onset and nonspecific, with clinical findings varying greatly because of the multisystemic nature of the infection. Depression, anorexia, fever, pale mucous membranes, and weight loss are common. Pulmonary involvement, as evidenced by dyspnea, tachypnea, or abnormal lung sounds, is seen in about 50% of affected cats. Cough is uncommon. Hepatomegaly, splenomegaly, or lymphadenopathy is noted in about a third of affected cats. Ocular involvement may result in abnormal retinal pigment proliferation, retinal edema, granulomatous chorioretinitis, anterior uveitis, panophthalmitis, or optic neuritis. Retinal detachment and secondary glaucoma are less common than in animals affected with blastomycosis. Fungal osteomyelitis may cause lameness in one or more limbs. Cutaneous lesions consisting of multiple small nodules that may ulcerate and drain or crust over are noted less commonly than in animals affected with blastomycosis. GI signs other than anorexia are uncommon in cats with histoplasmosis. Oral and lingual ulceration has been reported as an unusual manifestation. Icterus is occasionally seen in cats with hepatic involvement.

Canine histoplasmosis is also most commonly seen in dogs younger than 4 years of age. Male dogs are affected 1.2 fold as frequently as female dogs, and pointers, Weimaraners, and Brittany spaniels may be over-represented. The clinical findings are related to the route of infection and the extent of systemic dissemination. Clinically inapparent infection is probably common after inhalation of organisms. In those dogs showing clinical signs, findings vary greatly, but GI signs are most common (Table 174-2). Large-intestine diarrhea with tenesmus, mucus, and fresh blood is most common early in the disease course. Small-intestine diarrhea that may be voluminous and associated with malabsorption, protein-losing enteropathy, or both may become apparent as the disease progresses. Nonspecific clinical signs such as fever, anorexia, depression, and severe weight loss are common and may be caused by elaboration of inflammatory mediators such as TNF and interleukin-1 (IL-1). Abnormal lung sounds with or without coughing, tachypnea, or dyspnea are seen in less than 50% of affected dogs. Pleural effusion is seen in rare cases and may contribute to respiratory signs.[30] Splenomegaly, hepatomegaly, and lymphadenopathy are occasionally seen.

Diagnosis A normocytic-normochromic nonregenerative anemia is the most common CBC abnormality. It is caused by chronic inflammation, GI blood loss, and bone marrow infection. Neutrophilia and monocytosis are often seen, but leukocyte counts are variable. Neutropenia or pancytopenia (or both) is noted in a minority of affected animals, especially in cats. The CBC rarely results in a definitive diagnosis, because *Histoplasma* organisms are only occasionally seen in monocytes or neutrophils and rarely in eosinophils. Thrombocytopenia due to increased use or platelet destruction is seen in as many as one half of affected dogs and one third of affected cats. Serum chemistry abnormalities are nonspecific. Hypoalbuminemia is the most consistent abnormality. Increases in serum alanine aminotransferase (SALT), serum aspartate aminotransferase (SAST), alkaline phosphatase, and total bilirubin may indicate hepatic involvement. Hypercalcemia, although not as common as in dogs with blastomycosis, has been reported. Hypercalcemia is more common in cats than in dogs.[3] It should be noted that hypoalbuminemia lowers

Table 174-2

Differential Diagnosis for Gastrointestinal Signs Seen in Dogs and Occasionally in Cats With Histoplasmosis

Large-Intestine Disease

Diet-associated colitis
- Dietary hypersensitivity
- Foreign material–induced colitis

Idiopathic colitis
- Lymphocytic-plasmacytic colitis
- Eosinophilic colitis
- Granulomatous colitis
- Histiocytic ulcerative colitis of boxer dogs
- Suppurative colitis

Parasitic and protozoal colitis
- Trichuriasis (whipworms)
- Ancylostomiasis (hookworms)
- Strongyloidiasis
- Entamebiasis
- Balantidiasis
- Giardiasis

Bacterial colitis
- *Salmonella* spp.
- *Campylobacter jejuni*
- *Yersinia enterocolitica, Y. pseudotuberculosis*
- Mycobacteria
- *Clostridium perfringens, C. difficile*

Candidiasis
- Gastrointestinal (GI) pythiosis
- Protothecosis
- Cecocolic or ileocolic intussusception
- Pancreatitis-associated colitis

Small-Intestine Disease

Idiopathic inflammatory bowel disease
- Lymphocytic-plasmacytic enteritis
- Eosinophilic enteritis
- Granulomatous enteritis

Intestinal lymphosarcoma
- Parasitic enteritis (ancylostomiasis, toxocariasis)
- Chronic giardiasis
- Small-intestine bacterial overgrowth
- Gastrointestinal (GI) pythiosis
- Lymphangiectasia
- Exocrine pancreatic insufficiency
- Partial intestinal obstruction
- Chronic enteropathy of Shar Peis
- Immunoproliferative enteritis of basenjis

total serum calcium and may mask subtle hypercalcemia. Feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV) tests are usually negative in cats.

Thoracic radiographs often reveal a diffuse interstitial or linear interstitial pattern that tends to coalesce to a nodular interstitial pattern (Figure 174-9). Alveolar infiltrates are rarely reported. Hilar lymphadenopathy is common in dogs but unusual in cats. Calcified pulmonary infiltrates or hilar lymph nodes may indicate inactive disease in dogs. Osseous lesions consisting of osteolysis, periosteal new bone formation, and subperiosteal bone proliferation are rarely noted. Bones of the distal appendicular skeleton, especially carpal and tarsal bones, are affected most commonly.

Organism identification is required for definitive diagnosis. The most common means of organism identification is cytology. Cytology from affected tissue reveals pyogranulomatous inflammation, often with numerous small, round to oval intracellular yeast cells (2 to 4 μm in diameter) characterized by a basophilic center and a light halo caused by shrinkage of the cell away from the cell wall during fixation (Figure 174-10). Although multiple *Histoplasma* organisms are usually found within phagocytic cells of the mononuclear phagocyte system, a small number of the organisms are released from cells during slide preparation and may be seen free on the slides stained with a Wright-Giemsa–type stain. Samples for cytology should be collected from tissue with apparent abnormalities. In the cat, aspiration cytology from bone marrow or lymph nodes or cytology from tracheal wash or bronchoalveolar lavage is most likely to yield organisms. In the dog, cytology from rectal scrapings or biopsies and aspiration cytology from bone marrow, liver, lymph nodes, spleen, or tracheal wash or bronchoalveolar lavage are most likely to yield organisms. Buffy coat smears, cytology of pleural or peritoneal effusions, aspirates of lytic bone lesions, and aspirates or impression smears of nodular skin lesions may also yield organisms.

If organisms are not cytologically apparent, histopathology may be diagnostic. Pyogranulomatous lesions with multiple intracellular organisms are usually apparent. Histoplasmosis should be considered when granulomatous hepatitis or other granulomatous or pyogranulomatous disease is seen on biopsy.[31] The yeast does not stain well with routine hematoxylin-eosin (H&E) stains, so special stains such as PAS, Gridley's fungal, and GMS stain are often used to demonstrate organisms.

Fungal culture from affected tissue can be used for diagnosis but is rarely needed in clinical cases. The organism grows as buff-brown mycelial growth on Sabouraud's dextrose agar. It usually takes 7 to 10 days to grow at room temperature. The yeast produces white, moist colonies on blood agar when grown at 30° to 37° C. The cultured organism is of pathogenic potential, which precludes culture attempts in a practice setting.

Serology is presently an ineffective method of diagnosis. Both false-positive and false-negative results are common. Poor correlation between necropsy findings and complement-fixation tests has been seen in multiple studies.

Treatment Pulmonary histoplasmosis may be self-limited, but antifungal treatment is still recommended because of the potential for chronic dissemination. Dogs or cats with other systemic findings indicative of disseminated histoplasmosis usually die without treatment. Treatment protocols are similar to those described for blastomycosis, although they have not been as well studied. Longer treatment times are probably needed in most cases, but this is highly variable, depending on the severity of the infection and the response of the animal.

Itraconazole (4.5 mg/lb [10 mg/kg] orally once a day or divided twice a day) is considered the treatment of choice for feline histoplasmosis. At least 2 to 4 months of therapy is required. Few studies have evaluated the efficacy of itraconazole treatment, but in one study, all eight of eight treated cats were cured.[3] Ketoconazole is effective in about one third of affected cats. The addition of amphotericin B to ketoconazole treatment regimens may improve the efficacy, especially in severely affected cats. Fluconazole is likely effective but has not been well studied.

In dogs with histoplasmosis, ketoconazole has been described as the treatment of choice. Amphotericin B should

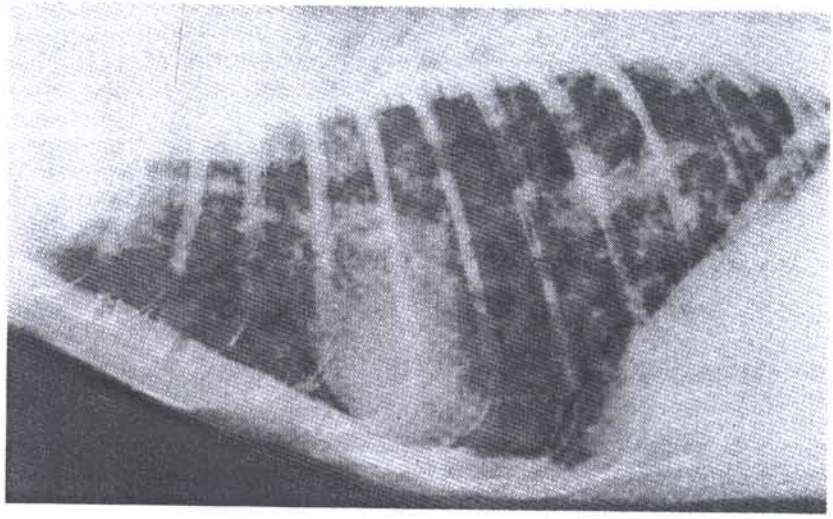


Figure 174-9 Lateral thoracic radiograph of an 8-year-old Siamese cat with a 2-week history of dyspnea caused by *Histoplasma capsulatum* infection. This coalescing pattern of interstitial infiltrates is commonly seen in cats with pulmonary histoplasmosis.

be added to the protocol in fulminant cases. Itraconazole or fluconazole is safer and may result in better efficacy than ketoconazole, but evaluation has been minimal. For dogs with GI disease, ancillary therapy should be considered along with antifungal therapy. A highly digestible diet should be fed to dogs with small-intestine involvement, and fiber may be useful in dogs with signs of colitis. Small-intestine bacterial overgrowth may occur in dogs with histoplasmosis and should be treated with tylosin (4.5 to 9 mg/lb [10 to 20 mg/kg] orally twice a day), metronidazole (3.4 to 4.5 mg/lb [7.5 to 10 mg/kg] orally two to three times a day), tetracycline (6.8 to 9 mg/lb [15 to 20 mg/kg] orally three times a day), or amoxicillin (4.5 to 9 mg/lb [10 to 20 mg/kg] orally twice a day). Nonspecific therapy for diarrhea can include loperamide (0.045 to 0.09 mg/lb [0.1 to 0.2 mg/kg] orally twice a day) for small-intestine diarrhea and sulfasalazine (4.5 to 13.6 mg/lb [10 to 30 mg/kg] orally two to three times a day) for large-intestine diarrhea. Ancillary respiratory therapy may include oxygen and bronchodilators in hypoxemic animals and antibiotics in dogs with secondary bacterial pneumonia. Corticosteroids have been recommended for treating dogs with airway obstruction secondary to hilar lymphadenopathy caused by histoplasmosis.[32]

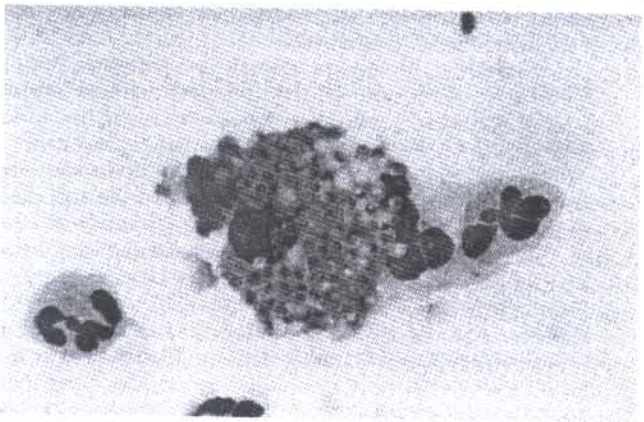


Figure 174-10 Cytology from a bronchoalveolar lavage sample revealing a macrophage containing many round to oval-shaped *Histoplasma* organisms in a cat with histoplasmosis. (Courtesy of Dr. Jan VanSteenhouse.)

Resolution of clinical signs is the best means of patient monitoring. Rechecks should be performed monthly while dogs or cats are being treated and should include physical and ocular examinations and a chemistry panel to evaluate liver enzymes in animals receiving azole antifungals. Treatment should be continued for 1 month beyond resolution of clinical signs, and animals should be reevaluated 3 and 6 months after discontinuing therapy to assess for relapse. Serology is not useful in monitoring response to therapy or evaluating for relapse.

The prognosis is good for dogs with only pulmonary signs, but dogs with GI or severe dissemination have a guarded prognosis. The prognosis is fair to good for cats treated with itraconazole, although long-term therapy may be required. Severely debilitated cats have a guarded prognosis.

Cryptococcosis

Cryptococcosis is an opportunistic systemic fungal infection of worldwide significance that usually originates in the nasal cavity, paranasal tissues, or lungs. It can then disseminate, most commonly to the skin, eyes, or CNS. Disease occurs in a wide variety of mammalian species. Among domestic animals, it occurs most commonly in the cat, in which it is the most common of the systemic mycoses. Unlike the other systemic mycoses, cryptococcosis does not follow strict geographic boundaries but is most common in the Southeastern and Southwestern United States, Southern California, and the east coast of Australia.

Cryptococcosis is caused by *Cryptococcus neoformans*, a saprophytic, round, yeastlike organism with a restricted ecologic niche. *C. neoformans* var. *neoformans* is the subspecies that most commonly causes disease and is environmentally associated with pigeon droppings or other avian habitats. *C. neoformans* var. *gattii* is a second subspecies that is capable of causing disease and is associated with bark and leaf litter of certain eucalyptus trees. In infected tissue, and often when cultured, the organism is a variable-sized yeast (3.5 to 7 μm) with a large heteropolysaccharide capsule (1 to 30 μm). Both subspecies have been shown to cause disease in cats and humans. *C. neoformans* reproduces primarily by budding from a narrow base.

The pigeon is thought to be the most important vector of *C. neoformans*. The *Cryptococcus* organism can be found in high numbers in pigeon roosts, barn lofts, haymows, and along cupolas and cornices where pigeons often sit. In the desiccated state, the *Cryptococcus* organism may be no larger than 1 μm and may survive up to 2 years.

Pathophysiology Cryptococcosis is not a contagious disease. Infection occurs most commonly via inhalation of yeast from the environment. Debris and droppings in and around avian habitats, especially pigeon habitats, contain the largest numbers of *Cryptococcus* organisms. Most yeasts are probably too large to be inhaled into the lungs and settle out in the nasal cavity or nasopharynx, where they can produce disease or result in animals becoming asymptomatic carriers of the organism. In one study, cryptococcal organisms could be cultured from nasal washings in 14% of asymptomatic dogs and 7% of asymptomatic cats.[33] The small, desiccated forms of the yeast are also infective and can be inhaled into the small airways and alveoli, leading to pulmonary disease. After inhalation into the nasal cavity, paranasal sinuses, or lungs, cell-mediated immune response results in granuloma formation. Dissemination can occur by either direct extension or hematogenous spread. Direct extension from the nasal cavity through the cribriform plate to the CNS or to the paranasal soft tissues and skin is common. Although dissemination can be to any organ system, the skin, eyes, and CNS are most commonly affected.

Lesions consist of either granulomatous inflammation with few organisms or gelatinous masses of organisms with little inflammation. The large capsule surrounding the cryptococcal organism contributes to pathogenicity by inhibiting phagocytosis, plasma cell function, and leukocyte migration. As with the other systemic mycoses, the immune response determines the severity of clinical disease. Antibodies are readily produced by the humoral immune system but are not considered protective. Recovery, therefore is dependent on cell-mediated immunity. Most human cases of cryptococcosis are associated with immune suppression, especially lymphoreticular neoplasia and AIDS. However, immune suppression has not been as apparent in most affected cats and dogs. An association with FeLV and FIV infections in cats has been reported, and chronic glucocorticoid use has been implicated as a predisposing factor in both cats and dogs.[4,30,34,35]

Clinical Signs Cats are more commonly affected by cryptococcosis than dogs. No apparent breed, sex, or age predilection exists in cats. Clinical findings are usually related to upper respiratory, nasopharyngeal, cutaneous, ocular, or CNS involvement. Unlike in other systemic mycoses, the lungs are not commonly affected. Nonspecific signs such as depression and anorexia are common in chronic cases, but fever is uncommon. Upper respiratory signs related to nasal cavity involvement are seen in 50% to 80% of affected cats. In these cats, sneezing and snuffling are common, and unilateral or bilateral mucopurulent nasal discharge with or without blood is typically seen. Proliferative soft tissue masses or ulcerative lesions within the nasal cavity or over the bridge of the nose are seen in approximately 70% of cases with upper respiratory involvement (Figure 174-11). Oral ulcerations are occasionally noted but are not common. Nasopharyngeal mass lesions causing snoring, stertor, and inspiratory dyspnea are occasionally noted.[36] The skin or subcutaneous tissues are affected in approximately 40% to 50% of infected cats. Primary lesions include papules or nodules that may ulcerate and drain. Multiple lesions are typical, and regional lymphadenopathy is common. Hematogenous spread from the respiratory system may result in lameness secondary to osteomyelitis, renal failure secondary to renal disease, and generalized lymphadenopathy.

The eyes are affected in 20% to 25% of infected cats, especially those with CNS involvement. Granulomatous chorioretinitis with or without exudative retinal detachment is the most common ocular manifestation and can lead to panophthalmitis. Less often, optic neuritis can be seen, resulting in blindness. Anterior uveitis is not as common as posterior segment disease. CNS involvement is reported in approximately

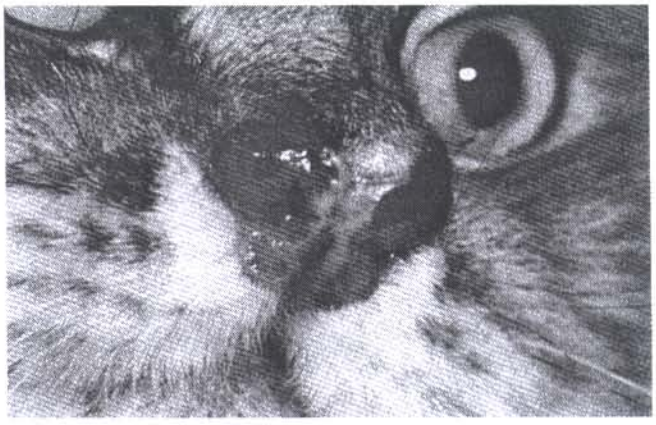


Figure 174-11 Nasal cryptococcosis in a cat. (Courtesy Dr. Carol Foil.)

20% of affected cats. This may be an under-representation of the actual number of cases with nervous system involvement.[35] The forebrain is most commonly affected, because invasion through the cribriform plate is thought to be common. Signs may include depression, behavior changes, seizures, circling, ataxia, blindness, head pressing, cranial nerve deficits, and paresis. Nasopharyngeal granulomas may occlude the auditory tube resulting in otitis media interna and resultant peripheral vestibular signs.[37] Cats with concurrent FeLV or FIV infection tend to be more severely affected and may be more likely to develop neurologic or ophthalmic signs.

Canine cryptococcosis is typically seen in dogs younger than 4 years of age. No apparent sex predilection exists, and American cocker spaniels, Labrador retrievers, Great Danes, and Doberman pinschers appear to be over-represented. In dogs, clinical findings are most often related to CNS, upper respiratory, ocular, or cutaneous involvement.[38] As in cats, depression and anorexia are common but fever is not. CNS involvement is reported in approximately 50% to 80% of affected dogs. The brain is affected in most of these dogs.[39,40] The spinal cord may be affected along with the brain, and rarely the spinal cord alone is affected, causing signs consistent with either meningitis or an extradural compressive lesion.[41] Signs of nervous system involvement may include mental depression, vestibular syndrome, ataxia, cranial nerve deficits (especially cranial nerves V, VII, and VIII), seizures, paresis, blindness, hypermetria, and cervical pain. In dogs with CNS signs, other systems are usually affected as well, reflecting multisystemic dissemination.

The upper respiratory system or perinasal tissues are affected in approximately 50% of dogs with cryptococcosis (Figure 174-12).[38] The caudal nasal cavity and frontal sinuses are affected more commonly than the rostral nasal cavity. Signs may include upper airway stridor, nasal discharge and sneezing, epistaxis, or firm swellings over the bridge of the nose. The eyes or periorbital tissues are affected in approximately 20% to 40% of dogs with cryptococcosis. Granulomatous chorioretinitis with or without exudative retinal detachment is the most common ocular manifestation and can lead to panophthalmitis. In addition to chorioretinitis, fundic examination may reveal retinal hemorrhage or retinal scarring. Optic neuritis may be noted as a cause of blindness. As with the other systemic mycoses, anterior uveitis is less common than posterior segment disease. The skin is affected in approximately 10% to 20% of dogs with cryptococcosis. Subcutaneous nodules with ulcerative draining lesions, often on the head, feet, nail beds, and mucous membranes of the mouth, occur most commonly.

Figure 174-12 Periocular swelling in a female Siberian husky, caused by cryptococcal infection.

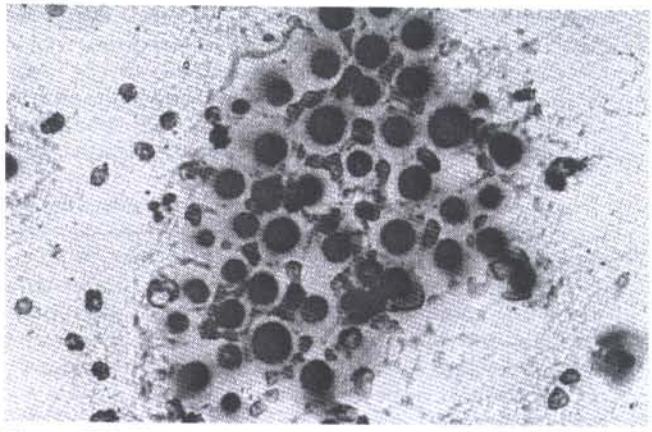


Figure 174-13 Cryptococcal organism noted on fine-needle aspirate cytology from the dog in Figure 174-12. Note the large capsules surrounding the organisms and the minimal inflammatory response.

Proliferative lesions in the ear canals may result from cryptococcal otitis externa. Direct extension from the ears to the CNS may occur. Multiorgan dissemination is more common in dogs than in cats. Disease may be subclinical or may result in clinical signs referable to the organ systems affected.

Diagnosis Hematology and clinical chemistries are often normal in animals with cryptococcosis. Mild nonregenerative anemia and mature neutrophilia or neutrophilia with a mild left shift may be seen. Because the nervous system is so commonly affected, CSF tap for culture and cytology should be considered. CSF commonly yields increased opening pressure, increased protein, and mixed mononuclear and neutrophilic pleocytosis. Organisms are visualized in approximately 90% of dogs with CNS cryptococcosis.[42]

Nodular infiltrates, an interstitial pattern, pleural effusion, and tracheobronchial lymphadenopathy are occasionally seen on thoracic radiographs. Nasal radiographs may demonstrate increased soft tissue density and bone destruction in the nasal passages and frontal sinuses.

Organism identification allows for definitive diagnosis and can usually be made cytologically or histologically. Cytology from affected tissue is the quickest and easiest means of identifying cryptococcal organisms. Nasal swabs, exudate from cutaneous lesions, aspirates of masses, subretinal or vitreal aspirates, and CSF often reveal organisms. Organisms are apparent in approximately 75% of cases. The large capsule makes identification easy (Figure 174-13).

Gram's stain is useful in looking for cryptococcal organisms, because the cells retain the crystal violet and the capsule stains lightly red with the safranin. If India ink is used, the organism and capsule appear unstained and silhouetted against the black background (Figure 174-14). Care must taken in interpreting India ink preparations, as lymphocytes, fat droplets, and aggregated ink particles may be confused with the organism. Budding is occasionally noted. The thin wall and the large capsule differentiate *Cryptococcus* from *Blastomyces*.

Histopathology should be used if cytology fails to identify organisms. Nodular to diffuse granulomatous lesions or areas of degeneration with little inflammation are seen in infected tissue. Yeastlike organisms are usually numerous. Special stains such as PAS, Gridley's fungal, and GMS stain are best at demonstrating organisms. Mucicarmine stains best demonstrate the capsule.

Cryptococcal organisms grow readily when cultured. The organism can be cultured from infected tissue, exudate, CSF, urine, joint fluid, and blood if large enough samples are submitted. Yeastlike growth occurs in 2 days to 6 weeks on Sabouraud's dextrose agar. Hyphae rarely grow, even at 37° C. Care must be taken in interpreting positive cultures from the nasal cavity, because 14% of asymptomatic random-source dogs and 7% of asymptomatic random-source cats were culture-positive in one study.[33] Animals in the previously mentioned study were all negative on serum latex agglutination tests and did not have macroscopic or microscopic findings supportive of cryptococcal infection.

Serology is useful as an inexpensive and noninvasive diagnostic test when cytology has failed to demonstrate organisms. Latex agglutination procedures are used to detect cryptococcal capsular antigen. Antibody titers are not useful diagnostically, because most infected animals do not mount a humoral immune response.[43] The commercially available latex cryptococcal antigen agglutination tests can be used on serum, urine, or CSF. CSF is the best sample to use in animals with neurologic signs, and serum is the best sample to use in animals with upper respiratory or cutaneous signs but without neurologic signs. Most cases are positive with titers between 1:10 and 1:100,000. The median titer in infected cats in one study

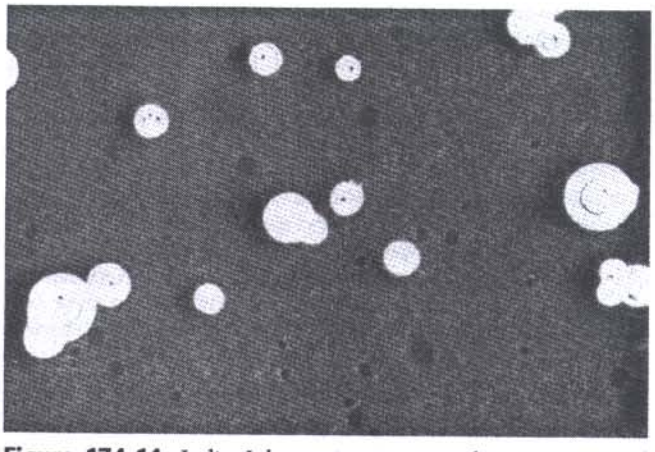


Figure 174-14 India Ink preparation revealing cryptococcal organisms. (Courtesy of Dr. Carol Foil.)

was 1:1000.[43] False-negative antigen titers are rare but may occasionally be seen in localized disease. False-positive antigen titers are uncommon and are usually related to technique or interfering substances such as rheumatoid factor (RF). The latex agglutination antigen titer tends to correlate well with the extent of disease but does not correlate well with prognosis.[44] It may be used to evaluate the treatment progress.

Treatment Amphotericin B is the most effective drug in vitro against cryptococcal isolates, but both itraconazole and fluconazole have proven to be equally efficacious in treating CNS cryptococcosis in people. Little information is available evaluating amphotericin B in the treatment of cryptococcal infections in dogs and cats. Amphotericin B is synergistic with flucytosine. Flucytosine can be used at a dose of 11.4 to 22.7 mg/lb (25 to 50 mg/kg) orally four times a day and has been used in dogs and cats. The combination of amphotericin B and flucytosine may be especially useful for treating CNS infections. Cryptococcal organisms may rapidly develop resistance to flucytosine, so it has limited efficacy as a sole treatment agent. The dose of flucytosine should be adjusted downward in animals with concurrent renal failure. Toxicity to flucytosine includes ulcerative drug eruptions on the skin (especially on the face) and mucocutaneous junctions, enterocolitis, leukopenia, and thrombocytopenia. Amphotericin B has also been effective when combined with azole antifungal agents.

Subcutaneously administered amphotericin B in combination with azole antifungals or flucytosine has been used to successfully treat both feline and canine cryptococcosis.[45] Amphotericin B (0.22 to 0.36 mg/lb; 0.5 to 0.8 mg/kg) is diluted in 0.45% saline containing 2.5% dextrose (400 mL for cats, 500 mL for dogs <20 kg, 1000 mL for dogs >20 kg) and administered subcutaneously two to three times per week. This protocol may allow larger cumulative doses of amphotericin B to be given with reduced toxicity. Concentrations greater than 20 mg/L of amphotericin B resulted in local irritation and sterile abscess formation; therefore more concentrated formulations of amphotericin B should not be used subcutaneously.

Ketoconazole is variably effective as a sole treatment agent but is ineffective in cases with CNS involvement. There were only scattered reports of successful treatment of cryptococcal infections in dogs and cats before the availability of the triazole antifungals, but since they became available, successful treatment has been reported more commonly. Fluconazole (50 mg/cat orally twice a day; 2.2 mg/lb [5 mg/kg] orally once to twice a day for dogs) is very effective and is the treatment of choice for cryptococcosis in cats and probably dogs. Itraconazole (4.5 mg/lb [10 mg/kg] orally daily) is effective in cats and dogs but appears to be less effective than fluconazole. Controlled trials in people have revealed the two drugs to be equally efficacious. Ketoconazole (4.5 to 13.6 mg/lb [10 to 30 mg/kg] orally twice a day) is even less effective but can be used if other drugs are unavailable.

Resolution of clinical signs is the best means of patient monitoring, but serially monitoring latex agglutination antigen titers can significantly augment the clinician's clinical observations.[30,44] Rechecks should be performed monthly while dogs or cats are being treated and should include a chemistry panel to evaluate liver enzymes in animals receiving azole antifungals and a latex agglutination antigen titer. Sequential titers should differ by two or more dilutions before they are considered significantly different. A decline of two- to fourfold per month during the initial few months of antifungal therapy generally corresponds to an adequate clinical response. Ideally, treatment should be continued until the titer is negative or for at least 2 months beyond resolution of clinical signs. In some animals, detectable cryptococcal polysaccharide antigen persists in the circulation long after the infection has been successfully treated. This is thought to be caused by continued elimination of unviable organisms and capsular material from infected tissues and macrophages. Most of these animals have low titers. High residual titers may indicate insufficient therapy and thus persistence of viable organisms.[30] One author's recommendation is to continue antifungal drug treatment to a titer of less than 1.[44] In cases in which there has been a thirty-twofold decrease and resolution of clinical signs, treatment may be discontinued; however, titers should be reevaluated periodically to ensure that they continue to decline or at least remain stable. Animals should be reevaluated at least 3 and 6 months after discontinuing treatment to assess for relapse. Negative antigen titers are occasionally seen in animals with localized disease, so they do not always indicate clinical cure.

The prognosis is good for cats with extraneural disease, and it is guarded for dogs with any form of the disease and for cats with CNS involvement.

Sporotrichosis

Sporotrichosis is a chronic granulomatous disease of worldwide significance caused by the dimorphic saprophytic fungus *Sporothrix schenckii*. The organism lives as a mycelium in the soil and when cultured at room temperature and as a yeast at body temperature. The mycelia are thin, finely branched, and septate. They produce clusters of conidiophores, which are the infective stage. The yeast form exists in infected tissue and is characterized as pleomorphic round, oval, or cigar-shaped cells that measure 2 by 3 µm to 3 by 10 µm (Figure 174-15). The yeast is fairly characteristic, and a diagnosis can usually be made from a cytologic preparation. Both dogs and cats can be infected. Dogs are infected less commonly and usually have only cutaneous or subcutaneous disease. Cats are infected more frequently and commonly have systemic dissemination.

Pathophysiology Infection with *S. schenckii* in dogs and cats usually occurs after trauma that results in inoculation of infective conidiophores. Yeast from cutaneous lesions can be infective and is a potential zoonotic source of infection via contamination of wounds or via scratches or bites. The skin is the primary organ system affected, but dissemination via lymphatics is common in cats and less common in dogs. Immune suppression predisposes to infection and increases the likelihood of dissemination.

Sporotrichosis occurs in three primary forms: (1) cutaneous, (2) cutaneolymphatic, and (3) disseminated disease. In the dog, the infection is usually cutaneous or cutaneolymphatic. Disseminated disease is rare and usually follows immune

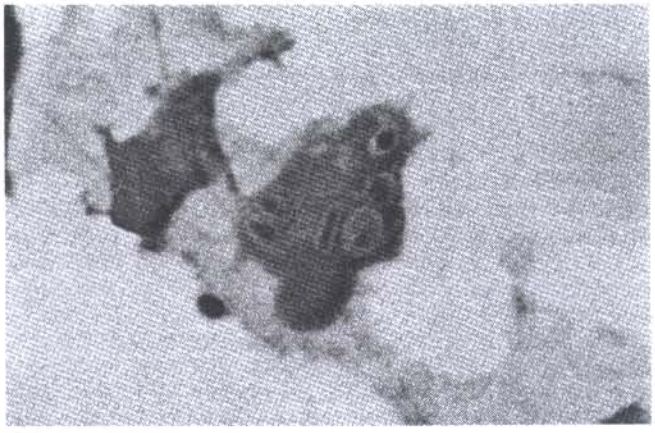


Figure 174-15 Impression smear from a skin lesion on a cat, revealing pleomorphic organisms characteristic of sporotrichosis.

suppression with corticosteroids. The cutaneolymphatic form is common in the cat, and dissemination is seen in more than 50% of feline cases. The lesions in cats are characterized by large numbers of yeasts, making zoonotic transmission more likely from cats than from dogs.

Clinical Signs Most affected cats are younger than 4 years of age, and males are affected approximately twice as commonly as females.[46] Young hunting dogs may be predisposed. Multiple subcutaneous or dermal nodular lesions that occur most commonly on the head, neck, trunk, and distal limbs characterize the cutaneous form of the disease. The tail base may also be involved in cats. The nodules typically ulcerate, drain a purulent exudate, and crust over (Figure 174-16). They are often confused with bite wound abscesses or cellulitis. Lesions on the distal limbs commonly result in regional lymphadenitis, which is manifested as linear ulcerating lesions and regional lymphadenopathy. Lesions in cats may be associated with extensive areas of necrosis. Otitis externa has been reported.

Dissemination may occur and be subclinical or may result in serious systemic disease. Too few cases have been reported to develop a clear picture of a dissemination pattern, but internal lymph nodes, spleen, liver, lungs, eyes, bones, muscles, and CNS have all been affected.

Diagnosis Cytology from skin lesions is the most common means of diagnosis. Lesions from cats contain large numbers of organisms, making diagnosis fairly easy; lesions from dogs usually contain very few organisms. The organisms may be seen intracellularly within macrophages or neutrophils or may be present extracellularly. Culture can be used to make a definitive diagnosis.

Material for culture should include exudate from deep within a draining tract and tissue samples from biopsy specimens. Cultured organisms pose a serious threat to persons working in the laboratory, so the laboratory should be notified whenever a sample is submitted from a dog or cat with suspected sporotrichosis. Histopathology reveals pyogranulomatous inflammation. Numerous organisms are commonly seen in lesions from cats, even when stained with H&E. Fungal stains such as PAS or immunofluorescent techniques may aid in finding organisms in dogs. Immunofluorescent testing can be performed by the Centers for Disease Control and Prevention in Atlanta, Georgia.

Therapy Traditionally, sporotrichosis has been treated with potassium iodide, ketoconazole, or combinations of the two. Approximately 55% of treated cats in the literature responded to one or both of these drugs.[46] Itraconazole is the treatment of choice in people and is effective in dogs and cats. It is especially valuable in cats because of the species' tendency to develop iodism on potassium iodide.

The response to itraconazole treatment in cutaneous and cutaneolymphatic cases is generally good. The prognosis must be guarded for disseminated disease, but too few cases have been reported to give a well-informed likelihood of response.

Public Health Significance Canine sporotrichosis is of minimal zoonotic potential, but feline sporotrichosis is a significant zoonotic disease. Veterinarians and veterinary assistants are at the highest risk of infection. Care should be taken to limit contact with exudate and lesions from infected cats. Gloves should always be worn when handling cats suspected of having sporotrichosis, and owners should be advised of the possibility of infection and the need for strict hygiene. After any contact, gloves should be removed carefully and disposed of, and hands, wrists, and arms should be washed thoroughly with either chlorhexidine or povidone-iodine scrub.

Candidiasis

Candida spp. are normal inhabitants of the GI, genitourinary, and upper respiratory systems. *Candida* may overgrow in cases of immune suppression or prolonged broad-spectrum antibiotic use, especially in wounds, the oropharynx, or the GI tract. Animals with neutropenia are especially predisposed to infection. Infections may be localized, or dissemination may occur via a hematogenous route, resulting in microabscesses at multiple sites.

Localized candidiasis is usually characterized as a nonhealing ulcer covered by a whitish-gray plaque in the oral cavity, in the GI tract, or on the genitourinary mucosa. Chronic moist, exudative lesions may occur on the skin or at the nail beds.

Disseminated disease is typified by fever and the acute appearance of multiple raised erythematous skin lesions in dogs. In dogs, pain is often caused by myositis and osteomyelitis, and other signs are referable to the systems affected. Cats are less likely to have multiple skin lesions. The CBC in systemically affected animals is often characterized by leukopenia and thrombocytopenia. Renal involvement is common, and yeast may be found in the urine, especially in cats.

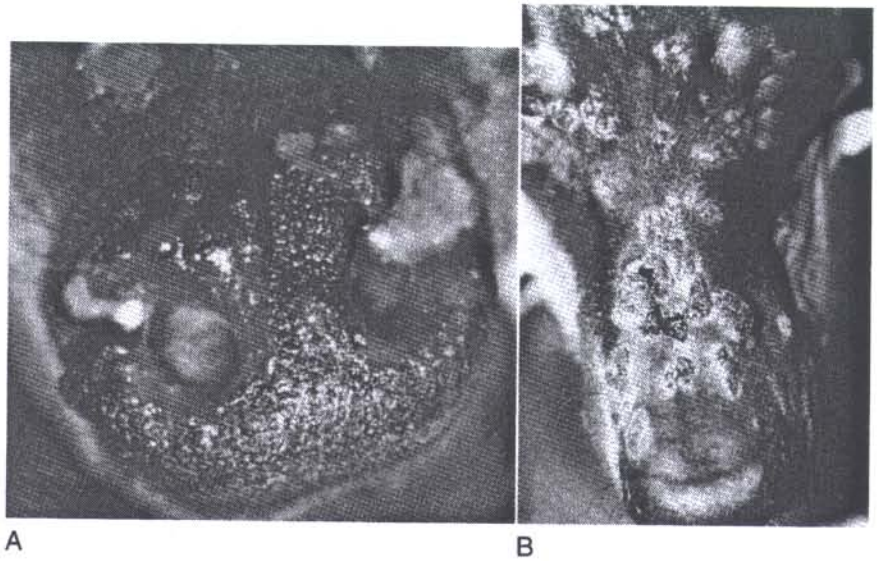


Figure 174-16 A and B, Sporotrichosis affecting the skin and nasal mucosa of a Doberman pinscher.

Itraconazole and ABLC are considered the treatments of choice, but few reports of successful treatment are available.

Pythiosis

Pythiosis is a devastating and often fatal cause of chronic GI or cutaneous disease in dogs and cats. It is caused by *Pythium insidiosum*, an aquatic pathogen belonging to the class Oomycetes in the Kingdom Stramenopila (Chromista). Recent phylogenetic studies have confirmed that oomycetes are more closely related to algae than to fungi. Chitin, an essential component of the fungal cell wall, is generally lacking in oomycetes, which instead contain predominately cellulose and β-glucan. In addition, oomycetes differ from fungi in that ergosterol is not a principal sterol in the oomycete cell membrane. In the United States, pythiosis is encountered most often in the Gulf Coast states, but has been recognized in animals living as far north as New Jersey, Virginia, Kentucky, and southern Illinois and Indiana, and as far west as Arizona, California, Oklahoma, and Kansas. Globally, pythiosis is most often encountered in Southeast Asia, eastern coastal Australia, and South America.

Pathophysiology The infective form of *P. insidiosum* is thought to be the motile biflagellate zoospore, which is released into aquatic environments and likely causes infection by encysting in damaged skin or GI mucosa. Many dogs with pythiosis have a history of recurrent exposure to warm freshwater habitats. However, some cases are observed in suburban house dogs with no history of access to lakes or ponds. Affected animals are typically immunocompetent and otherwise healthy.

Clinical Findings Pythiosis occurs most often in young, large breed dogs and is especially common in outdoor working breeds such as Labrador retrievers. Affected dogs are presented to the veterinarian more often in the fall, winter, and early spring than in the summer months. In cats, specific breed and sex predilections have not been observed in the few cases that have been reported to date. However, of ten cats with cutaneous pythiosis diagnosed through our laboratory since 1999, five were less than 10 months old, with an age range of 4 months to 9 years.

Cutaneous pythiosis in dogs typically causes nonhealing wounds and invasive masses that contain ulcerated nodules and draining tracts, most often involving the extremities, tail head, ventral neck, or perineum.[47,48] Cats with pythiosis may have nasopharyngeal lesions, invasive subcutaneous masses in the inguinal, tail head, or periorbital regions, or they may have draining nodular lesions or ulcerated plaquelike lesions on the extremities, sometimes centered on the digits or footpad.[48,49]

GI pythiosis in dogs is characterized by severe segmental transmural thickening of the stomach, small intestine, colon, rectum, or (rarely) the esophagus or pharyngeal region (Figure 174-17).[50] Mesenteric lymphadenopathy is common and is occasionally observed without accompanying GI tract lesions. The gastric outflow area, duodenum, and ileocolic junction are the most frequently affected portions of the GI tract. Involvement of the mesenteric root may cause severe enlargement of mesenteric lymph nodes, which are often embedded in a single, large, firm granulomatous mass in the midabdominal region. Extension of disease into mesenteric vessels may result in bowel ischemia, infarction, perforation, or acute hemoabdomen. Clinical signs associated with GI pythiosis include weight loss, vomiting, diarrhea, and hematochezia. Physical examination often reveals a thin body condition and palpable abdominal mass. Signs of systemic illness are not typically present unless intestinal obstruction, infarction, or perforation occurs.

Laboratory abnormalities that may be associated with pythiosis include eosinophilia, anemia, and hyperglobulinemia.

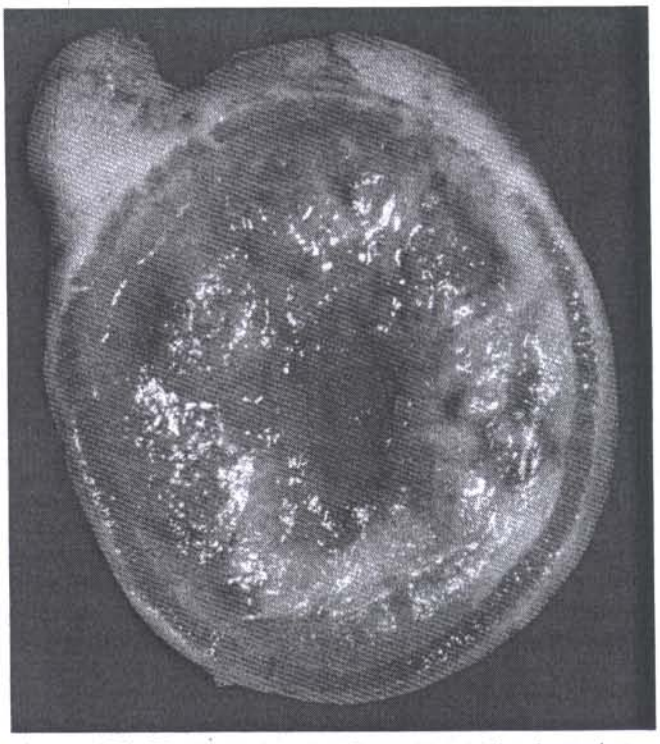


Figure 174-17 Cross-section of a segmental colonic lesion resected from a 3-yr old female Doberman with gastrointestinal (GI) pythiosis. The reader should note the thickening of the submucosa and narrowing of the colonic lumen.

In dogs with GI pythiosis, abdominal radiographs usually reveal an abdominal mass or thickened segment of the GI tract. Ultrasonography typically demonstrates severe segmental thickening of the GI tract and mesenteric lymphadenopathy.

Diagnosis Histologically, pythiosis is characterized by eosinophilic pyogranulomatous inflammation. Although *P. insidiosum* hyphae are difficult to visualize on H&E-stained sections, they are easily identified in sections stained with GMS as broad (mean, 4 μ; range, 2 to 7 μ), rarely septate, occasionally branching structures. Because inflammation in GI pythiosis centers on the submucosal and muscular layers rather than mucosa and lamina propria, the diagnosis may be missed on endoscopic biopsies that fail to reach deeper tissues. Therefore pythiosis should be considered when endoscopic biopsies reveal eosinophilic or pyogranulomatous inflammation without identification of a causative agent.

Isolation of *P. insidiosum* from infected tissues is not difficult when appropriate sample handling and culture techniques are used. For best results, unrefrigerated tissue samples should be wrapped in a saline-moistened gauze sponge and shipped at ambient temperature to arrive at the laboratory within 24 hours. Identification of *P. insidiosum* should be based on morphologic features; growth at 37° C; production of motile, reniform, biflagellate zoospores; and, if possible, specific PCR amplification or ribosomal RNA gene sequencing.[51] Although the production of zoospores is an important supporting feature for the identification of pathogenic oomycetes, it is not specific for *P. insidiosum*.

An ELISA for the detection of anti-*P. insidiosum* antibodies in dogs and cats has been found to be highly sensitive and specific for the diagnosis of pythiosis.[51] In addition to providing a means for early, noninvasive diagnosis, this assay also appears to be useful for monitoring response to therapy. Immunohistochemical techniques have previously been used

to confirm the diagnosis of pythiosis. However, the specificity of these antibodies has not always been well established. A new polyclonal anti-*P. insidiosum* antibody raised in chickens and adsorbed with *Lagenidium* and *Conidiobolus* hyphae appears to be highly specific for the immunohistochemical detection of *P. insidiosum* hyphae in tissues.

Therapy Aggressive surgical resection is the treatment of choice for pythiosis. When cutaneous lesions are limited to a single distal extremity, amputation is recommended. In animals with GI pythiosis, segmental lesions should be resected with 3 to 4 cm margins if possible. Unfortunately, most dogs with GI pythiosis are not presented until late in the course of disease, when complete excision is not possible. Local postoperative recurrence of pythiosis is common and can occur either at the site of resection or in regional lymph nodes. For this reason, medical therapy with a combination of itraconazole (10 mg/kg orally every 24 hours) and terbinafine (5 to 10 mg/kg orally every 24 hours) is recommended for at least 2 to 3 months after surgery. To monitor for recurrence, ELISA serology should be performed prior to and 2 to 3 months after surgery. In animals that have had a complete surgical resection and go on to have no recurrence of disease, serum antibody levels drop significantly within 3 months of surgery.[51] If this occurs, medical therapy can be discontinued, with subsequent reevaluation of serum antibody levels in 2 to 3 months.

Medical therapy for pythiosis is typically unrewarding, likely because ergosterol (the target for most currently available antifungal drugs) is generally lacking in the oomycete cell membrane. Despite this fact, clinical improvement has been documented in a small number of *P. insidiosum*–infected dogs treated with either itraconazole (10 mg/kg every 24 hours for 6 to 9 months) or ABLC (2 to 3 mg/kg administered three times weekly to a cumulative dose of 24 to 27 mg/kg). More recently, clinicians have observed clinical and serologic improvement or cure in several patients treated with a combination of itraconazole (10 mg/kg every 24 hours) with terbinafine (5 to 10 mg/kg every 24 hours). Although the percentage of animals responding is still poor (<20%), the combination protocol seems superior to itraconazole or amphotericin B alone.

Lagenidiosis

Until recently, *Pythium insidiosum* was considered to be the only mammalian pathogen in the class Oomycetes. However, in 1999, a second pathogenic oomycete was isolated from a dog with multifocal cutaneous lesions and regional lymphadenopathy. The dog died acutely after rupture of a caudal vena caval aneurysm, and necropsy revealed severe sublumbar lymphadenitis and pyogranulomatous vasculitis. Sequencing of a portion of the ribosomal RNA gene of the isolate recovered from this dog identified it as member of the genus *Lagenidium*.[52] Presently, more than 40 dogs with serologic, histologic, or culture evidence of *Lagenidium* spp. infection have been identified.

The majority of species in the genus *Lagenidium* are parasites of algae, fungi, nematodes, crustaceans, and insect larvae. The most well-studied species, *Lagenidium giganteum*, is a mosquito larval pathogen approved for use as a biocontrol agent for mosquito populations. Although antigenic and molecular similarities suggest that the canine pathogenic *Lagenidium* species is closely related to *L. giganteum*, differences in their *in vitro* growth characteristics and the failure of *L. giganteum* to infect rodents in mammalian safety studies suggest that they are likely distinct species. Although little is currently known about the life cycle of the canine pathogenic *Lagenidium* species, it is likely similar to that of *P. insidiosum*.

Clinical Findings The epidemiologic and clinicopathologic features of lagenidiosis are similar in many respects to those previously associated with cutaneous pythiosis. Affected animals are typically young to middle-aged dogs living in the Southeastern United States. Although most of these dogs have been from Florida or Louisiana, cases in Texas, Tennessee, Virginia, and Indiana have been identified as well. A number of infected dogs have had frequent exposure to lakes or ponds.

Dogs with *Lagenidium* spp. infection are typically presented for progressive cutaneous or subcutaneous lesions (often multifocal) involving the extremities, mammary region, perineum, or trunk.[52] Grossly, these lesions appear as firm dermal or subcutaneous nodules or as ulcerated, thickened areas with areas of necrosis and numerous draining tracts (Figure 174-18). Regional lymphadenopathy is often noted and may occur in the absence of cutaneous lesions. Similar to the clinical course associated with cutaneous pythiosis, skin lesions in dogs with lagenidiosis tend to be progressive, locally invasive, and poorly responsive to therapy. In contrast to pythiosis, however, the majority of dogs with lagenidiosis have been found to have lesions in distant sites, including great vessels, sublumbar and inguinal lymph nodes, lung, pulmonary hilus, and cranial mediastinum.

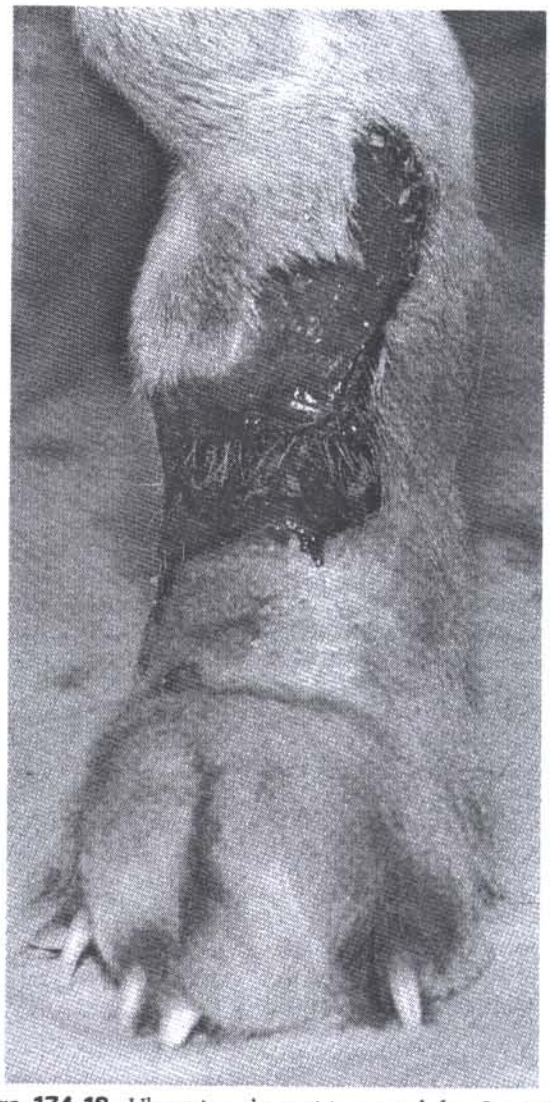


Figure 174-18 Ulcerative dermatitis caused by *Lagenidium* sp. infection in a 2-year-old female border collie presented for progressive skin lesions and generalized lymphadenopathy. This dog had similar lesions on all four limbs. The reader should note a large eschar distal to the ulcerative lesion.

Diagnosis The histologic features of lagenidiosis are similar to those associated with pythiosis and zygomycosis and are characterized by pyogranulomatous and eosinophilic inflammation associated with broad, irregularly branching, sparsely septate hyphae. In contrast to *P. insidiosum*, *Lagenidium* spp. hyphae are usually visible on H&E-stained sections. On GMS-stained sections, numerous broad, thick-walled, irregularly septate hyphae are easily recognized. *Lagenidium* hyphae typically demonstrate a great deal of variability in size but in general are much larger than *P. insidiosum*, ranging from 7 to 25 μ in diameter, with an mean of 12 μ.

Immunoblot serology for the detection of anti-*Lagenidium* antibodies in canine serum can provide a presumptive diagnosis of lagenidiosis but must be interpreted in conjunction with results of serologic testing for *P. insidiosum* infection.[52] The definitive diagnosis of *Lagenidium* spp. infection is best made by culture. Because of current limitations associated with its morphologic characterization, definitive identification of *Lagenidium* spp. should be based on ribosomal RNA gene sequencing or specific PCR amplification.

Treatment Aggressive surgical resection of infected tissues is the treatment of choice for lagenidiosis. In animals with lesions limited to a single distal extremity, amputation is recommended. Because dogs with lagenidiosis often have occult systemic lesions, radiographic imaging of the chest and abdomen and sonographic imaging of the abdomen is recommended to determine the extent of disease prior to attempting surgical resection of cutaneous lesions. Unfortunately, the vast majority of *Lagenidium*-infected dogs have nonresectable disease in regional lymph nodes or distant sites by the time the initial diagnosis is made. Medical therapy for lagenidiosis is typically ineffective, and in general, the prognosis for dogs with lagenidiosis is grave.

Zygomycosis

The term *zygomycosis* refers to infections caused by fungi in the class Zygomycetes, including the genera *Basidiobolus* and *Conidiobolus* in the order *Entomophthorales*, as well as the genera *Rhizopus*, *Absidia*, *Mucor*, *Saksenaea*, and others in the order *Mucorales*. Although infections caused by the *Mucorales* have not been well documented in small animals, the *Entomophthorales* have been reported in dogs to cause pyogranulomatous lesions that are grossly and histologically similar to those caused by *P. insidiosum* and *Lagenidium* spp. *Basidiobolus ranarum*, *Conidiobolus coronatus*, *Conidiobolus lamprauges*, and *Conidiobolus incongruus* are saprophytes found in soil and decaying plant matter. Cutaneous infection likely occurs by direct implantation of spores via minor trauma or insect bites. Systemic infection may result from inhalation or ingestion of spores. Affected animals are typically immunocompetent.

Clinical Findings In humans and other mammals, conidiobolomycosis occurs most often as a nasopharyngeal infection

Table • 174-3

Drug Appendix

GENERIC	TRADE	DOSE	ROUTE	FREQUENCY
Amphotericin B	Fungizone	Dog: 0.22-0.5 mg/lb (0.5-1 mg/kg) Cat: 0.11-0.25 mg/lb (0.25-0.5 mg/kg)	IV	q48h
		Dog/cat: 0.22-0.36 mg/lb (0.5-0.8 mg/kg) diluted in 0.45% NaCl and 2.5% dextrose	SQ	q48h
Lipid amphotericin B complex (ABC)	Abelcet	Dog: 0.5-1.5 mg/lb (1-3 mg/kg)	IV	q48h
Flucytosine	Ancobon	Dog: 11.4-22.7 mg/lb (25-50 mg/kg)	PO	q6h
Ketoconazole	Nizoral	Dog: 4.5-13.6 mg/lb (10-30 mg/kg)	PO	q12h
Itraconazole	Sporanox	Dog: 2.2-4.5 mg/lb (5-10 mg/kg) Cat: 4.5 mg/lb (10 mg/kg)	PO	q24h
Fluconazole	Diflucan	Dog/cat: 1-4.5 mg/lb (2.5-10 mg/kg)	PO	q12h
Enilconazole		Dog: 4.5 mg/lb (10 mg/kg)	Intranasal	q12h
Clotrimazole	Lotrimin	Dog: 1 g	Intranasal	Once
Sodium iodide		Dog: 20 mg/lb (44 mg/kg) Cat: 10 mg/lb (22 mg/kg)	PO	q8
Terbinafine	Lamisil	Dog/cat: 4.5-9 mg/lb (10-20 mg/kg)	PO	q24h
Lufenuron	Program	Dog: 2.2-4.5 mg/lb (5-10 mg/kg)	PO	q24h

with or without local dissemination into tissues of the face and retropharyngeal region. In two dogs evaluated in the authors' hospital, culture-confirmed conidiobolomycosis was associated with ulcerative lesions of the hard palate.[53] In two additional dogs, a presumptive diagnosis of nasopharyngeal conidiobolomycosis was made based on histologic and serologic findings. One of these dogs was presented for signs of chronic nasal cavity disease, and the other had a severe chronic ulcerative dermatitis of the nasal planum. In a fifth dog described in the literature, *Conidiobolus* infection was associated with multi-focal nodular draining subcutaneous lesions and regional lymphadenopathy.[54]

Basidiobolomycosis is a rare cause of ulcerative draining skin lesions in dogs and has also been reported in a single case as a cause of respiratory disease.[55] Disseminated *Basidiobolus* spp. infection involving the GI tract and other abdominal organs has been described in two dogs.

Diagnosis The histologic features of zygomycosis are similar to those associated with pythiosis and lagenidiosis. On GMS-stained sections, hyphae appear broad, thin-walled, and occasionally septate. The histologic hallmark of entomophthoromycosis is the presence of a wide eosinophilic sleeve surrounding the hyphae. In general, hyphal diameter tends to be significantly larger for *Basidiobolus* spp. (mean, 9 μ; range, 5 to 20 μ) and *Conidiobolus* spp. (mean, 8 μ; range, 5 to 13 μ) than for *P. insidiosum* (mean, 4 μ; range, 2 to 7 μ).

The diagnosis of zygomycosis is based on isolation of the pathogen from infected tissues. Identification of zygomycetes in the laboratory is based on morphologic characteristics of asexual reproductive structures (conidia) and sexual reproductive structures (zygospores).

Treatment Attempted therapy has only been described in a few patients with confirmed zygomycosis. Although anecdotal information and a small number of cases in the literature suggest that cutaneous entomophthoromycosis may be less aggressive than pythiosis or lagenidiosis, progression of cutaneous lesions and sometimes even dissemination despite treatment have also been described. Perhaps the most appropriate current recommendation for the treatment of entomophthoromycosis is aggressive surgical resection of infected tissues whenever possible, followed by itraconazole therapy for 2 to 3 months. If resection is not possible, therapy with either itraconazole or ABLC should be recommended (Table 174-3).

CHAPTER 175

Coccidioidomycosis and Aspergillosis

Autumn P. Davidson

INTRODUCTION

Unique among the continents, North America is host to three of the geographically defined major endemic mycoses: histoplasmosis, blastomycosis, and coccidioidomycosis. The three endemic pathogenic fungi share several characteristics. All are soil-dwelling organisms existing only within defined geographic regions based on specific environmental (soil and climatic) conditions. All are dimorphic, capable of undergoing morphologic change from a native saprophytic form (infectious to mammals; also found in vitro) to the parasitic form causing disease in vivo. *Histoplasma capsulatum* and *Blastomyces dermatitidis* convert in vivo into a "yeast form", and *Coccidioides immitis* converts to a "spherule." Infection in mammals occurs most commonly by inhalation of airborne spores. Inhaled saprophytic spores cannot be killed by neutrophils and are small enough (3 to 5 μm) to lodge in host alveoli. Recovery from infection depends on the competence of the host's cell-mediated immunity. Compromised cell-mediated immunity, due to chemotherapy for neoplasia, organ transplant, or immune mediated disease or as a consequence of immunocompromising viral infection, renders the host less able to resist colonization and dissemination of these fungi.[1]

Fungi and the infectious diseases they cause have become increasingly important in modern human and veterinary medicine, challenging mycologists to better understand their epidemiology, pathophysiology, and the host response. Popular current therapeutic targets include ergosterol in the fungal cell membrane and fungal RNA and DNA synthesis. Novel targets include enzymes involved in cell wall biosynthesis (1,3-beta glucan synthase and chitin synthase), as well as nonergosterol cell membrane molecules, DNA-related enzymes, intermediary fungal metabolism, and fungal virulence factors. Unfortunately, the prevalence of antifungal drug resistance appears to be increasing. Antifungal susceptibility testing is becoming more available and standardized. Data concerning combination therapy and sequential therapy as compared with single-agent therapy are accumulating. Adjunctive therapy with cytokines capable of immunohematologic modulation (granulocyte colony–stimulating factor [G-CSF], granulocyte macrophage colony–stimulating factor, macrophage colony–stimulating factor, and interferon-gamma) also have potential roles in the treatment and prevention of fungal infections. Stem cell and granulocyte transfusions and effective and safe vaccinations offer other avenues under development for restoration and improvement of host defense against mycotic disease.[2]

COCCIDIOIDOMYCOSIS

History and Mycology

Coccidioidomycosis ("valley fever," "valley rheumatism") was experimentally studied in dogs in the 1890s, but it was not described as a clinical entity in the veterinary literature until 1940. Coccidioidomycosis was recognized as a fatal granulomatous disease in humans during the late nineteenth century. Initially, the pathophysiology of coccidioidomycosis was

thought to be neoplastic, a cancer induced by a protozoal organism because of the coccidial-like appearance of the spherule detected in biopsy specimens from affected individuals. Recognition of the mycotic cause of coccidioidomycosis and fulfillment of Koch's postulates occurred in 1900. *Coccidioides immitis* (within California) and *C. posadasii* (in all other endemic Southwestern regions) are the two pathogenic species causing coccidioidomycosis.[3-6]

The alkaline sandy soil environment characteristic of the lower Sonoran life zone in the southwestern United States, western Mexico, and Central and South America is the normal habitat for *Coccidioides* spp., which produce mycelia during seasonal rainfall. Arthroconidia (arthrospores) develop with soil drying, subsequently becoming airborne under appropriate environmental (dry and windy) conditions. In the dog and cat, inhalation of infectious and hardy arthroconidia is the major route of infection. Cutaneous contamination via a penetrating wound occurs less commonly. Experimentally, the canine infectious dose of inhaled arthroconidia is low (<10).[7]

Pathophysiology and Epizootiology

The severity and extent of clinical disease resulting from an infectious exposure depends upon the immunocompetence of the host, and ranges from a mild, clinically silent pulmonic form to fatal, multisystemic dissemination. *C. immitis* transforms in tissue to its parasitic form, the spherule, which undergoes internal division (endosporulation) and ruptures at maturity. Each endospore can become an endosporulating spherule, promoting continuation and expansion of the parasitic phase (Figure 175-1). Spherules or endospores can revert to the mycelial form of growth under appropriate environmental conditions, such as might be found under bandages covering a draining tract. As such, the disease is not believed to be directly contagious among mammals except by direct innoculation of infectious body fluids (blood, semen). Pulmonary infection is characterized by extension from the bronchioles and alveoli, through peribronchiolar tissues, to the subpleura and the tracheobronchial and mediastinal lymph nodes. Dissemination is defined as spread of coccidioidal infection beyond the tracheobronchial and mediastinal lymph nodes. Disseminated disease most commonly involves the axial and appendicular skeleton and overlying skin, abdominal viscera, central nervous system (CNS) (including the eye), pericardium, myocardium, and the prostate gland (Figures 175-2 and 175-3).[8]

The incidence of coccidioidomycosis is increased in young, male, medium to large breed outdoor dogs. The boxer, pointer, Australian shepherd, beagle, and Scottish terrier were found to have increased incidence in one study, although it is not believed that pure breed dogs are generally at greater risk than mixed breed dogs. A breed-specific susceptibility based in host immunocompetence may exist.[9]

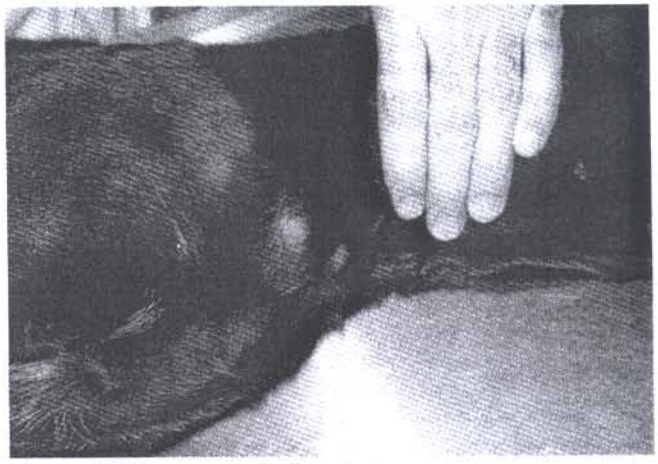


Figure 175-2 Prescapular lymphadenopathy secondary to disseminated coccidioidomycosis in a dog.

Diagnosis

The diagnosis of coccidioidomycosis should be first based on clinical signs compatible with the infection (most commonly cough, lethargy, anorexia, fever, chronic lameness, cervical or head pain, and weight loss) and positive serologic findings. Early in the course of disease (2 to 5 weeks), a positive precipitin test reflects increased IgM levels. Subsequent (8 to 10 weeks) positive complement fixation (CF) testing marks the presence of IgG antibodies. Canine anticomplementary factors can interfere with CF testing, making quantitative immunodiffusion with concentration techniques more reliable than CF. Persistence or reappearance of a positive precipitin test can indicate dissemination. Early CF titers of greater magnitude may suggest more likelihood of dissemination. CF titers may persist at low levels (1:4) during recuperation. Negative serology in an infected individual reflects fulminating disease or anergy.[2,10]

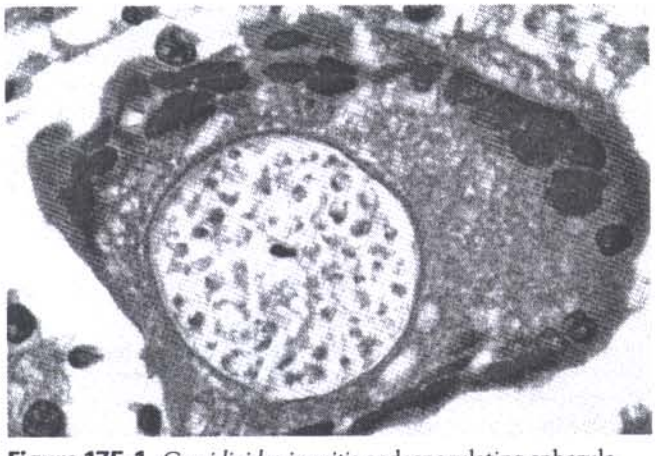


Figure 175-1 *Coccidioides immitis* endosporulating spherule.

Figure 175-3 Osseous coccidioidomycosis, dissemination to the carpi of a dog.

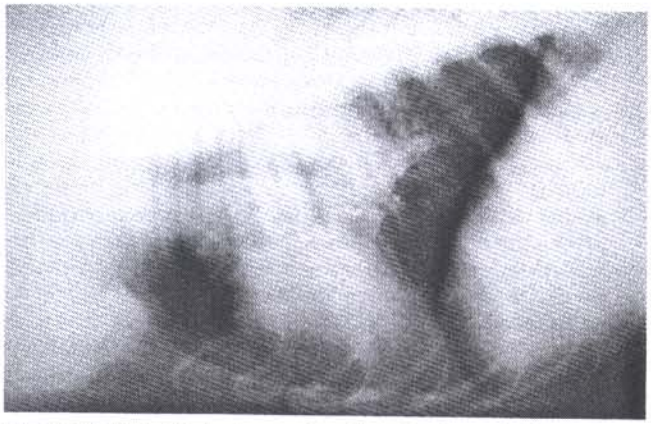


Figure 175-4 Marked sternal and tracheobronchial (perihilar) lymphadenopathy caused by pulmonary coccidioidomycosis in a dog.

Figure 175-6 Disseminated coccidioidomycosis with vertebral (L3) spondylitis in a dog.

Radiographic changes occurring with coccidioidomycosis are well described. Pulmonary lesions vary in character and severity. Most commonly, peribronchiolar and interstitial nodular lesions are associated with hilar lymphadenopathy (Figures 175-4 and 175-5). Skeletal lesions also vary, productive lesions are more common than lytic lesions, and both may be present simultaneously (Figures 175-6 and 175-7). Characteristic laboratory changes associated with coccidioidomycosis include a mature neutrophilic leukocytosis, mild anemia, monocytosis, hyperglobulinemia, and hypoalbuminemia. Histopathology, mycology, and cytology can also enable a positive diagnosis of coccidioidomycosis but are more invasive (biopsy), are hazardous to laboratory personnel (culture), and are less sensitive (cytology) than serology. A specific and sensitive polymerase chain reaction (PCR) assay for detection of *Coccidioides immitis* DNA is anticipated to assist with earlier diagnoses and subtle cases.[11-13]

Coccidioidomycosis is a reportable disease in humans and considered a serious biohazard due to the highly infectious nature of the saprophytic phase (present in laboratory cultures and the soil). One half to two thirds of humans with primary coccidioidal pulmonic infection are subclinical and resolve their disease and then have durable cellular immunity.

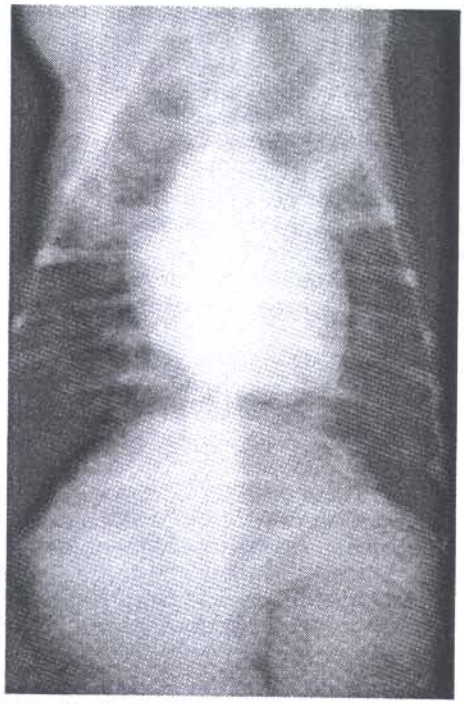


Figure 175-5 Nodular pulmonary infiltrates caused by pulmonary coccidioidomycosis in a dog.

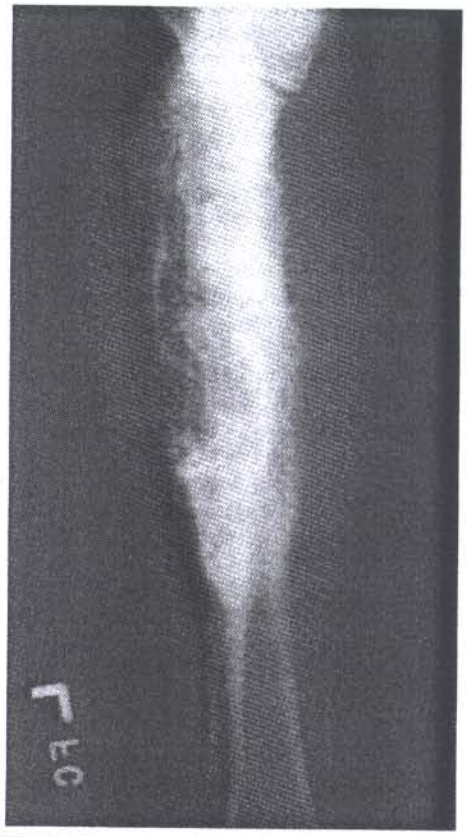


Figure 175-7 Disseminated coccidioidomycosis with radial and ulnar osteomyelitis in a dog.

The intradermal skin test has been used in humans to identify individuals with such immunity. The outcome of infection in humans is highly correlated with patient profiling (age, sex, race, and reproductive status). The elderly, young, dark-skinned races, men, and women in the third trimester of pregnancy are at increased risk of serious infection. Five to 10% of primary pulmonary infections in humans result in pulmonary sequelae (nodules or cavities), and only 0.5% to 1.0% progress to chronic pulmonary infection or significant extrapulmonary dissemination. Humans with primary uncomplicated respiratory coccidioidomycosis usually resolve their infection without specific therapy, and it is not believed that therapy adds significant benefit. Pulmonary sequelae may not cause symptoms but warrant close clinical monitoring for evidence of progression to extrapulmonary infection. Treatment of dogs showing clinical signs of pulmonary coccidioidomycosis has traditionally been encouraged and is thought to reduce the potential for dissemination that results in a poorer prognosis. It is not known how many dogs in endemic areas recover from occult, clinically inapparent pulmonary infection with coccidioidomycosis. Epizootiologic studies evaluating serologic evidence of previous infection are underway in parts of the endemic area. A 20% rate of exposure adequate to cause seroconversion is apparent. The intradermal skin test is not reliable in the dog. The incidence of actual illness resulting from *Coccidioides* infection in animals living within endemic areas is not known. Treatment of symptomatic cats is supported by the fact that disseminated disease is already likely present once the diagnosis is made. Weight loss and cutaneous lesions (chronic draining tracts) are the most commonly reported symptoms in the cat. A lack of familiarity with the disease in nonendemic areas may hamper diagnosis in dogs and cats having traveled through endemic regions.[13,14]

Therapy

Therapy of coccidioidomycosis has involved both amphotericin B (standard and novel lipid formulations) and the azoles (ketoconazole, itraconazole or fluconazole) as sole agents, in combination, or in succession. Numerous clinical reports exist in the veterinary literature regarding therapy for coccidioidomycosis, with variable recommendations for length of treatment based on the assessment of clinical cure. Treatment for a minimum of 4 to 6 months beyond clinical cure, with marked reduction or resolution of positive serologic findings, is advised. Relapse reportedly occurs commonly and it is not known if resolution of disease in the dog and cat results in lifelong immunity as is believed in humans. Humans living in endemic areas and undergoing immunosuppressive therapy associated with organ transplant experience a 3% (approximate) infection rate. If past exposure to coccidioidomycosis can be documented pretransplant, concurrent antifungal and immunosuppressive therapy is given. Immunosuppression-induced recrudescence of disease in a dog after occult infection has recently been reported.[16]

The soil organism *Streptomyces nodosus* is the source of the gold standard antimycotic agent amphotericin B. Amphotericin B is a polyene antibiotic with antifungal activity due to binding ergosterol, a sterol moiety in the fungal cell membrane, forming channels that increase the permeability of the membrane. Amphotericin B is both fungistatic and fungicidal, depending on the concentration of the drug and the sensitivity of the fungal organism. It is not absorbed to any large extent through the skin or across mucous membranes. Amphotericin B (Fungizone) was introduced in the 1950s and was the first effective parenteral drug available for the treatment of invasive mycoses. Amphotericin B has the widest spectrum of activity of the clinically available antifungal agents. Its major limitation is its narrow therapeutic window. Amphotericin B is administered as an intravenous or intrathecal agent, usually every 48 hours. The intravenous dose, given in 5% dextrose, is 0.25 (feline) to 0.5 (canine) mg/kg intravenously Q 48 hr to a final dose of 5 to 10 mg/kg. The intrathecal dose is up to 0.5 mg in 3 to 5 mL spinal fluid, three times weekly. Amphotericin B is cumulatively nephrotoxic and its use is limited by associated azotemia). Phlebitis, chills, fever, anorexia, renal tubular acidosis, hypokalemia, hypomagnesemia, anemia, thrombocytopenia, leukopenia, and anaphylaxis are other side effects associated with its use. Slow intravenous infusions and pretreatment saline diuresis reduce nephrotoxicity. Recent reports suggest success using amphotericin B subcutaneously diluted in large volumes of saline (0.5 mg/kg in 400 ml 0.45% saline, given every 2 to 3 days to a cumulative dose of 10 to 20 mg/kg). The original formulation of amphotericin B is a micellar suspension with sodium deoxycholate. Recently, novel preparations of amphotericin B in lipid and liposomal-based formulations have been developed that are significantly less nephrotoxic but more costly. Slightly higher doses of these lipid formulations are required for efficacy equal to Fungizone, but the higher doses are well tolerated. Nephrotoxicity is still possible with lipid formulations, and infusional reactions remain a complication. Amphotericin B lipid complex (ABLC) (Abelcet) is dosed at 1 mg/kg intravenously Q 48 hr to a total dose of 12 mg/kg. ABLC and amphotericin B in colloidal dispersion (ABCD) are other lipid formulations. Amphotericin is recommended for serious disseminated coccidioidal infections.

Azole agents for treating mycotic infections were developed during the 1980s and 1990s. Miconazole and clotrimazole were early azoles intended for topical use (see Aspergillosis, Therapy). Ketoconazole (Nizoral), an imidazole, was the first oral agent with an acceptable performance against the endemic mycoses and permitted outpatient therapy. The development of the triazoles, itraconazole (Sporanox) and fluconazole (Diflucan), followed. Azoles are usually fungistatic, inhibiting ergosterol synthesis from lanosterol by interacting with C-14 alpha demethylase, an enzyme dependent on cytochrome P-450. The result is increased cell membrane permeability and inhibition of fungal cell growth. At high concentrations achievable topically, some azoles may be fungicidal due to direct damage to fungal cell wall components (disturbed membrane lipid organization resulting in cell lysis). Other antifungal actions of the azoles include inhibition of endogenous respiration, toxicity to membrane phospholipids, and inhibition of the transformation of yeasts to their mycelial form. The interaction with cytochrome P-450 enzyme systems causes some of the side effects in mammals associated primarily with ketoconazole. Inhibition of adrenal and gonadal steroid synthesis can occur with ketoconazole administration. Ketoconazole, itraconazole, and fluconazole are available as oral preparations (pill form). Itraconazole and fluconazole are also available as parenteral preparations. Itraconazole has recently become available as an oral solution and a novel intravenous formulation, both in a beta cyclodextrin carrier that vastly improves absorption and bioavailability, allowing higher concentrations in affected tissues. Ketoconazole and itraconazole undergo hepatic metabolism and can be associated with hepatotoxicity, gastrointestinal (GI) intolerance, and cutaneous reactions. Fluconazole is excreted largely unchanged through the kidneys, is well absorbed orally, and has good CNS penetration. With increased prophylactic and long-term use of the azoles, fungal resistance is emerging, especially in immunocompromised humans on extended periods of therapy. The recommended dose of ketoconazole (brand name or its newly available generic equivalent) is 5 to 15 mg/kg orally every 12 hours (given with food). The recommended dose for itraconazole is 5 mg/kg orally (given with food) or intravenously every 12 to 24 hours, and for fluconazole it is 2.5 to 5.0 mg/kg orally or intravenously every 24 hours.

Currently, ketoconazole therapy, although expensive by veterinary standards, is less cost prohibitive than the expense of hospitalization, supportive care, and renal monitoring required by the appropriately conservative use of amphotericin B. In addition, it is less costly than the later generation azoles, itraconazole, and fluconazole. Amphotericin B therapy in rapidly progressing, serious fungal infection should be followed by long-term oral azole therapy. The use of amphotericin should thus probably be reserved for refractory, disseminated, or fulminating cases. The increased cost of itraconazole and fluconazole may be offset by the suspected, but not yet well-documented, increased efficacy in animals. The improved bioavailability of itraconazole solution supports its use in serious or refractory disease. Fluconazole is indicated for animals with CNS involvement. The use of liposomal amphotericin will permit higher doses to be administered for longer periods of time with less nephrotoxicity. Voriconazole (Pfizer) is a newly approved azole being used in humans with refractory fungal infection. It has excellent oral absorption and favorable pharmacokinetics. Little data are available on its use in coccidioidomycosis.[2,17,18]

Chitin makes up a higher percentage of the fungal cell wall when the organism is in a mycelial phase. Nikkomycin Z, discovered in the 1970s and currently undergoing development, is a natural chitin synthase inhibitor, resembling the precursor substrate. Nikkomycin Z holds great promise as a fungicidal agent, also exhibiting marked in vitro synergism with the azoles.

Lufenuron, a benzoylphenyl urea, is a nonspecific insect chitin synthase inhibitor used in veterinary medicine to sterilize female fleas. Anecdotal clinical reports suggested that lufenuron was useful against coccidioidal infection. Controlled studies have subsequently shown no apparent efficacy or synergy of the compound as an antifungal agent in vitro or in vivo.[19-21]

ASPERGILLOSIS

Mycology and Epizootiology

Aspergillus species are filamentous fungi that are ubiquitous under appropriate environmental conditions and not typically infectious due to host resistance (Figure 175-8). Aspergillosis in humans is typically a pulmonary hypersensitivity reaction rather than an infectious disease entity, except in immunocompromised individuals where disseminated infection with *Aspergillus* species is problematic. Pets acquire infectious aspergillosis in two forms: (1) localized (usually sinonasal) and (2) disseminated (involving two or more noncontiguous organs), both more common in the dog than cat. Aspergillus species typically proliferate by producing spores in vegetative decaying soil and water (Figure 175-9).

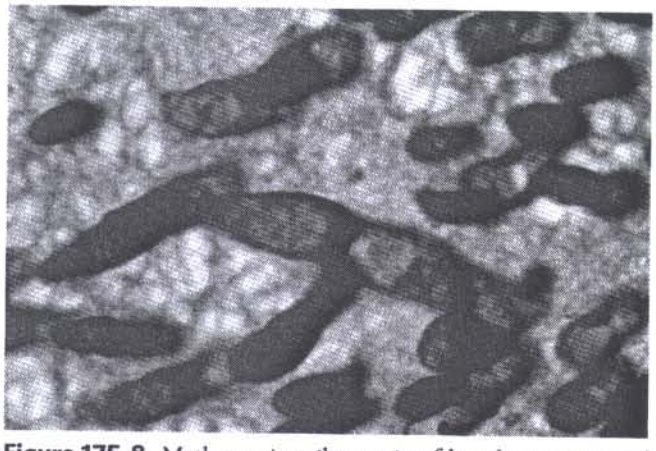


Figure 175-8 Methenamine-silver stain of histologic section of *Aspergillus* spp. showing characteristic parallel septate hyphae with acute angle branching.

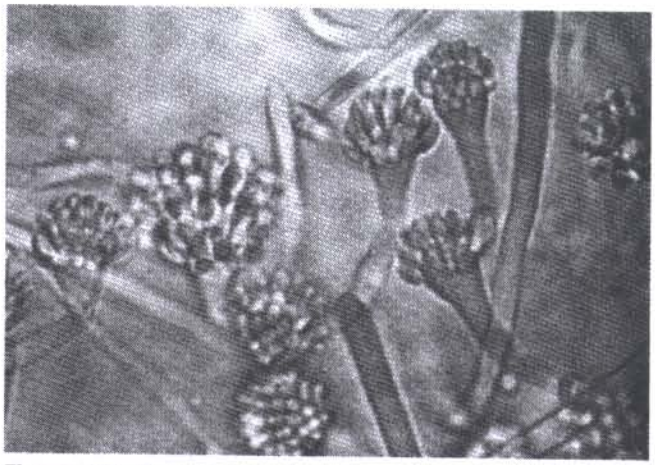


Figure 175-9 *Aspergillus flavus* in culture showing conidiophores bearing fruiting heads.

Localized (Sinonasal) Aspergillosis

Canine sinonasal aspergillosis is characterized by colonization and invasion of the nasal passages and frontal sinuses by the saprophytic fungus, *Aspergillus fumigatus*. *A. fumigatus* is regarded as an opportunistic pathogen, suggesting that some pre-existing local nasal mucosal immunocompetence allowed its establishment in the upper respiratory tract. Alternatively, an in vitro inhibition of B and T lymphocyte transformation by *A. fumigatus* products has been described, suggesting that immunosuppression may both result from or be perpetuated by infection. Sinonasal aspergillosis may occur as an opportunistic primary infection or it may occur secondary to the presence of a foreign body (foxtail, splinter), nasal trauma, or neoplasia (Figure 175-10). The disease primarily affects young to middle-aged mesaticephalic and dolichocephalic breeds and is progressive unless effective specific therapy is given.

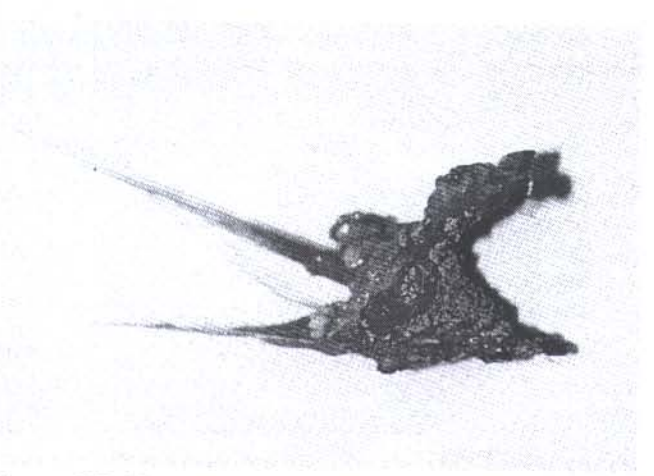


Figure 175-10 Foxtail removed from the nasal passage of a dog with sinonasal aspergillosis.

German shepherds and Rottweilers are the breeds more commonly affected.[22,23]

Pathophysiology

Colonization and invasion of the nasal mucosa by *A. fumigatus* results in destruction and necrosis of the nasal turbinates, often accompanied by frontal sinus osteomyelitis. The cribriform plate, palatine bones, and orbit are sometimes involved. Facial pain, anorexia, sneezing, and copious mucoid to hemorrhagic nasal discharge and crusting are common clinical signs (Figure 175-11). Life-threatening epistaxis can occur secondary to erosion of the nasal vasculature. With chronicity, depigmentation and ulceration of the nares and masticatory muscle atrophy result (Figures 175-12 and 175-13). CNS involvement (encephalitis, meningitis) precipitating seizures can result after erosion of the cribriform plate.

Diagnosis

The condition should be differentiated from other inflammatory causes of rhinitis such as infestation with nasal mites, idiopathic lymphocytic-plasmacytic rhinitis, bacterial or other mycotic rhinitis, chronic nasal foreign body, and nasal neoplasia. The diagnosis of sinonasal aspergillosis is best made by direct observation and microscopic demonstration of invasive fungal plaques on the nasal mucosa (Figure 175-14). Culture of *A. fumigatus* from affected tissues is supportive of the diagnosis, but fungi can contaminate nasal mucosa diseased from other causes. It is a good rule to suspect neoplasia as the primary condition in older dogs with confirmed aspergillosis. Serologic evaluation of sinonasal aspergillosis is unreliable, both false-positive and false-negative results occur. Additionally, serology is not prognostic in aspergillosis. Biopsy of affected tissue and histopathologic evaluation for mucosal invasion is confirmatory.[24]

Radiology of the nasal passages and frontal sinuses (radiography and computed tomography [CT]) is useful in the diagnosis of sinonasal aspergillosis but must be performed before rhinoscopic evaluation to avoid artifacts resulting from lavage, tissue manipulation, and hemorrhage. Radiography shows loss of fine nasal turbinate detail and fluid density in the nasal passages and frequently the frontal sinuses (Figure 175-15). In advanced cases, an aspergilloma may exist in the frontal sinus (Figure 175-16). CT evaluation is useful because characteristic lesions may be identified and evaluation of the extent of disease is optimized. CT has provided a new appreciation for the aggressive nature of fungal rhinitis. Mild cases of sinonasal aspergillosis result in relatively little structural change within the nasal cavity other than the regional lysis of nasal turbinates. Dogs that are chronically infected often demonstrate dramatic turbinate destruction, gross epithelial thickening, formation of dense fungal colonies and granulomas, and penetration into adjacent bone causing hyperostosis and in some instances gross bony destruction. Dogs with sinonasal aspergillosis frequently have copious, thick nasal exudate obscuring radiographic identification of granulomas. Administration of intranasal iodinated contrast medium can help define mass lesions in the presence of surrounding fluid.[24-26]

Numerous techniques have been described to obtain tissue specimens for the definitive histopathologic diagnosis of sinonasal aspergillosis. General anesthesia is usually required, with a cuffed endotracheal tube placed to prevent aspiration of blood and lavage fluids. The external surface of the nasal

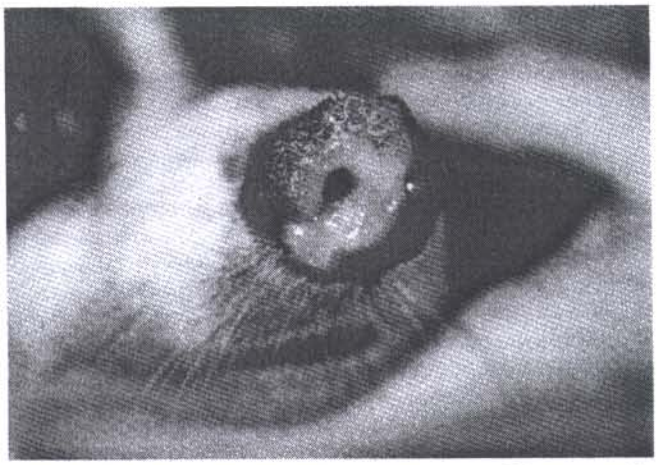


Figure 175-12 Ulceration and depigmentation of the nares of a dog with chronic sinonasal aspergillosis.

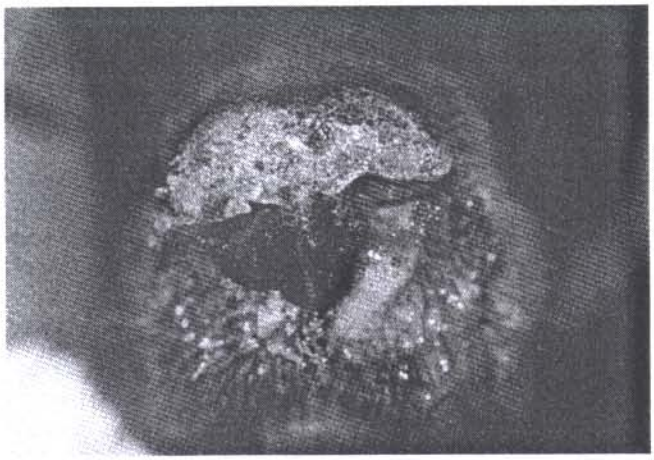


Figure 175-11 Severe crusting of nasal planum and nares in a dog with sinonasal aspergillosis.

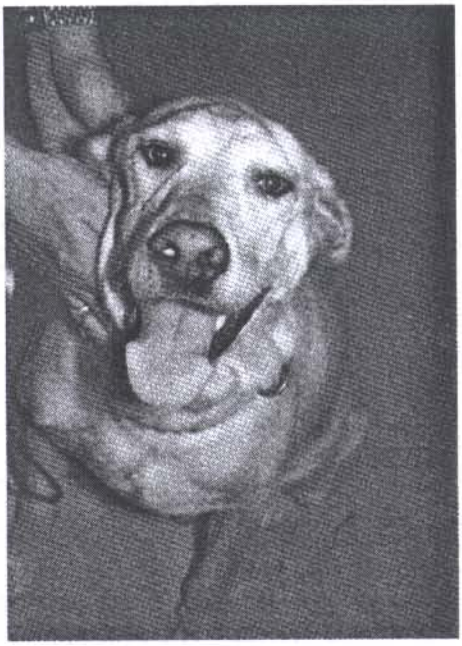


Figure 175-13 Masticatory muscle atrophy in a Labrador retriever previously diagnosed with sinonasal aspergillosis.

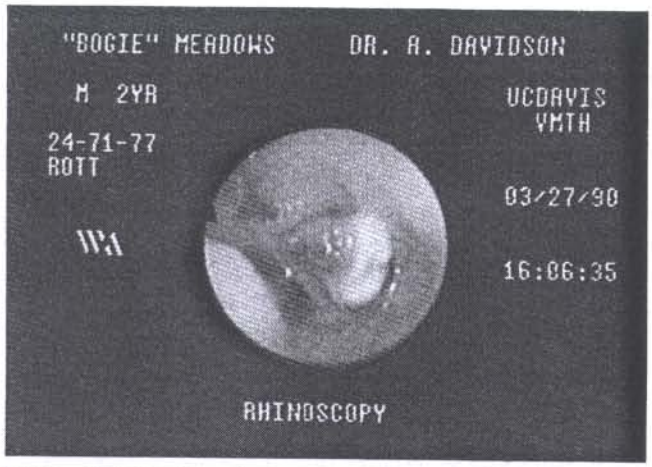


Figure 175-14 Fungal plaque, nasal passage of a dog, viewed rhinoscopically.

cavity is visually and digitally examined for evidence of swelling, asymmetry, and ulceration. This includes a thorough oral examination and visualization of the nasopharynx with either a flexible fiber-optic scope or an angled, warmed dental mirror. Placement of precounted gauze sponges in the pharynx, for further protection of the airways, is then performed. Larger laparotomy sponges should be used if possible because these are less easily swallowed by dogs that may swallow with manipulation of sensitive nasal tissues. The clinician should then measure the distance from the nares to the area of interest noted on the nasal radiographs or CT. This distance serves as a guide for obtaining nasal biopsy and culture specimens. In addition, prior to inserting any instrument in the nasal cavity, the distance from the nares to the medial canthus of the ipsilateral eye is noted and should not be exceeded or penetration of the cribriform plate may result (Figure 175-17).

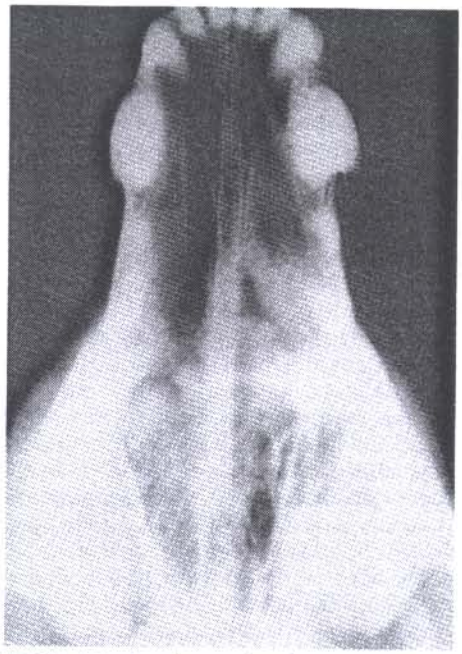


Figure 175-15 Nasal radiography showing loss of turbinate detail and fluid density associated with nasal aspergillosis in a dog.

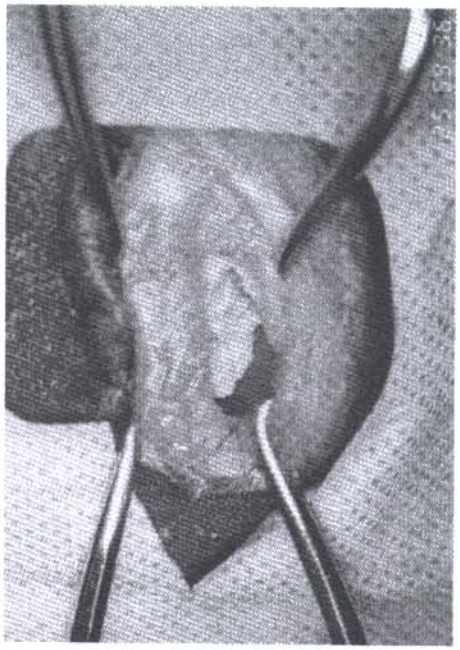


Figure 175-16 Aspergilloma in the frontal sinus of a dog.

Rhinoscopy should be performed while the animal is in sternal recumbency. Only a limited examination of the rostral nasal cavity can be performed with an otoscope. A rigid arthroscope with a 1.9 to 2.7 mm outside diameter and a 5 to 25 degree angle of view (Richard Wolf Medical Instruments Corp., 7046 Lyndon Avenue, Rosemont, IL 60018) permits a more comprehensive evaluation of the nasal passages. A flexible bronchoscope with a 3.5 to 4.8-mm outside diameter (Olympus Corporation, 4 Nevada Drive, Lake Success, NY 11042-1179) has the added benefit of allowing visualization of the nasopharynx by retroflexing the scope around the soft palate, but it is more difficult to manipulate through the nasal passages. Light resistance is usually felt while inserting the scope through the nares. The scope can then be directed ventrally into the ventral nasal meatus toward the nasopharynx or dorsally into the dorsal nasal meatus toward the olfactory epithelium, openings (ostia) of the frontal sinuses, and the cribriform plate. The advantages of direct visualization of the nasal cavity are that a more thorough understanding of the nature of the disease process might be obtained and placement of a biopsy instrument at the area of interest is facilitated.

Indirect methods of obtaining tissue specimens via the nares have also been described. As with rhinoscopic examination, prebiopsy imaging studies are recommended. Biopsy instruments should never be inserted beyond the level of the ipsilateral medial canthus, and protection of the airways under general anesthesia is recommended. The simplest of these techniques involve flushing the nasal cavity with saline in an attempt to dislodge diagnostic tissue. A catheter should be placed in the nares, or retroflexed 180 degrees around the soft palate. Gauze sponges are used to catch tissues that are flushed out through the nares or into the pharynx. More aggressive blind techniques include flushing the nasal cavity while reaming the area of interest with a stiff plastic tube or biopsy with a biopsy needle (Tru-Cut® Disposable Biopsy Needle; Travenol Laboratories Inc., Morton Grove, IL 60053), a plastic catheter, or by applying suction to a Foley urethral catheter. These techniques do not allow the characterization of the disease process that is possible with direct visualization and may result in nondiagnostic or misleading tissue samples.

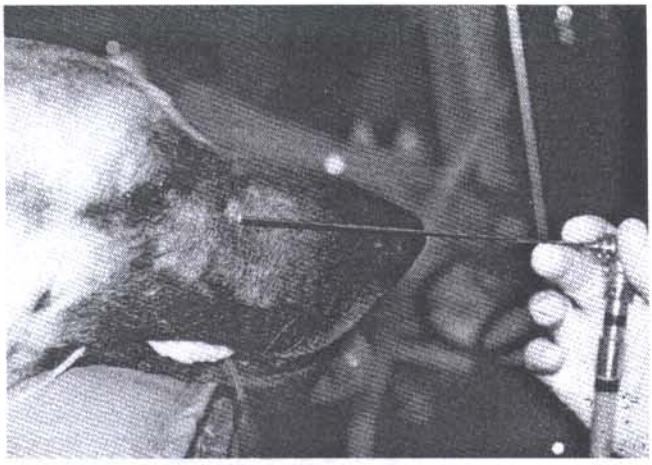


Figure 175-17 Marking the distance from the rostral nares to the ipsilateral medial canthus before rhinoscopic evaluation.

However, they do not require specialized equipment, are easy to perform, and may result in a definitive diagnosis. If the cytologic diagnosis is inconsistent with the signalment, history, or imaging studies, the clinician should repeat the procedure or consider one that allows direct visualization of the area of interest.[24]

Therapy

Therapeutic recommendations for sinonasal aspergillosis have included surgery and systemic and topical antimycotic medications. Rhinotomy and turbinectomy with perioperative thiabendazole administration resulted in improvement in 50% or less of dogs in one study. Oral ketoconazole administration was reportedly efficacious in 47%, oral itraconazole in 60% to 70%, and oral fluconazole in 60% of infected dogs. Enilconazole applied topically through frontal sinus tubes (twice daily for 7 to 10 days) was reportedly efficacious in 80% to 90% of dogs but is cumbersome and not readily available in the United States. Extensive débridement of the nasal cavities and frontal sinuses followed by infusion of 1% to 2% enilconazole via endoscopically placed catheters has been advocated. Invasive surgical exposure of the nasal passages and frontal sinuses, topical application of 10% povidone iodine, and delayed closure 6 to 8 weeks postoperatively was recommended for refractory cases but had poor client acceptance and a small study size.[22]

Clotrimazole is a synthetic imidazole derivative. At concentrations achieved during systemic use, imidazoles impair the biosynthesis of ergosterol, the major component of fungal cell membranes, resulting in interference with certain membrane-bound enzyme systems and fungistatic inhibition of growth. In addition, clotrimazole is fungicidal topically, reaching higher concentrations (1.5×10^{-4}M). Electron microscopic observations indicate that at high concentrations, clotrimazole causes alteration in the fungal cell membrane with consequent changes in permeability and leakage of cellular constituents in a manner similar to the effect of polyene antifungal antibiotics. This drug is available in human topical preparations for cutaneous, oral or vaginal applications. Administered orally, it is poorly absorbed and rapidly absorbed undergoes hepatic metabolism and biliary excretion. GI irritation and contact hypersensitivity are reported human side effects.[23,27]

Clotrimazole solution has been used successfully for the topical treatment of nasal aspergillosis in the dog. The topical delivery of clotrimazole has been accomplished using two techniques. In the first, an infusion of clotrimazole is delivered through infant feeding tubes placed into the frontal sinuses and caudal nasal passages through the skull (a somewhat invasive procedure requiring surgical expertise for trephination and tube placement). An alternative technique, based on studies of the distribution of topical agents in the frontal sinuses and nasal passages, involves the retrograde infusion of clotrimazole through polypropylene catheters placed into the nares. This technique is equally successful, technically simpler, and associated with less morbidity. Based on a previous study in cadavers, the average volume of the frontal sinuses in breeds predisposed to fungal rhinitis is 25 mL per side. Flooding the nasal cavity and sinuses with a larger volume of infusate (50 to 60 mL per side) results in distribution to all areas of the nasal cavity and frontal sinuses. Delivery by trephination and feeding tube placement can bypass areas within the frontal sinuses. At present, the recommendation is to use 50 to 60 mL per side in middle to large breed dogs, regardless of head size.

Catheters should be placed with the dog in lateral recumbency. A 24 F Foley catheter is placed per os so that the tip of the catheter lays dorsal to the soft palate. This process can be aided initially by grasping the catheter tip with a pair of right-angle forceps (Meeker) or long-handled needle holders so that the catheter tip is directed rostrally. A mouth gag is then placed, and an assistant should retract the tongue rostrally to improve visualization during catheter placement. The catheter can then be advanced until its balloon is dorsal to the junction of the hard and soft palates. The balloon of the Foley catheter is then inflated to occlude the nasopharynx. The balloon can be palpated through the soft palate to confirm its position just caudal to the hard palate. Moistened laparotomy sponges should be counted and then placed in the pharynx so that the catheter cannot migrate caudally and will absorb any infusate that might escape around the balloon. During sponge placement the index finger of the opposite hand is used to maintain balloon position. Once this process is complete, the mouth gag is removed. One 10 F polypropylene infusion catheter is then advanced through each nostril, beginning dorsomedially; each is advanced into the dorsal nasal meatus to the level of the medial canthus of the ipsilateral palpebral fissure. A Foley catheter (12 F) is then inserted into each nostril and the balloons inflated so that they lay just caudal to and occluding the nostrils. Occasionally a nylon suture is placed across each nostril to prevent cranial migration of the nasal balloons. After three Foley catheters (one nasopharyngeal, two nasal) are placed, and their balloons should be inflated to slow the leakage of clotrimazole from the nasal cavity and frontal sinuses (Figures 175-18 and 175-19). The dog is then repositioned in dorsal recumbency, and an additional laparotomy sponge is placed just caudal to the upper incisors (between the endotracheal tube and the incisive papilla) to absorb leakage of clotrimazole through the incisive ducts.

Clotrimazole (1 g) in 100 mL of polyethylene glycol 200 (a 1% solution) is then evenly divided between two 60 mL syringes (50 mL per syringe). Initially the nasal passages and frontal sinuses must be filled with solution. When clotrimazole is noted within the lumen of a Foley catheter it should be clamped shut, eventually creating a closed system for saturation of the nasal and frontal sinus mucosa. The clotrimazole should then be continuously and slowly infused over a 1-hour period (50 mL per infusion catheter). The polypropylene catheters are maintained in a horizontal position, parallel to the table, throughout infusion. Positioning the dog so that its nose protrudes beyond the edge of the treatment table allows clotrimazole escaping around the nasal catheters to drip into a receptacle. While the dog's body is maintained in dorsal recumbency, the head can be tilted and maintained in the following positions to ensure drug contact with all mucosal surfaces: dorsal

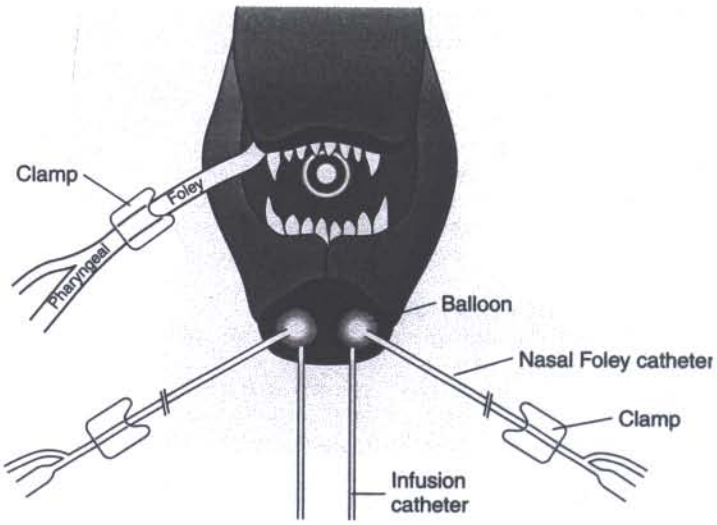


Figure 175-18 Catheter position with the dog in dorsal recumbency. A Foley catheter with the balloon inflated in the nasopharynx and pharyngeal gauze sponges (not shown) minimize leakage of infusion caudally. A cuffed endotracheal tube *(et)* further diminishes the risk of aspiration. Syringes (60 mL) are used to inject infusion into the dorsal nasal meatus via polypropylene infusion catheters. Inflated Foley catheter balloons obstruct the nares to diminish leakage of infusion rostrally. Tubing clamps on Foley catheters are closed when fluid is observed within the catheter lumen. (Adapted from Mathews KF et al: Computed tomographic assessment of noninvasive intranasal infusions in dogs with fungal rhinitis, *Vet Surg* 25:309, 1996.)

recumbency (15 minutes), left lateral recumbency (15 minutes), right lateral recumbency (15 minutes), and dorsal recumbency (15 minutes). The dog is then placed in sternal recumbency, the catheters and sponges removed and counted, the clotrimazole allowed to drain rostrally, and the pharynx and proximal esophagus suctioned before recovery from anesthesia.

Topical administration of clotrimazole into the frontal sinuses and nasal passages is generally well tolerated. Pharyngitis, conjunctivitis, and pharyngeal edema have been reported as transient side effects. The success rate with one or more topical clotrimazole applications has been reported to be 86%. The infection will resolve in most dogs after a single treatment. A favorable response to clotrimazole therapy is usually indicated by resolution of nasal discharge by 2 weeks after therapy. Unabated persistence of nasal discharge 2 weeks after therapy is an indication for repeat evaluation and treatment if aspergillosis persists. Concurrent systemic antibiotic therapy may be indicated if secondary bacterial rhinitis is present. Some dogs with advanced disease may require multiple 1-hour clotrimazole infusions. Cases selected for topical therapy should have aspergillosis limited to the frontal sinuses and nasal passages, without CNS involvement. Pretreatment CT scans are encouraged so that the extent of the disease is determined and the integrity of the cribriform plate evaluated. Remember, however, that no test (including CT scan) is 100% reliable in determining if the cribiform is intact. Informed consent should be obtained from clients if CT is not performed. Topical infusion of clotrimazole solution is not

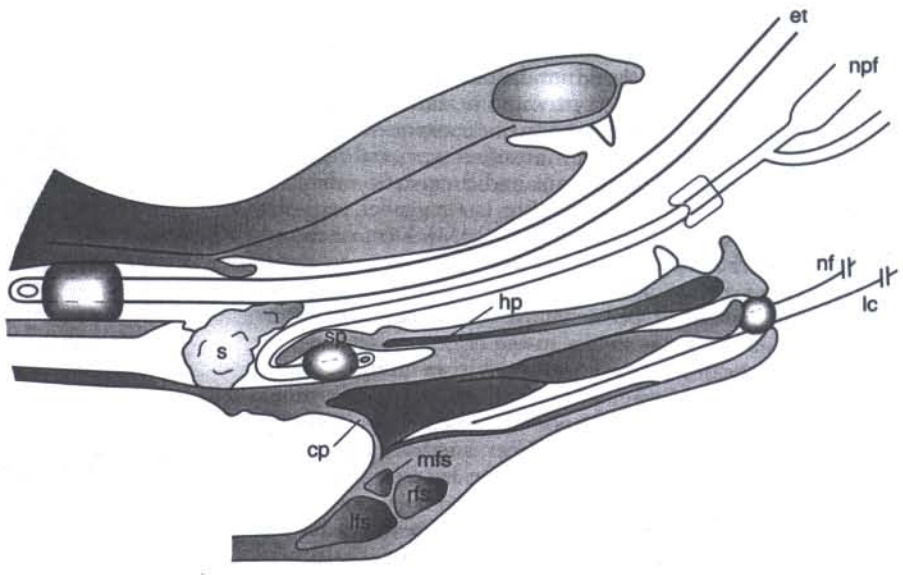


Figure 175-19 Sagittal section showing the position of the endotracheal tube *(et)*, pharyngeal sponges *(s)*, infusion catheter *(ic)*, and rostral nasal Foley catheter *(nf)* in relation to the hard palate *(hp)*, soft palate *(sp)*, cribriform plate *(cp)*, rostral frontal sinus *(rfs)*, medial frontal sinus *(mfs)*, and lateral frontal sinus *(lfs)*. (From Mathews KG et al: Computed tomographic assessment of noninvasive intranasal infusion in dogs with fungal rhinitis, *Vet Surg* 25:309, 1996.)

advised if the cribriform plate is not intact, because serious meningitis and encephalitis may result. Cases with CNS involvement, characterized by a lack of integrity of the cribriform plate or orbit (ocular or retrobulbar involvement), should receive systemic antifungal therapy (preferably fluconazole). Only the formulation of clotrimazole in polyethylene glycol is advised. The use of clotrimazole in propylene glycol-isopropyl alcohol vehicles is problematic due to the tendency of the latter to significantly irritate oronasal mucosa. Topical therapy with itraconazole oral suspension in refractory cases is currently under clinical investigation.[28-30]

Disseminated Aspergillosis

Disseminated aspergillosis is most commonly diagnosed in dogs and cats that are terminally ill from the disease. Disseminated aspergillosis typically involves multiple organ systems with no history of nasal or pulmonary involvement. *Aspergillus terreus*, *A. deflectus*, *A. flavipes*, and rarely *A. fumigatus* have been reported in cases where the species has been identified. Disseminated aspergillosis is believed to occur after inhalation of small spores (<8 μm) and hematogenous spread. The pathogenicity of the causative species is reported to be associated with their production of highly infective aleuriospores in tissue and their inherent ability to invade blood vessels. In dogs, disseminated aspergillosis has been most commonly reported in the German shepherd between 2 and 8 years of age. Genetic predisposition and dysfunctional mucosal immunity are suspected. Defective IgA production or regulation has been identified in some affected German shepherds. Cats with disseminated aspergillosis generally have identifiable concurrent immunosuppressive disease (usually viral) or other debilitation and are less than 2 years of age.

The clinical signs associated with disseminated aspergillosis are nonspecific and related to organ involvement. Uveitis, enophthalmitis, and chorioretinitis may precede the onset of generalized disease. Osteomyelitis and mycotic granulomas of the kidneys, liver, spleen, intervertebral discs, pancreas, lymph nodes, myocardium, prostate, brain, uterus, and thyroid gland have been reported. Bone pain, paraparesis, draining sinus tracts, anorexia, weight loss, pyrexia, lethargy, muscle wasting, and fever are the most common signs. Animals with disseminated aspergillosis may have fungal hyphae observed on cytologic examination of urine sediment, serum, synovial fluid, lymph node centesis, bone biopsy, or intervertebral disc aspiration. The diagnosis is confirmed by culture on Sabouraud's dextrose agar. Serology is not reliable (false negatives have been reported).

The prognosis for recovery is poor despite aggressive antifungal therapy and supportive care. Intravenous amphotericin B, itraconazole, or fluconazole are advised initially. Long-term (sometimes for life) oral azole therapy can be attempted if an initial positive response to intravenous antimycotic drug administration occurs. Surgical excision of fungal granulomas may be helpful, if feasible.[31-33]

CHAPTER 176

Tropical Diseases

Remo Lobetti

In the past, the term *tropical diseases* referred to diseases that occurred only in the tropic regions of the world. However, the distinction between tropical and nontropical disease is becoming increasingly blurred, and diseases that traditionally were considered tropical now occur in many nontropical places. Moreover, some of the parasitic infections formerly thought to be uncommon or very localized are now recognized to have a wide distribution. Possible reasons for the expansion of tropical diseases to other parts of the world include global warming, especially with diseases that are vector borne, and the ever-increasing movement of both people and animals, which allows dissemination and spread of disease. The presence of tropical diseases is compounded by socioeconomic factors, pet-owner relationships, and nutritional disorders. Diseases that may still be considered of a tropical nature are listed in Table 176-1.

AFRICAN HORSE SICKNESS

African horse sickness is caused by a double-strand RNA orbivirus. In addition to equines, the dog is the only other species that can contract African horse sickness.[1] Dogs usually contract the disease by ingesting infected horsemeat, but they can also become infected through vector-borne transmission by *Culicoides* midges.[2] Typical clinical signs include fever, cough, and diarrhea, and the disease progression is often acute. Postmortem examination demonstrates severe pulmonary edema, pleural effusion, and splenomegaly.[1] Antibodies to African horse sickness have been detected in healthy dogs from Egypt, India, and South Africa.[2] No specific therapy is available for the disease.

FLAVIVIRIDAE

Flaviviridae are vector-borne, single-strand RNA viruses.[3] Of all the viruses in this group, the two that are of a tropical nature and that affect the dog and cat are yellow fever and Wesselsbron disease.

Yellow fever, which is transmitted by *Aedes* mosquitoes, produces a subclinical infection in cats that is characterized by a transient viremia, whereas dogs are resistant to the virus.[4] Affected cats may show a transient febrile reaction. Wesselsbron disease has been reported in a dog that died from encephalitis. When three dogs were challenged with the viral isolate from the succumbed dog, two showed a transient

Table • 176-1

Diseases That May Still Be Considered of a Tropical Nature

ORGANISMS	DISEASE
Viruses	Orbivirus (African horse sickness)
	Wesselsbron disease
	Yellow fever
	Rift Valley fever
Bacteria	Melioidosis
	Anthrax
Protozoa	Southern African canine babesiosis
	Feline babesiosis
	Trypanosomiases
	Sarcocystosis
Ectoparasites	*Hyalomma* tick bite necrosis
	Cordylobia infestation
Endoparasites	Spirocercosis

febrile reaction and one developed transient paresis.[5] Antibodies to Wesselsbron disease have been detected in healthy dogs from Botswana and South Africa.[5] The diagnosis is usually made retrospectively on postmortem examination. No specific therapy is available for the disease.

It is likely that transient, nonspecific signs of encephalitis in dogs and cats may in fact be the result of infection with Flaviviridae.

BUNYAVIRIDAE

Bunyaviridae, the largest family of vector-borne, single-strand RNA viruses, includes many important pathogens of both humans and animals.[6] Of all the viruses in this group, the only one of a tropical nature is Rift Valley fever. The *Aedes* mosquito is the most common vector, although midges, ticks, and sand flies also can transmit the infection. Direct transmission, by inhalation or ingestion, from affected animals is also possible.[6] In young puppies and kittens, infection with Rift Valley fever virus results in viremia, hepatic and myocardial necrosis, meningitis, diffuse petechial hemorrhages, and death.[4] Although adult animals do not succumb to the infection, they can develop a viremic state, and infection in a pregnant animal can result in abortion or stillbirths.[4,6] The diagnosis is usually made retrospectively on postmortem examination. No specific therapy is available for the disease.

MELIOIDOSIS

Melioidosis is a bacterial infection caused by *Burkholderia (Pseudomonas) pseudomallei*. The disease occurs in Southeast Asia, northern Australia, and the South Pacific. The organism is a ubiquitous soil saprophyte that results in chronic nodular or purulent generalized systemic inflammatory disease in dogs, cats, and other species.[7] The route of infection is by inhalation, ingestion, or direct transmission into wounds or tissues by bites of arthropod vectors or by direct contact with contaminated soil.[7,8] Isolation of the organism from blood or lesions is diagnostic. Therapy is aimed at surgical drainage of large abscesses and long-term systemic antibiotic therapy.[8]

ANTHRAX

Anthrax is an acute bacterial systemic disease of mammals caused by *Bacillus anthracis*. In dogs and cats the infection is rare and is manifested by local inflammation, necrosis, and edema of tissues of the upper gastrointestinal tract, which first come into contact with the organism.[9] Although death is usually by asphyxiation, the toxin can also exert systemic effects. The cat and dog are usually infected by the ingestion of meat from contaminated carcasses of animals that have died from anthrax.[9,10] The diagnosis is made by detection of the bacillus on a blood or edema fluid smear. Postmortem examination is not recommended, because this results in dissemination of the bacterial spores.[10] Treatment is with penicillin antibiotics.[10]

CANINE BABESIOSIS

Canine babesiosis is an important worldwide, tick-borne disease that ranges in severity from relatively mild to fatal. The causative organism is either *Babesia canis* or *Babesia gibsoni*. Three subtypes of *B. canis* are recognized: *B. canis canis*, *B. canis vogeli*, and *B. canis rossi*. The first two subtypes occur in Europe and North Africa, respectively, and the third subtype occurs in Southern Africa.[11] *B. gibsoni* occurs in Asia, North America, and North and East Africa.[12] *B. canis canis*, *B. canis vogeli*, and *B. gibsoni* all result in mild clinical disease; *B. canis rossi* results in severe clinical disease and is the focus of this section.

Canine babesiosis may be clinically classified as uncomplicated and complicated forms.[13] Uncomplicated cases typically present with signs relating to acute hemolysis, including fever, anorexia, depression, pale mucous membranes, splenomegaly, and a waterhammer pulse. This form is further characterized as mild, moderate, or severe disease, according to the severity of the anemia.

With the complicated form of babesiosis, clinical manifestations include acute renal failure, neurologic dysfunction, coagulopathies, liver dysfunction, acute respiratory distress syndrome, myocarditis, hypotension, and pancreatitis. Rare complications include myalgia, ocular involvement, upper respiratory signs, necrosis of the extremities, and fluid accumulation.[14]

Primary hematologic abnormalities include anemia, thrombocytopenia, and leukocytosis. Alterations in biochemical parameters vary, depending on the severity of the case. Typically, uncomplicated cases may show no biochemical changes. However, increased liver enzyme activities, hypokalemia in more severely affected cases, and an increased blood urea nitrogen (BUN) with a normal serum creatinine may be evident. In complicated cases, biochemical changes reflect the underlying complication.[14]

The diagnosis of babesiosis is made by demonstrating *Babesia* organisms (2 × 5 μm, pear-shaped organisms, usually in pairs) in infected erythrocytes on a blood smear stained with a Romanowsky-type stain.

The primary therapeutic aim in the treatment of babesiosis is the reversal of life-threatening anemia through blood transfusions and elimination or suppression of the parasite with specific antibabesial drugs, such as diminazene aceturate and imidocarb. Mild to moderate, uncomplicated cases require only antibabesial therapy; severe uncomplicated cases require antibabesial therapy and blood transfusions. The complicated forms of the disease require additional therapy aimed at treating the complication present.[14]

FELINE BABESIOSIS

Feline babesiosis is caused by *Babesia felis*, a small *Babesia* parasite that has been reported from France, Germany,

Thailand, and Zimbabwe but that only appears to cause clinical disease in South Africa.[15]

Common clinical signs include anorexia, weight loss, and anemia. Less common signs may include icterus, vomiting, pica, and respiratory signs. The disease can be protracted and often is clinically silent until fairly far advanced. Anemia is the most consistent hematologic finding; white cell and thrombocyte counts are variable and inconsistent. The most remarkable changes on serum biochemistry are increased alanine aminotransferase (ALT) activity and hyperbilirubinuria. Other biochemical parameters are generally variable and inconsistent.[15] The diagnosis of babesiosis is made by demonstrating *Babesia* organisms in infected erythrocytes on a blood smear stained with a Romanowsky-type stain.

The drug of choice for treating feline babesiosis is the antimalarial drug primaquine phosphate, given at a dosage of 1 mg per cat every 36 hours for four treatments, then 1 mg per cat per os every 7 days for four treatments. The drug does not sterilize the infection. Another drug that reportedly has some effect is doxycycline, given at a dosage of 5 mg/kg per os twice a day for 21 days.[16]

AFRICAN TRYPANOSOMIASES

Trypanosomiasis is a hemoparasitic protozoal disease that in the dog is caused either by *Trypanosoma brucei* or *Trypanosoma congolense.*[17] The disease is transmitted by the tsetse fly, although dogs may become infected by eating infected fresh meat.[18]

Relapsing fever, anemia, weakness, anorexia, and emaciation are common clinical signs. Other clinical signs include anasarca, conjunctivitis, keratitis, and occasionally neurologic signs (depression, incoordination, circling, and paralysis).[18] In untreated cases, death may occur in 1 week to 3 months.

The diagnosis is made by direct visualization of parasites on blood smear evaluation. Indirect fluorescent antibody (FA) and enzyme-linked immunosorbent assay (ELISA) methods and species-specific monoclonal antibodies can also be used in the diagnosis.[19] Hematologic changes include regenerative anemia, leukopenia, and thrombocytopenia.[17]

Few drugs are effective against African trypanosomiases; however, drugs that have been used include diminazine (most effective), difluoromethylornithine, ethidium, isometamidium, and quinapyramin.[17,18]

SARCOCYSTOSIS

Sarcocystosis is a protozoal disease caused by organisms of the genus *Sarcocystis.*[20] The dog and cat are definitive hosts, and cattle, sheep, and pigs are intermediate hosts. When a dog or cat ingests meat containing sarcocysts, bradyzoites develop into macrogametocytes and microgametocytes in the epithelial and goblet cells of the intestine. Oocysts then form, which sporulate in situ within the intestinal wall; they are released into the intestinal lumen, where they leave the host via the feces. Sarcocystosis in the dog and cat is usually asymptomatic, but acute to chronic diarrhea may occur.

In the dog and cat the diagnosis is made by finding the small sporocysts in the feces using a supersaturated sodium chloride solution. Potentiated sulfonamides can be used in the dog and cat to eliminate the intestinal infection.[20]

HYALOMMA TICK BITE NECROSIS

Skin necrosis induced by the bite of the *Hyalomma* tick is a common disease of southern Africa. Dermatrophic skin necrosis is thought to be caused by a cytotoxin produced in the salivary gland of the tick.[21] The initial stage the disease is characterized by severe pain at the site of the tick attachment. This is followed by erythema and edema at the site of the tick bite. Full-thickness skin necrosis follows. The size of the necrotic area, which can vary from 5 to 30 cm, appears to be directly related to the length of time the tick was attached.

The diagnosis is based on clinical signs and the presence of one or more *Hyalomma* ticks. Treatment involves removal of the tick and general principles of wound management.

CORDYLOBIA ANTHROPOPHAGA

The larvae of the *tumbu* or mango fly *(Cordylobia anthropophaga)* produce myiasis in humans and animals in sub-Saharan Africa. The adult fly deposits the eggs on skin that usually is soiled with urine or feces. Within 2 days the larvae hatch and penetrate the skin to form a furuncular lesion with a small central opening. The larvae are obligate parasites and usually provoke a localized furuncle, but aberrant migrating larvae may result in necrotic and inflammatory lesions in many tissues.[23][22] The larave pupate after 8 or 9 nine days, and the whole life cycle can be completed in less than 4 weeks.[22][23]

Therapy includes mechanical removal of the larvae, covering the breathing hole in the skin with petroleum jelly, or the use of systemic ivermectin drugs. Prevention involves grooming, good hygiene, and the use of topical insecticidal shampoos and repellants.

SPIROCERCOSIS

Spirocerca lupi is a nematode parasite of carnivores found primarily in dogs but that also can occur in numerous wild carnivores.[24] Spirocercosis occurs throughout the world, having a tropical and subtropical distribution, although some colder regions have a high incidence.[24,25] Infection depends on the canine population density and the degree of contact between definitive, intermediate, and transport hosts.[24] The adult parasite is most commonly found embedded in a nodule in the host's thoracic esophagus, although it can occur in other parts of the body.[25] In the esophagus the adult worm passes larvated eggs into the lumen; these hatch only after being ingested by an intermediate host (coprophagous beetles).[24,25] Transport hosts (birds, amphibians, reptiles, and small mammals) can become infected if they ingest the intermediate host.[24]

The definitive host becomes infected by ingestion of the intermediate or the transport host. Once ingested, the larvae are liberated in the stomach. From there they penetrate the stomach wall, enter an arteriole, and migrate in the wall of the gastric and gastric-epiploic arteries to the celiac artery and then to the thoracic aorta. From the aorta, the larvae emerge and migrate to the adjacent esophagus. This process takes approximately 6 months.[24,25] The pathology of spirocercosis results from larval migration, the presence of adult worms in granulomas in the esophagus, and secondary bacterial infections.[24] In some cases, the esophageal granuloma can undergo malignant transformation to form a sarcoma, with and without metastases.[26]

Clinical signs of spirocercosis include vomiting, regurgitation, weight loss, salivation, and dysphagia.[24,27] Aortic infection is asymptomatic unless rupture occurs, in which case hemothorax and sudden death may occur. The diagnosis is based on survey and contrast radiographs, esophagoscopy, and the finding of larvated eggs on fecal flotation.[24,25,27] The larvated eggs are not a common finding, however, because the adult female can shed eggs only if an opening exists in the granuloma; also, the eggs are shed only for an unpredictable short

period.[24] Because the eggs are heavier than other helminth eggs, a flotation fluid of higher specific gravity is required. Doramectin has been shown to be effective in the therapy of spirocercosis.[28]

It has been speculated that in endemic areas, the incidence of spirocercosis infection may be 100%, a rate probably associated with the many opportunities for acquiring infection from the various intermediate and transport hosts.

CHAPTER 177

Public Health Aspects of Small Animal Practice

Leonard C. Marcus

Veterinarians must protect clients, staff, and the general public from diseases acquired from animals. This chapter reviews prevention and control of zoonoses in small animal practice. The diagnosis and treatment of these diseases in animals are discussed elsewhere in this text.

BITE- AND SCRATCH-RELATED INFECTIONS

Animal bites and scratches can range from trivial and self-healing to severely mutilating or fatal. Rabies is the most feared consequence of an animal bite. Almost all cases of dog rabies and all cases of cat rabies in the United States and Canada are acquired from wildlife. The last focus of enzootic domestic canine rabies is along the U.S.-Mexican border, and the disease there is being brought under control. Because dogs and cats remain an important bridge of infection between wildlife and humans, veterinarians should vigorously support animal control legislation and mandatory rabies immunizations for dogs and cats.

All veterinary clinical staff in the United States and Canada (except Hawaii, which is rabies free) should be immunized against rabies before exposure.[1] A vaccine grown on human diploid cells (Imovax; Aventis Pasteur, Swiftwater, PA) or on chick embryo cells (RabAvert; Chiron Corp., Emeryville, CA) is currently available. Both are inactivated. They are given on days 0, 7, and 21 or 28.

Anyone exposed to rabies after completing the pre-exposure series should be given two booster immunizations 3 days apart. Anyone who was not previously immunized should be given one weight-based dose of rabies immune globulin (RIG), with as much as possible infiltrated into the area of the bite or scratch; also, rabies vaccine should be given on days 0, 3, 7, 14, and 28. RIG should not be given to anyone who had pre-exposure immunization. Rabies vaccine should be given to adults in the deltoid muscle, not in the buttocks, to avoid injection into fat rather than muscle. Intradermal vaccine is not available in the United States at this time.

After completion of the pre-exposure series, veterinary staff should have titers checked every 2 years, and a booster should be given if the indirect fluorescent focus inhibition test (IFFIT) result drops below a titer of 1:5 or 0.5 IU/mL.

Testing for antibody before administration of a rabies booster is advisable to reduce adverse side effects, which are more common with boosters than with the primary series. It is also cost-effective, because most individuals maintain an adequate titer for many years, and the cost of testing is much lower than that of immunization.

In addition to transmission through bites or scratches, rabies can be transmitted through contact of saliva, cerebrospinal fluid (CSF), or infected tissue with a mucous membrane or opening in the skin. Possible veterinary occupational exposures include being cut with a surgical or necropsy instrument, using bare hands while performing an oropharyngeal examination, or being sprayed in the eyes or mouth with saliva during a dental procedure or with CSF while decapitating an animal or performing a spinal tap. The use of gloves, masks, and goggles reduces risk. Areas exposed to infective material should be cleaned thoroughly; soap and water should be used for cutaneous exposure, and flushing or rinsing with water should be done for ocular and oral exposures. Contact with blood, urine, or feces is not considered an exposure risk.

Bacterial infections associated with dog and cat bites include *Pasteurella multocida*, *Pasteurella canis*, *Staphylococcus* and *Streptococcus* species, plague, tularemia, and *Capnocytophaga canimorsus*.[2] Bite wounds should be washed immediately with soap and water to reduce the risk of infection. Bite victims should be advised to consult a physician about further treatment. Tetanus boosters, rabies immunizations, suturing, or prophylactic antibiotics may be indicated, depending on the circumstance, location, and condition of the wound, the likely pathogen, and the underlying health status of the individual.

Bartonella henselae causes several human ailments, the most common in immunocompetent people being cat scratch disease. Other forms of infection (e.g., bacillary angiomatosis, peliosis hepatis, endocarditis, and retinitis) occur mostly in immunocompromised individuals, such as those with acquired immunodeficiency syndrome (AIDS).[3]

B. henselae is usually transmitted to humans through a scratch from a cat. Cats are infected by interfeline fights and by fleas *(Ctenocephalides felis)*. Fleas may possibly infect humans as well. Transmission can be reduced by eliminating fleas and avoiding actions that are likely to result in a bite or scratch, such as teasing a cat with a short string.

The occupational risk of bites and scratches can be reduced through proper animal restraint, including the use of protective gloves, muzzles, and tranquilizers. Staff, not clients, should handle animals in the veterinary office. Signs to that effect (available from the American Veterinary Medical Association [AVMA] Professional Liability Insurance Trust) should be on display. Clients should be educated about bite prevention, including selection of appropriate pets and avoiding situations that result in bites, especially with small children. The AVMA has brochures for clients on these topics. Aggressive animals should receive behavior modification therapy.

FECAL-ORAL TRANSMITTED INFECTIONS

Animal feces are an important source of human disease. *Salmonella*, *Campylobacter*, *Giardia*, and *Cryptosporidium* spp. are major fecal pathogens with a wide host range, including cats and dogs.

Most cases of human giardiasis and cryptosporidiosis are transmitted person to person. When pets and humans are infected in the same household, it usually cannot be determined if all were infected through a common or different source or if the humans acquired the infection from the animals (or vice versa). Animals can be infected by drinking from toilet bowls, a practice that should be discouraged. Although differences in strains exist, all feline and canine cases of salmonellosis, campylobacteriosis, giardiasis, and cryptosporidiosis should be considered potentially zoonotic.[4]

Toxoplasma gondii has an indirect life cycle, with felids as the only definitive host. Although humans can be infected transplacentally, by organ transplant, or by ingestion of oocysts in soil or cysts in meat, traced back far enough, all human cases ultimately have a feline source.[5]

Most cats acquire toxoplasmosis within the first year of life. The patent period is only 1 to 2 weeks. Infection usually induces protective immunity, with little likelihood of much additional shedding of oocysts. Therefore the probability of finding *Toxoplasma* oocysts in randomly collected feline feces is small and has little public health value. Serologic testing for toxoplasmosis may be useful to diagnose clinical disease in the cat. It has little value in public health, except (if negative) to exclude a particular cat as the source of human toxoplasmosis.

Hydatid disease is infection with the larval stage of *Echinococcus* tapeworms, usually *E. granulosus* or *E. multilocularis*. The space-occupying lesions cause severe disease in humans; *E. multilocularis* is frequently fatal.[6,7] Infection is acquired through ingestion of eggs passed in animal feces.

Veterinarians should know the geographic distribution of adult *Echinococcus* infections and should screen definitive host species for these infections if they come from enzootic areas. *E. granulosus* is an adult tapeworm in the small intestine of wild and domestic canids. It is found in sheep dogs and, less commonly, other dogs in some western states. It is also found in canids from parts of Canada, South America, Europe, the Middle East, Africa, and Australia.

E. multilocularis is found in wild and domestic canids and domestic cats in Canada, the north-central United States, northern and central Europe, and parts of the Middle East and Asia. It may have been introduced into the U.S. southern states with the importation of foxes from Canada for hunting.

Visceral and ocular cases of larva migrans are most commonly caused by the larvae of *Toxocara canis* and less commonly by *Toxocara cati* or *Baylisascaris procyonis*.[6,7] Humans become infected by ingesting embryonated eggs. Cutaneous larva migrans, or *creeping eruption*, is usually caused by the larvae of cat and dog hookworms; infection occurs through skin contact with contaminated soil.[6,7] The pinworm *(Enterobius vermicularis)* is host specific for humans and is never acquired from dogs or cats.

Because of the long external incubation period (which averages 2 weeks), transmission of ascarids and hookworms in a veterinary hospital is unlikely. *Salmonella*, *Campylobacter*, *Giardia*, *Cryptosporidium*, and *Echinococcus* species are infective at the time of passage and can be transmitted in veterinary hospitals. *Toxoplasma* oocysts have an external incubation period of 2 to 3 days, therefore daily disposal of feline feces should eliminate the risk of transmission.

Prevention of fecally transmitted diseases requires education of clients and staff in hygiene and sanitation. Hands should be washed with soap and water or alcohol skin cleaners after animals, cages, or fecally contaminated equipment has been handled, even if gloves were worn.[8] Feces should be flushed down toilets or incinerated. Veterinarians should promote "pooper scooper" laws to reduce the risk of fecally transmitted diseases in public areas. Personnel that clean cages and kennels should wear protective masks and eyewear to avoid ricocheting water from high-pressure hoses. Two-inch wide slides are safer than the standard 1-inch slide for microscopic fecal examinations. Sealing the edges of cover slips with Permount or nail polish further increases safety. Gloves should be worn to clean cages or handle fecal specimens in the laboratory. Tools used for cage cleaning should be disinfected between cages to reduce nosocomial and zoonotic infections.

Fecally soiled surfaces should be decontaminated using approved disinfectants. Steam or flaming may be needed to kill ascarid eggs.

Prophylactic deworming schedules should be followed to reduce the infection of dogs and cats with ascarids, hookworms, and *Echinococcus* organisms.[7] Treatment for other parasites and pathogenic bacteria should be given if they are diagnosed by stool examination or culture. However, antibiotic treatment of intestinal *Salmonella* infection usually is contraindicated because of the risk of the development of antibiotic resistance.

Intestinal infections can be reduced by feeding cooked, canned, or dry food and by preventing predatory behavior by cats and dogs (e.g., keeping cats indoors).

Cutaneous Zoonoses

Various infections can be transmitted by direct contact between an animal and human skin. Several species of ringworm are zoonotic, the most common being *Microsporum canis*. Sporotrichosis is a fungal infection usually acquired by inoculation of spores in soil or organic matter. Transmission by contact with feline lesions has occurred in rare instances.

Parasitic mites vary considerably in host specificity. *Notoedres cati* very rarely infects humans; *Sarcoptes scabiei* var. *canis* does occasionally, usually transiently; *Cheyletiella* spp. readily bite humans but do not remain on them, therefore the diagnosis is made by finding mites on contact animals. Dermanyssid mites thrive in the nests of birds and rodents and bite the animals while they are nesting. These mites also bite humans, but diagnosis and control may depend on finding the nesting site.

Ctenocephalides felis and *C. canis* commonly bite humans, but their life cycle depends on the use of cats and dogs as preferred hosts. *C. felis* transmits *B. henselae* to cats and possibly to humans. *C. felis* and *C. canis* are intermediate hosts for *Dipylidium caninum*, a tapeworm that rarely infects humans because transmission requires ingestion of the flea. Because there is no approved (human) medical treatment for fleas in the United States, the animal hosts and their environment must be treated.[9] Lice are host specific. Pediculosis in humans is transmitted person to person, not from animals.

Dogs and cats that hunt can acquire fleas from prey (e.g., rodents) and bring them home. The fleas can bite humans and transmit infections such as plague and murine typhus. Dogs and cats can also bring ticks into a house. If the ticks are unattached, they could transfer to a person, but humans usually acquire ticks outdoors.

Zoonotic skin disease can be reduced through prompt diagnosis and treatment of animals, disinfection or removal of fomites, and adequate hand washing.

Zoonoses Associated with Animal Genitourinary Products

Leptospirosis is acquired through contact with infected animal urine. Dogs are commonly infected, cats rarely are. The disease can vary from mild to severe or fatal in humans.

Occupational risk can be reduced by ensuring that personnel wear gloves, a mask, and goggles while cleaning cages or handling urine specimens in the laboratory, by disinfecting exposed surfaces, and by washing the hands. Exposure would appear to be high in veterinary facilities, but reported cases are rare among veterinary staff in the United States. In a high-risk situation, a single dose of doxycycline (200 mg given orally) is prophylactic.[10]

Q fever, caused by *Coxiella burnetii*, is usually transmitted by aerosol or by ticks. The source of infection often is the products of conception. Individuals who assist in obstetrical delivery of animals are at risk. Although most infections are associated with cattle, sheep, and goats, dogs and cats also harbor the organism.[11]

Brucella canis is rarely transmitted to people by contact with canine genital secretions or products of conception or abortion.

Zoonoses Associated with Respiratory Infections in Animals

The worst respiratory infection of cats and dogs directly transmissible to humans by aerosol is plague, which is enzootic in the western United States and parts of Asia, Africa, and South America. Suspected human or animal cases should be reported immediately to the appropriate health agencies and confirmatory diagnostic procedures done. Suspect and proven cases and their contacts (human and animal) must be quarantined and treated. Veterinarians have contracted fatal pneumonic plague from cats.[12]

Bordetella bronchiseptica is a rare cause of human disease. "Strep throat" in humans is caused by *Streptococcus pyogenes*. It is transmitted person to person, and rarely, if ever, by an animal. Animals often carry other, non-group A streptococci in their oropharynx or skin. Definitive diagnosis of *S. pyogenes* requires Lancefield group serotyping.

Dogs and cats rarely get *Mycobacterium tuberculosis*. It is more often transmitted from humans to pets than vice versa, therefore the human source should be traced and treated.

Systemic mycoses, such as histoplasmosis, coccidioidomycosis, and blastomycosis, are transmitted by contact with or inhalation of spores from the soil. They can cause pulmonary, cutaneous, or multiorgan infection in humans and animals. Finding these infections in animals indicates an environmental source to which humans may be exposed.

Zoonoses in Immunocompromised People, Pregnant Women, and Children

Individuals with AIDS or some forms of leukemia, those who are undergoing chemotherapy or corticosteroid or other immunosuppressive therapy for cancer, autoimmune disease, arthritis, or organ transplant, or those who have congenital immunodeficiency are uniquely susceptible to opportunistic infections. Many of these are zoonoses (e.g., cryptosporidiosis, toxoplasmosis, salmonellosis, and bartonellosis). Asplenia increases the risk for potentially fatal sepsis with *C. canimorsus* and babesiosis.

If a woman acquires toxoplasmosis during pregnancy, the fetus could become infected and suffer severe congenital defects. Infection in the woman before conception provides protective immunity for the fetus, therefore antibody screening could provide assurance (if positive) that future pregnancies are not at risk.

It is inappropriate for veterinarians to delve into a client's health status, because such inquiry could be interpreted as practicing human medicine.[13] However, if a person volunteers the information that he or she is immunocompromised, it is appropriate for the veterinarian to advise the person to be especially careful to avoid zoonotic diseases.[14,15] If an opportunistic zoonosis is diagnosed in an animal, the owner can be advised in an open-ended way that the organism can infect humans and could cause severe illness in pregnant or immunocompromised individuals.

Because of their behavior, ignorance of risk, and poor sanitary habits, children are more at risk than adults of being injured or infected by animals. Special efforts should be made to educate parents of young children about the prevention of zoonoses and injuries from animals.

GENERAL PRINCIPLES OF VETERINARY PUBLIC HEALTH

Animals often carry *Salmonella*, *Campylobacter*, *Giardia*, *Cryptosporidium*, *Toxoplasma*, *Echinococcus*, and roundworms in the intestine asymptomatically. They also can harbor ringworm without dermatitis and can shed *Leptospira* organisms in the urine and appear well. Therefore the practice of putting warning signs on cages and applying precautions only with sick animals ignores the risk from subclinical carriers.

Hands should be washed after animals or items contaminated by their excretions have been handled. Veterinary staff should wash hands between each patient. Items soiled by urine or feces should be disposed of in a sanitary manner. Food should not be stored in refrigerators used to hold laboratory specimens. Veterinary hospitals should have effective isolation rooms and procedures for animals with contagious diseases, including the use of antiseptic footwear baths, eyewear, disposable booties, gowns, gloves, and masks; and safe sharps disposal.

Clients and staff should be educated about disease prevention, and this information should be reinforced with pamphlets and written protocols. Posting signs about washing hands, no smoking zones, and safe food storage helps. Written guidelines can cover specific situations, such as who will feed and handle rabies suspects and the way in which feces will be handled in the laboratory.

People seeking to reduce zoonotic risks when acquiring a pet can be advised to get a healthy-appearing, mature animal from a known source with no recent history of fleas, diarrhea, or respiratory or cutaneous disease. Pets should be immunized and dewormed according to standard protocols and examined regularly (e.g., annually as adults). Pets with diarrhea, cough, dermatitis, or fever should be evaluated and treated definitively and promptly.

Veterinarians should interact constructively with physicians, educating them about the transmission of zoonoses but avoiding litigious risk of involvement with individual patient care. Consultation between knowledgeable veterinarians and physicians is mutually beneficial.

BIOTERRORISM

Most potential agents of germ warfare directed against humans are zoonoses (e.g., anthrax, brucellosis, glanders, plague, Q fever, tularemia, viral encephalitides, and viral hemorrhagic fevers). Some of these occur naturally in dogs and cats, others do not, but genetic manipulation could change the host range of pathogens. It is possible that animals could become a persistent reservoir of infection after an initial attack. Veterinarians should promptly report unusual presentations or patterns of disease suggestive of bioterrorism to appropriate government authorities.

MEDICAL-LEGAL ASPECTS OF VETERINARY PUBLIC HEALTH[13]

Veterinarians can be sued if their malpractice results in human injury or zoonotic disease. Damages can include medical

expenses, lost wages, and pain and suffering. Malpractice includes failure to diagnose a zoonotic disease, treat it properly, or warn potential human contacts of the risk of transmission. The veterinary record should include the advice given to clients and others in potential contact with the animal (e.g., ways to reduce exposure and to seek medical care). Records should be kept of injuries and disease exposures that occur among staff and the response to those incidents.

Veterinarians should not offer (human) medical advice or treat human patients. The only exception might be immediate first aid that would reasonably be expected of any lay person (e.g., washing a bite or scratch wound or applying pressure to reduce bleeding from an injury inflicted by an animal).

Reportable diseases must be reported. Criminal as well as civil consequences can ensue if damages occur because of failure to report.

SUMMARY AND CONCLUSION

The great majority of zoonoses are preventable through education of clients, staff, and the general public, as well as sanitation and treatment of animal carriers. Veterinarians are obligated to incorporate public health measures into their practice. Even with these precautions, the benefits of pet ownership far outweigh the risks.

SECTION IX

Cancer

CHAPTER • 178

Principles of Chemotherapy

Angela E. Frimberger

INTRODUCTION

Chemotherapy is the principal modality used to treat systemic cancers such as hematologic malignancies and metastatic solid tumors. In managing chemotherapy, communication between the veterinarian and the owner is essential, and it must be frank and compassionate. All options should be presented to the owner without regard to the clinician's preconceptions of the owner's preferences. The goal of chemotherapy in human oncology is usually to cure the patient; however, in veterinary medicine, palliation is often a more appropriate goal. It is important to determine the goal of treatment at the outset because it often determines the course of therapy. If treatment is to be undertaken with curative intent, a greater likelihood of side effects is accepted because of greater long-term benefit. In palliative treatment it is accepted that survival is likely to be relatively short, and the primary goal is to improve quality of life, which in veterinary medicine may result in prolonged survival because euthanasia is delayed. Therefore the drug doses and schedules used are less likely to result in side effects. Because quality of life for humans depends largely on preservation of body image and essential organ function, owners may interpret their pet's well being in similar terms; the clinician can help them to understand that these are not necessarily valid for animals. A continuing, open dialogue will allow an owner to make an informed decision and will ultimately create a "team" approach to treatment of the pet's cancer.

TUMOR BIOLOGY IN CHEMOTHERAPY

In general, chemotherapy drugs are most active against cells that are actively dividing and in a particular phase of the cell cycle. In the cell cycle, cells may be in mitosis (M phase), or undergoing RNA and protein synthesis (G_1 and G_2 phase) or DNA synthesis (S phase, which occurs between G_1 and G_2). Cells may also exit the active cell cycle and enter G_0, during which time they are mitotically quiescent and may not be affected by chemotherapy. The proportion of cells in G_1, G_2, S, and M phases (the active phases of the cell cycle) compared with G_0 is referred to as the *growth fraction*. Thus it is most advantageous to use chemotherapy when tumors have a relatively high growth fraction.

Tumors grow most rapidly when they are small. As they grow larger, the growth rate decreases due to a decrease in the proportion of cells in active phases of the cell cycle, increased loss of cells, and cell death due to poor circulation, poor nutrition, and hypoxia. This decrease in growth fraction as tumors age is referred to as *Gompertzian growth*. Larger tumors may also have a poor blood supply; thus chemotherapy drugs may not be delivered to cancer cells at cytotoxic levels. In addition, resistance to chemotherapy can occur through spontaneous mutations that occur with each cell division at a rate intrinsic to each tumor. Thus the likelihood that mutation resulting in drug resistance has occurred is related to the number of cell divisions that have taken place, and therefore resistance to chemotherapy is more likely in large tumors. Furthermore, the larger the absolute number of tumor cells present, the higher the likelihood that a resistant clone is present. Finally, chemotherapy cytotoxicity follows fractional-kill kinetics; for example, if a particular dose of drug kills 4 logs of cells, then it will reduce a tumor of 10^{13} cells to 10^9 cells and a tumor of 10^{10} cells to 10^6 cells. Either will appear clinically as a complete response; however, the latter scenario is obviously preferable. Therefore it is most advantageous to begin treatment with the smallest tumor, and in general, chemotherapy will be most active either after early detection or after a cytoreductive ("debulking") procedure such as surgery or radiation therapy. Except in vincristine treatment for canine transmissible venereal tumor and combination chemotherapy for lymphoma, chemotherapy is rarely effective for large bulky tumors.

CHEMOTHERAPY STRATEGIES

Before undertaking any treatment, it is important to determine a definitive diagnosis of tumor type, the clinical stage of disease, and the patient's overall health. The histologic diagnosis and stage are important both in establishing a prognosis and prescribing a treatment plan. The prognosis assists the client in choosing a goal of treatment. The general health screen is necessary to determine if other conditions are present that may affect the patient's life expectancy (i.e., other systemic disease), conditions that need to be resolved prior to starting chemotherapy (e.g., subclinical urinary tract infection), or conditions that need to be taken into account in planning chemotherapy (e.g., subclinical cardiac or renal disease).

Goal of Treatment

As discussed previously, it is important to determine the goal of treatment at the start of therapy, because the goal usually determines the course of treatment.

Cure is the eradication of all tumor cells and is an ideal outcome, although not always realistic in veterinary oncology. The restriction on chemotherapy doses to keep side effects within an acceptable range in veterinary oncology means that cures are only possible in a small number of patients. Often defined as 2 years of unmaintained remission (not receiving chemotherapy), cure is possible for up to 15% of dogs with lymphoma and 20% of dogs with osteosarcoma.

Palliation is designed to improve quality of life—and thus possibly to extend life—but without expectation of cure. Palliative treatment is often done when the prognosis is poor and significant toxicity cannot be justified in the face of a short expected survival. It is rarely effective to begin treatment with palliative intent and then later to switch to a more aggressive approach. However, it is common to begin treatment with curative intent and then later switch to a palliative course.

Treatment Response

To determine if a given treatment is effective, it is necessary to evaluate treatment response at each visit. This is important to avoid unneeded expense and toxicity from continuing to administer an ineffective drug and so that a more effective treatment can be instituted. Clinicians can determine the tumor volume by measuring each tumor in three dimensions when possible and multiplying them. If multiple masses are present, they are each measured and the total tumor volume for the patient is determined. The response to treatment is then determined as follows:

- Clinical remission/complete response (CR)—No evidence of any detectable tumor by routine physical exam and imaging techniques but not necessarily the same as cure
- Partial response (PR)—A decrease in tumor volume of greater than 50% and no new masses
- Stable disease (SD)—A decrease of less than 50% or increase of less than 10% in tumor volume
- Progressive disease (PD)—An increase in tumor volume of greater than 10% or the appearance of any new masses

Combination Chemotherapy

To understand combination chemotherapy, it is necessary to have a brief overview of the common classes of drugs in use in veterinary oncology.

Alkylating agents create cross-links in DNA, causing strand breaks. An interesting feature of this class of drugs is the apparent lack of cross-resistance between different alkylating agents or with other classes of drugs.

Antitumor antibiotics (anthracyclines) act by interfering with topoisomerases, DNA intercalation, and other mechanisms. These drugs usually exhibit cross-resistance with others in their class and with drugs in other classes, particularly mitotic inhibitors.

Mitotic inhibitors act to inhibit assembly (vinca alkaloids) or disassembly (paclitaxel) of the mitotic spindle.

Platinum compounds create cross-links in DNA. These drugs are similar to alkylating agents, and no cross-resistance with other classes of chemotherapeutic drugs is seen.

Antimetabolites are analogs of normal metabolites and are incorporated into DNA where they interfere with enzyme activity, transcription, or translation. These drugs often have significant toxicity with low efficacy at veterinary doses and so are not in frequent use in veterinary oncology.

Early therapeutic trials for the treatment of lymphoma using single-agent chemotherapy drugs, such as vincristine or cyclophosphamide, produced dramatic clinical responses in both dogs and cats. However, these responses were often of short duration, and further treatment using the same drug did not provide further response. In other words, these animals had resistant tumors. Tumor resistance to chemotherapy is common even before treatment is started, and tumor cells acquire resistance rapidly after drug exposure due to their high mutation rate.

Combination chemotherapy may overcome some of these problems by affecting different metabolic pathways in cells that are resistant to other drugs in the combination. The object is to kill cells that may be resistant to drug A by a different mechanism using drug B before the drug A–resistant clone has a chance to expand and develop cross-resistance. Although combination chemotherapy could potentially be more toxic to normal cells, patterns of toxicity vary between drugs, and judicious scheduling of chemotherapeutic agents so that their toxicities do not overlap appears to improve tumor kill without compounding toxicity. For example, drugs that do not produce significant bone marrow suppression (such as vincristine or L-asparaginase) may be scheduled to be given 1 week after a myelosuppressive agent (doxorubicin, cyclophosphamide) or even on the same day in combination.

When chemotherapy combination regimens are designed, each drug included must be at least partially effective against the target tumor as a single agent. When drugs are given in combination on the same day it is sometimes necessary to reduce the dose of each individual drug for a higher total dose intensity. However, care must be taken not to reduce the dose of a highly effective drug to allow administration of a less effective one. The drugs are then scheduled, taking into account both the mechanism of action and the toxicity profile of each drug, to expose the tumor to the highest possible number of agents and maximize dose intensity while minimizing toxicity.

To reduce the risk of drug resistance occurring, it is important not to administer drugs at subtherapeutic doses; the highest dose intensity possible should be delivered. It is important not to modify the planned doses or schedule in anticipation of a toxicity that has not occurred. For example, a dog that became neutropenic after receiving doxorubicin is not at increased risk for myelosuppression from other chemotherapeutics such as cyclophosphamide, so doses should not be reduced. It is also important not to change the protocol for short-term or nonlife-threatening toxicities such as emesis or diarrhea. On the other hand, if tumor growth occurs, it is not good practice to continue the same treatment protocol at the same doses. Instead, an alternative, noncross-resistant regimen should be used.

Although bacterial culture and sensitivity testing appears reliable, similar tests for chemotherapeutic sensitivity using tumor cells do not appear to have the same power of prediction. Such tests appear able to predict drug resistance and may have a role in identifying agents that could cause side effects without antitumor effects. However, because the ability of such tests to predict tumor sensitivity is low, combination chemotherapy is recommended over single agents suggested by assays.

Chemotherapy in Combination with Other Treatment Modalities

Chemotherapy can be used in combination with other modalities, including surgery, radiation therapy, or both.

Adjuvant chemotherapy is used after resection of a primary tumor, when the animal is at significant risk of recurrence or metastasis. The most obvious veterinary example is the effectiveness of adjuvant cisplatin, doxorubicin, or carboplatin in the treatment of canine osteosarcoma. The effectiveness of adjuvant chemotherapy lies in the fact that it is used at the earliest stages of growth. When a primary tumor is resected, micrometastatic foci of tumors cells have a high growth fraction and a low number of resistant cells. As the tumors grow, the growth fraction decreases, the cell cycle time increases, cellular heterogeneity increases (leading to a higher level of spontaneous resistance), and areas of poor vascular perfusion increase. The disadvantage of adjuvant chemotherapy is that some patients may be cured with surgery, and the animals are exposed to needless risks of toxicity. For tumors such as osteosarcoma and hemangiosarcoma in dogs and mammary tumors in cats, this percentage is small, but for animals with other tumors, the decision may be more difficult.

Neoadjuvant chemotherapy is used prior to localized treatment modalities such as surgery or radiation therapy with the objective of reducing the size of the primary tumor and reducing the scope and side effects of other definitive treatment.

Chemoradiotherapy refers to the use of chemotherapy drugs primarily as radiation sensitizers rather for their direct antitumor effect.

Modes of Administration

The majority of chemotherapy is delivered either intravenously or orally, and occasionally subcutaneously or intramuscularly. However, other modes of administration are sometimes used,

particularly for cisplatin. Cisplatin can be delivered to dog as an intracavitary infusion into the pleural or peritoneal cavities to successfully control malignant effusions or intravesicularly (into the urinary bladder) for bladder tumors. Cisplatin has also been injected intralesionally, in a collagen or oil-based vehicle, to control localized tumors. In this method, great care must be taken to avoid exposure of personnel because spillage occurs easily and drug may leak from the injection sites. Topical administration is available (5-fluorouracil—dogs only) but is rarely used because of drug toxicity and the risk of exposure to humans who apply the medication and play with the dog. Certain drugs can also be administered intra-arterially and intrathecally for specific treatment protocols; however, this is rarely done in veterinary medicine.

Encapsulation in liposomes can reduce or alter the toxicity of some chemotherapy drugs. Conjugation of the liposome with polyethylene glycol reduces clearance by the reticuloendothelial system, producing "stealth" liposomes with greater circulating time. A liposome-encapsulated doxorubicin formulation has been reported to be less cardiotoxic in veterinary patients but resulted in a new cutaneous toxicity.

Chemoprotection

The administration of a second drug specifically to reduce the host organ toxicity of a chemotherapy drug is termed *chemoprotection*. Chemoprotectants in use in human and veterinary oncology include mesna, which reduces the risk of cystitis associated with ifosfamide and cyclophosphamide by binding toxic metabolites in the urine, and dexrazoxane, which protects against doxorubicin-associated chronic cardiotoxicity.

Metabolic Dosing

Because their desired effect is cellular cytotoxicity, most chemotherapy drugs have a very narrow therapeutic margin; that is, the host toxic dose is very close to the effective dose. Therefore it is important to be as accurate as possible when calculating doses. For some drugs, dosing is based on a "metabolic body size" to decrease the risk of toxicity to the patient. Although imperfect, current dose recommendations for these drugs are based on body surface area (BSA, m^2). This scheme implies that smaller animals have a higher metabolic rate and therefore should receive a higher dose on a body weight basis. For other drugs (e.g., doxorubicin) dose based on BSA is imperfect, and small dogs and cats should be dosed at lower rate than larger dogs. Until further guidelines are available, the veterinarian should check the dosing basis for any drug to be used, become familiar with the individual drugs that require lower dose for small pets, and use a BSA conversion table when metabolic dosing is indicated.

In human oncology, dosing is sometimes tailored to the individual patient either by monitoring drug levels or based on patient characteristics. For example, the appropriate dose of carboplatin can be determined from a formula based on the patient's glomerular filtration rate (GFR) and the desired area under the curve (AUC). This type of calculation is not usually done in veterinary oncology; however, similar principles are recognized: in patients with reduced GFR reflected as elevated serum creatinine level, carboplatin dosing should be adjusted based on the serum creatinine level (see Practical Chemotherapy).

Dose Intensity

The concept of dose intensity is an important principle of chemotherapy. It is defined as mg/m^2 of drug per week of therapy and should be the highest tolerated by the animal with minimal toxicity. For example, in dosing of myelosuppressive drugs, because there will be variation in individual metabolism of drugs and in the sensitivity of normal tissues, the aim should be to deliver doses that produce a neutrophil nadir of between 1000 and 1500 cells per µl. Ample evidence in both human and veterinary oncology suggests that optimal dose intensity improves the outcome for chemotherapy.

Chemotherapy dose intensification with bone marrow support has been used with success in veterinary oncology. The use of autologous (patient's own) bone marrow transplant to allow higher doses of a myelosuppressive drug has been used in myeloablative bone marrow transplantation in human patients and dogs, but the toxicity of such dose intensification is high. Intensifying chemotherapy doses with autologous bone marrow support, but only into the submyeloablative range, appears to improve remission times without increasing toxicity for selected dogs with lymphoma.

Toxicity After Chemotherapy

Because most chemotherapy drugs are effective in the active phases of the cell cycle, toxicity from chemotherapy is most common in tissues that are renewing and is usually related to the dose of the drug. This has implications for both the patient (toxicity and efficacy) and for owner and veterinary staff safety in handling the drugs during administration and patient care. (See Practical Chemotherapy for more on chemotherapy safety.) Although most tumor cells are in active phases of the cell cycle, most normal tissues have a relatively low growth fraction. Normal tissues can be classified as static (nerve, striated muscle) in which the capacity for mitosis is limited; expanding (organs, glands) in which mitosis can be induced; and renewing (hematopoietic cells, mucosa, epidermis, gametes, fetal tissues) in which the growth fraction approaches that of tumor tissue. The major toxicities of chemotherapy affect the latter group.

Myelosuppression is a general term applied to the toxic effects of chemotherapy on the bone marrow (Table 178-1). In general the prognosis for uncomplicated myelosuppression is good, and most veterinary patients recover within a few days. Most dogs and cats that have myelosuppression have no clinical signs at all. The most chemosensitive cells in the bone marrow are the proliferating hematopoietic progenitors and precursors, which are starting to commit to a particular lineage but are still immature. The more differentiated cells form a nonproliferating pool of maturing hematopoietic cells that will be unaffected by chemotherapy and will provide mature cells for 5 to 10 days. This means that the nadir (or low point) of peripheral cell counts occurs at this time. The time at which the nadir occurs also depends on the life span of the hematopoietic cell. Neutrophils live only hours in both dogs and cats, and their nadir occurs first at 5 to 10 days postchemotherapy; platelets live for approximately 10 days, and their nadir occurs 1 to 2 weeks after chemotherapy. Erythrocytes live for 120 days in the dog and 70 days in the cat; although anemia may occur over a prolonged course of chemotherapy, it is rarely clinically significant. Like the maturing cells, hematopoietic stem cells are largely nonproliferating and so are relatively resistant to chemotherapy toxicity. However, they are stimulated to divide by the loss of proliferating precursor cells and rapidly replace the lost cells so that nadirs after chemotherapy rarely last more than several days. This also has implications for the interval between administrations of myelosuppressive drugs. If these drugs are given when the stem cell pool is dividing (i.e., soon after the previous administration), then severe prolonged myelosuppression due to stem cell destruction may occur. The usual timing for myelosuppressive drug administration is every 2 to 3 weeks. Some drugs (such as lomustine and carboplatin) may have delayed or prolonged nadirs, and dosing intervals are longer for these drugs.

When administering chemotherapy, a complete blood count (CBC), including a platelet count, should be collected at the expected neutrophil nadir, usually 1 week after administration. The absolute neutrophil count (not the total leukocyte count)

Table • 178-1

Myelosuppressive Potential of Some Commonly Used Chemotherapeutic Agents

HIGHLY MYELOSUPPRESSIVE	MODERATELY MYELOSUPPRESSIVE	MILDLY MYELOSUPPRESSIVE
Doxorubicin	Melphalan	L-asparaginase*
Vinblastine	Vincristine (0.75 mg/m2)*	Vincristine (0.5 mg/m2)*
Cyclophosphamide	Methotrexate	Corticosteroids
Carboplatin	Cisplatin	Bleomycin
Mitoxantrone	Chlorambucil	
Lomustine (CCNU)	Hydroxyurea	
	5-Fluorouracil	

*However, the combination of vincristine and L-asparaginase can be highly myelosupportive.

should be evaluated. Although many animals have a low neutrophil count without clinical signs, a count of less than 1000 cells per µl is sufficient reason to reduce all subsequent doses of that myelosuppressive drug.

Thrombocytopenia rarely causes clinical signs; however, at counts less than 50,000, the risk of bleeding increases and the veterinarian should be alert to petechiation, ecchymoses, or mucosal bleeding.

The gastrointestinal (GI) mucosa is another site of renewing tissue, and toxicity may occur anywhere in the GI system. Clinical signs include nausea, vomiting, inappetence, anorexia, or diarrhea. The management of this toxicity will depend on the severity of signs. Again, most GI toxicity is mild, self-limiting, and carries a good prognosis. For inappetence, tempting with palatable foods or using appetite stimulants such as cyproheptadine may be helpful. For occasional or mild vomiting, withholding food for 24 hours, then introducing multiple small feedings of a bland diet is usually sufficient. Metoclopramide may reduce the severity of vomiting; for diarrhea in dogs, subsalicylate may be therapeutic. For severe GI signs, intravenous fluid support and antiemetic treatment should be considered. Antiemetics include metoclopramide infused at a constant rate, chlorpromazine, or ondansetron (a serotonin antagonist that is an excellent antiemetic). Cisplatin is a powerful emetogen, and the prophylactic administration of butorphanol immediately after cisplatin administration reduces both the incidence and severity of vomiting. Ondansetron may also be used in the same setting. If vomiting occurs after cisplatin treatment (and particularly if it is prolonged or associated with anorexia), intravenous fluids should be administered, because dehydration may exacerbate the nephrotoxic effects of cisplatin. Severe hemorrhagic colitis after doxorubicin administration increases the risk of subsequent sepsis due to breakdown of the protective mucosal barrier to gram-negative intestinal bacteria at a time when the animal is myelosuppressed. Antibiotics should be administered to these animals in addition to supportive and symptomatic care.

In veterinary oncology, cardiotoxicity is only clinically a problem with doxorubicin chemotherapy. Although both cats and dogs show histologic cardiac changes, cats have not been reported to have clinical cardiotoxicity. Acute cardiotoxicity is related to peak plasma level and occurs during administration that is too rapid. Although the arrhythmias are self-limiting, they can cause collapse. The infusion should be stopped and then restarted at a slower rate. Chronic cardiotoxicity is related to the total cumulative dose of doxorubicin rather than the amount of each individual dose, and it carries a poor to grave prognosis. The end result resembles dilated cardiomyopathy and may progress to congestive heart failure (CHF). Although cardiotoxicity in dogs can occur at any cumulative dose, it is most frequent above 180 mg/m^2, and doxorubicin should not be given above this level without echocardiographic monitoring. Electrocardiographic changes are inconsistent and a poor indicator of early cardiac damage. Although echocardiographic changes usually occur before clinical signs, the damage will progress even after doxorubicin has been discontinued. Breeds susceptible to dilated cardiomyopathy, particularly Dobermans, appear to be more sensitive to this toxicity; pretreatment cardiac evaluation and close monitoring is mandatory in these dogs. The risk of cardiotoxicity is reduced by delivering the drug as a continuous infusion over several hours, by using liposome-encapsulated doxorubicin, or by pretreatment with the cardioprotectant drug, dexrazoxane. The latter two options are yet to be fully evaluated in clinical veterinary practice.

Nephrotoxicity is the primary dose-limiting toxicity of cisplatin and depends on both the individual and cumulative dose. This toxicity also carries a poor prognosis. Cisplatin should not be administered to dogs with pre-existing renal disease and should be used with caution in dogs with urinary tract tumors. It is important to check the serum creatinine level before each cisplatin treatment. Cisplatin should not be administered if the serum creatinine is above normal range. In addition, cisplatin should always be delivered with appropriate saline diuresis. Doxorubicin has been anecdotally associated with nephrotoxicity in cats.

Urothelial toxicity (sterile hemorrhagic cystitis) is associated with cyclophosphamide and ifosfamide administration. Although this toxicity is uncommon after cyclophosphamide administration, it will occur after ifosfamide treatment unless the urothelial protectant, mesna, is given concurrently. When it occurs, it is usually self-limiting and carries a fair to good prognosis. Clinical signs of stranguria, dysuria, and hematuria can be severe and prolonged over many weeks. This toxicity should be distinguished from infectious cystitis by bacterial culture; however, even if bacteria are isolated and signs resolve with antibiotic administration, the drug should not be administered again because infectious cystitis could have been secondary to chemical cystitis. Chlorambucil is usually substituted for cyclophosphamide if urothelial toxicity occurs in lymphoma patients. If urothelial toxicity occurs, steroidal or nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the severity of signs. In persistent cases, intravesicular instillation of 25% dimethyl sulfoxide (DMSO) for 20 minutes may help reduce signs and may be repeated weekly.

Extravasation is rarely a problem if chemotherapy is administered carefully through a "first-stick" venous catheter. The catheter should be tested with a saline flush both before the drug is administered and after infusion is complete.

Although a butterfly catheter is acceptable for volumes less than 1 mL, larger volumes should be administered through a secure over-the-needle catheter. If any drug is extravasated, the clinician should aspirate as much drug as possible before removing the catheter. If vincristine is extravasated, the area should be flooded with 10 mL of 0.9% NaCl and warm compresses applied. The resulting reaction is rarely severe and will be reduced further by preventing self-trauma. If doxorubicin is extravasated, ice compresses should be applied for 6 to 12 hours. Dilution of drug will only increase the area affected. Doxorubicin extravasation results in a slough that can be severe, and the full extent of the reaction may not be apparent for 3 to 4 weeks. Surgical resection or débridement may be necessary.

Hypersensitivity reactions may occur during doxorubicin administration due to histamine release from mast cells. This effect only occurs with rapid administration and is not a problem if the drug is given as a slow infusion or an intravenous injection at a rate of 1 mL per minute. A similar but more severe reaction occurs after intravenous administration of etoposide and paclitaxel due to "carrier" solutions in these formulations. Both carriers cause massive histamine release, the effects of which are only partly prevented by pretreatment with antihistamines and corticosteroids. True anaphylaxis may occur after L-asparaginase administration, particularly by the intravenous or the intraperitoneal route. This toxicity occurs very rarely if L-asparaginase is administered intramuscularly or subcutaneously. If anaphylaxis occurs, treatment with corticosteroids and antihistamines plus any necessary supportive measures should be instituted. The patient should not receive any further L-asparaginase. Attachment of polyethylene glycol conjugates to the L-asparaginase abrogates the immune response, and extends its half-life while preserving efficacy.

Hair loss is rarely a problem in pets that have fur. However, in dog breeds with hair (e.g., poodles, terriers, old English sheepdogs), alopecia can be significant although regrowth usually occurs in 4 to 8 weeks. In addition, dog breeds with "feathers" will lose these (e.g., golden retrievers). Cats will lose whiskers and sometimes body fur, and they may experience hair coat color changes. These problems are cosmetic and rarely of consequence to an adequately prepared owner.

Specific cat toxicities may occur with chemotherapy. Cisplatin causes a fatal, acute pulmonary edema in cats and should not be administered systemically. Intralesional administration of a colloidal suspension of cisplatin may be safe in cats, but care should be taken if this route is to be used. Topical and systemic administration of 5-fluorouracil causes acute fatal neurotoxicity in cats, and products containing this drug should not be used.

The major dose-limiting toxicity in veterinary cancer chemotherapy is myelosuppression. Recombinant hematopoietic growth factors and autologous bone marrow transplantation are widely available in human oncology practice and are in the initial stages of evaluation in veterinary oncology. Such techniques may allow the use of higher dose intensity without increasing the risk of myelosuppression. Similarly, advances that are being made in the treatment of pain and nausea and in the prevention of toxicities such as cystitis (mesna with ifosfamide or cyclophosphamide) will reduce the incidence of other toxicities. These will improve the ability of the veterinary oncologist to deliver adequate chemotherapy doses and result in better quality of life for pets with cancer.

Chemotherapy Drug Resistance

Resistance to chemotherapy may be either inherent or acquired. Drugs may be physically unable to reach tumors that are in sanctuary sites such as the central nervous system (CNS) or that are poorly perfused. Tumor cells may inherently lack receptors for a drug or not be susceptible to the mechanism in some other way (e.g., cells that have asparagine synthetase will be resistant to L-asparaginase).

Tumor cells may develop drug resistance spontaneously through mutation. The mutation rate is higher in tumors than in normal tissue because of the genetic instability characteristic of malignancy. With each cell division comes the risk of a resistance mutation; therefore the larger a tumor is (i.e., the more cell divisions it has undergone), the higher the likelihood that this has occurred. Tumor cells can also develop drug resistance specifically. Exposure to sublethal drug concentrations can result in gene amplification of detoxifying proteins.

Although combination chemotherapy may circumvent individual drug resistance, it does not avoid the problem of cross-resistance to multiple unrelated chemotherapy drugs. The transmembrane pump protein (P-glycoprotein) is present at increased levels in some tumor cells, and both the level and prevalence increases with exposure to chemotherapy. This phenomenon of multiple drug resistance (mdr) occurs between anthracyclines, mitotic inhibitors, and others. However, alkylating agents are not substrates for the mdr pump, and so they become the mainstay of treatment in patients that appear to have this type of drug resistance.

CHAPTER • 179

Practical Chemotherapy

Antony S. Moore

This chapter is best read in conjunction with Chapter 178, Principles of Chemotherapy. The two chapters include many of the same topics, but they are complementary in their treatment of those topics.

CLIENT PREPAREDNESS

The greatest challenge the veterinarian faces in using chemotherapy is addressing owners' preconceptions, biases, and negative experiences with chemotherapy. The side effects of treatment in human patients, which the owner may have experienced or may have heard about from television, the Internet, or family and friends, usually are inconsistent with the quality of life clients want for their pet. It is important for the veterinarian to acknowledge these feelings and to inform the owner that the goal of chemotherapy in cats and dogs is different; that is, that the pet should be given the maximum dose that improves quality of life without causing undue toxicity, as defined by the veterinarian and the owner. For some owners, this definition may mean preventing *any* loss of quality of life; for other clients, it may have a much different meaning. In any situation, the veterinarian should establish the goals of therapy before starting treatment. If owners understand that quality of life takes precedence in their pet's treatment they are more likely to trust the veterinarian and to treat their pet. The reality of supportive care for cancer chemotherapy patients in veterinary medicine is that component transfusions, sterile wards, and allogeneic transplant support are unavailable. For these reasons, lower drug dosages must be used, and dosages must be reduced even further if toxicity is observed. This should be emphasized to owners.

Provision of accurate information in understandable terms about the type of cancer, the prognosis, and the predictable side effects of treatment is an important responsibility of any veterinarian. Being honest while maintaining a feeling of hope and caring is one of the most important aspects of establishing trust with the owners of a pet with cancer. Encouraging owners to ask questions and to communicate their concerns is equally important.

Supplementation of verbal instructions with written information about the specific disease, the treatment protocol, and the drugs to be used greatly assists owners in making their decision. Many such information sheets can be obtained from veterinary oncologists and the Internet.

Furthermore, it is important to discuss with owners not only the potential toxicities of treatment, but also the owners' goals for chemotherapy, in particular what they would consider a successful outcome.

Palliative Intent Treatment

For many older veterinary patients, the diagnosis of cancer is made at a time when other diseases may limit survival to a greater extent than does the cancer. For these animals, palliative care may be most appropriate, and the choice of chemotherapy must be weighed against the risk of toxicity. An example would be a Doberman pinscher with cardiomyopathy and osteosarcoma. Such a dog may benefit from pain relief for the bone cancer. Cardiac disease makes doxorubicin a poor choice for chemotherapy, and the diuresis required for cisplatin administration may result in cardiac decompensation. An alternative, therefore, would be carboplatin. However, if a poor prognosis due to cardiac disease makes it unlikely that the benefits of extended survival through chemotherapy will be realized, chemotherapy may not be a good choice for this pet, and treatment should focus on pain relief.

Curative Intent Treatment

For younger dogs and cats that are in good health and have no concurrent illnesses and for which chemotherapy holds the possibility of prolonged control of the cancer with little risk of toxicity, chemotherapy with curative intent may be undertaken. An example would be an asymptomatic, middle-aged dog with stage 3, B-cell lymphoma, for which the prognosis is guardedly optimistic. The owners of such a dog may even elect to try more aggressive combination chemotherapy to improve the chance of long remission.

SUITABILITY OF THE PATIENT

When evaluating an animal for treatment of cancer, it is important not only to obtain a definitive diagnosis, but also to assess the pet's general health through clinical examination and ancillary diagnostics. Prognostic information gained by determining the extent of organ involvement by the tumor and by identifying unrelated or secondary conditions that must be treated or controlled before the appropriate therapy can be instituted is mandatory in order to make recommendations regarding the suitability of a patient for chemotherapy. This information is also vital for individualizing the type and intensity of a treatment regimen.

Staging and Health

Staging is a clinical process that enables the veterinarian to quantitate the extent of cancer involvement in the dog or cat. Staging is sometimes confused with *grading*, which characterizes the histopathologic features of a tumor. Staging often carries prognostic significance that may help both the veterinarian and the client make informed, rational decisions about the type of therapy best suited for a pet. Most staging systems are based an assessment of three major components of the malignant process: the size of the primary tumor (T), lymph node metastasis (N), and distant metastasis (M). Ancillary diagnostics, often incorporating sophisticated imaging techniques, are important for obtaining this information. The majority of pets for which chemotherapy may have therapeutic benefit have systemic or metastatic disease that either is physically evident or is presumed through historical knowledge of tumor behavior (e.g., osteosarcoma and hemangiosarcoma in dogs).

The likelihood of a successful outcome for a dog or cat treated with chemotherapy is as dependent on drug metabolism and elimination (and drug absorption for orally administered chemotherapy) as it is on the sensitivity of the tumor.

Consequently, information gained during staging may identify problems that can affect the type and dosage of chemotherapy, in order to optimize efficacy while limiting toxicity. For example, hepatic dysfunction may lead to delayed elimination of some drugs (e.g., vinca alkaloids, doxorubicin) and therefore to greater toxicity, such as myelosuppression. In contrast, because cyclophosphamide is activated in the liver, hepatic dysfunction may result in poor efficacy.

Similarly, renal dysfunction may worsen toxicity for some drugs that are themselves nephrotoxic. For example, cisplatin and streptozocin should not be used in animals with renal azotemia. Reduced renal excretion of carboplatin exacerbates myelosuppression.

Particularly in breeds with a predisposition to the development of cardiomyopathy, treatment with doxorubicin should be accompanied by cardiac evaluation. Pretreatment echocardiography should be performed, and dogs with reduced contractility should not be given doxorubicin. Although valvular dysfunction should not be a reason to withhold doxorubicin, mild changes in cardiac muscle function may exacerbate the valvular disease. In these dogs, echocardiography should be performed periodically, ideally prior to each doxorubicin treatment. Treatment with doxorubicin should be discontinued if contractility is below normal and while the dog is still asymptomatic. Cardiac dysfunction caused by doxorubicin is irreversible and usually progressive. For this reason, monitoring for signs of early cardiac failure before discontinuing doxorubicin is unacceptable practice.

SUITABILITY OF THE TUMOR

The most rapidly changing aspect of veterinary oncology involves published data on tumor sensitivity to chemotherapy. Although good published data are available on dogs with osteosarcoma and lymphoma, information on the most effective chemotherapy for adjunctive treatment of other, even common, malignancies often is unavailable or is based on small case series. As larger, multi-institutional and organizational studies are completed and the results published, this will change. For example, the recent finding that high-grade soft tissue sarcomas in dogs are more likely to metastasize implies that it may be possible to assess adjunctive chemotherapy for efficacy in this select group of dogs. In contrast, appendicular osteosarcoma in cats rarely metastasizes (approximately 25%), and it would be difficult to demonstrate adjuvant efficacy for any chemotherapeutic agent, given the rarity of the tumor.

CHOOSING A DRUG

Clinical veterinary chemotherapy research is advancing at a great rate. However, even when studies are completed, it may be a year or more until the results are published, and they often appear in less accessible journals. The best resources for veterinarians are veterinary oncologists, the Veterinary Cancer Society (www.vetcancersociety.org), other Internet-based resources and Internet literature data bases, such as Medline.

In addition to efficacy, and possibly more important, the final choice of a drug (or protocol) depends on toxicities, an owner's tolerance for side effects, the treatment goals, the cost, and the veterinarian's level of comfort in delivering chemotherapy and supportive care.

CHEMOTHERAPEUTIC DRUGS

No chemotherapeutic drugs are labeled for veterinary use only. All veterinary cancer chemotherapy is performed off label. However, most of the available drugs have an established track record, particularly those that have been used to treat lymphoma and osteosarcoma. The body of literature available means that veterinarians should feel secure in using dosages and schedules provided in published protocols. Treatment using most veterinary drugs is expected to result in less than 5% risk of life-threatening toxicity (hospitalization, severe neutropenia) when established dosages are used. The risk of death from chemotherapy should be considerably lower than that.

Drug Cost

The cost of many of these drugs may be high. However, generic versions of several chemotherapeutic agents (e.g., vincristine, doxorubicin, cisplatin) are available, making them more affordable. Some pharmacies supply small amounts of injectable drugs to veterinarians, and compounding pharmacies will reformulate smaller dosages of oral medications (e.g., lomustine [CCNU] or procarbazine for cats and small dogs). The cost of therapy often is not as much a deterrent to owners interested in chemotherapy for their pet as is quality of life. Veterinarians should inform owners of the best available options and allow them to make the decision on cost.

WHEN TO GIVE CHEMOTHERAPY

Veterinary chemotherapy protocols are often simple, consisting of one or two chemotherapy agents given at an interval that minimizes the risk of toxicity but maintains the highest possible dose intensity (e.g., cisplatin as an adjuvant to surgery for dogs with osteosarcoma). In contrast, lymphoma protocols are often complex, with many agents scheduled in combination (see Tufts VELCAP-SC, Figure 179-1). Descriptions of different "phases" of a protocol apply best in these lymphoma treatment schedules.

Timing

Primary Treatment

In veterinary oncology, primary chemotherapy usually is reserved for hematopoietic tumors (lymphoma, leukemias, multiple myeloma). The phases of a primary treatment protocol for lymphoma are presented in Box 179-1. Chemotherapy for dogs with metastatic solid tumors (carcinomas and sarcomas) is rarely successful and is better considered to be palliative.

Adjuvant Treatment

After surgery, adjuvant chemotherapy may be given to slow the progress of metastatic disease or possibly to provide a cure. The optimum time to administer primary chemotherapy is when the dog or cat has microscopic disease, rather than when gross metastases have developed. An example of successful adjuvant veterinary chemotherapy is the use of platinum compounds and doxorubicin after surgery for canine osteosarcoma.

ADMINISTRATION OF CHEMOTHERAPY

The proper administration of chemotherapy has been covered in great detail by many authors. In brief, the regulations set by the U.S. Occupational Safety and Health Administration (OSHA) should be followed, and owners, as well as all personnel coming in contact with chemotherapeutic agents, should be protected to the best of the veterinarian's abilities. A chemotherapy logbook, which includes identification of animals treated and the personnel involved in the treatments, should be maintained to track exposures.

Box • 179-1

Phases of a Primary Treatment Protocol for Lymphoma

Induction
The induction phase encompasses the often intensely scheduled initial treatments. During this phase, a dog or cat has a relatively higher risk of toxicity but usually also the greatest chance of response (e.g., during the first 12 weeks of VELCAP; see Figure 179-1).

Consolidation
Consolidation is sometimes used at the end of induction; unrelated, effective drugs are administered to further reduce the proportion of surviving cancer cells (e.g., the combination of mechlorethamine, vincristine (Oncovin), procarbazine, and prednisone [MOPP] and CCNU in VELCAP; see Figure 179-1).

Maintenance
Maintenance is a less intense phase (usually involving decreased frequency of administration) during which the drugs previously used for induction are administered. Maintenance therapy probably has little influence on whether an animal is cured, but it may prolong survival by increasing the time to relapse.

Rescue
Rescue is therapy given when the drugs used during the other three phases no longer result in remission. Unrelated drugs (often alkylating agents because they are less likely to show cross-resistance) are used for rescue therapy.

Handling

Veterinarians can greatly reduce the risk of exposure by familiarizing themselves with the hazardous properties included in the Material Data Safety Sheet (MSDS) for each drug and by using appropriate protective equipment. The information contained in each MSDS covers specific health hazards, including carcinogenicity; primary routes of exposure; protective equipment; treatment of personnel acutely exposed; chemical activators; solubility; stability; volatility; and specific procedures to be undertaken in case of a spill. The MSDS should be requested with the initial shipment of any chemotherapeutic agent and should be kept on file in an easily accessible location.

Most chemotherapeutic agents are both toxic and mutagenic. Alkylating agents have been associated with the highest risks to handlers. Organ damage and increased risk of fetal loss have been reported in individuals handling and administering chemotherapy with inadequate attention to personal safety. Precautions should be taken in handling chemotherapeutic drugs during any phase of preparation, administration, and disposal of drugs or waste. Ideally, a vertical laminar flow biologic safety cabinet would be used to prepare all chemotherapeutic drugs. If this is not available, protective eyewear, a respirator mask, and a disposable gown with closed-cuff sleeves and latex (not vinyl) gloves should be worn. All these items usually are available through distributors of chemotherapeutic agents. Hydrophobic filters that insert into chemotherapeutic drug vials can prevent aerosolization of drugs during preparation for dosing. If a filter is not used, gauze moistened with alcohol should be wrapped around the vial top and needle to protect personnel from aerosolized drug. Latex gloves should be worn when the drugs are administered, whether parenterally or orally. With parenteral administration, Luer-Lok syringes reduce the risk of drug leakage or spills. Pills should not be broken.

If owners are administering drugs orally at home, gloves and a waste bag should be provided. For drugs excreted in the urine (particularly cisplatin), the pet should be encouraged to urinate on soil where urine drains quickly, and any urine in other areas should be handled and disposed of as chemotherapy. These precautions should be followed for approximately 48 hours after administration.

Route of Administration

For most intravenous chemotherapy administrations, injection through a peripherally located over-the-needle catheter is safest, reducing the risk of extravasation even when a small volume is to be administered. For longer infusions (more than 30 minutes), a through-the-needle catheter is less likely to become dislodged.

When long infusions are required, either for prolonged drug delivery or for the saline diuresis that accompanies nephrotoxic drugs such as cisplatin or streptozocin, an infusion pump is recommended. Free-flowing fluid administration, even when monitored continuously, may not ensure continued diuresis or could result in uneven delivery of the drug dose. Both of these factors could affect the risk of toxicity. A calibrated infusion pump allows predictable administration of the chemotherapeutic dose.

Some cats and many dogs are small, and their vascular integrity may be compromised by multiple administrations of anesthesia (e.g., surgery, radiation therapy) prior to receiving chemotherapy. Because the risk of extravasation reactions is greater in these animals, an indwelling, subcutaneously located, implantable vascular access port may ensure timely drug delivery and reduce stress during restraint for catheter placement and administration of chemotherapy. Such a port may be maintained for the duration of therapy and then removed. The implantable vascular access port must be placed surgically, in a similar manner to a tunneled catheter, with a subcutaneous pocket for positioning of the port. Ports for veterinary use are available from Norfolk Vet Products, Skokie, Illinois.

Most oral medications are administered as tablets or capsules, although a cyclophosphamide elixir can be compounded using the injectable form of the drug. Tablet formulations should not be split, because distribution of the drug may not be uniform throughout the tablet; this is particularly true of cyclophosphamide. For small animals, reformulation of oral medications by a compounding pharmacy is more accurate and safer (e.g., CCNU or procarbazine for cats).

Intracavitary chemotherapy (intrathoracic, intra-abdominal, intrapericardial, or intravesicular [urinary bladder]) has been reported. The drugs used for this purpose logically should have little vesicant activity. The drugs most commonly used are the platinums (cisplatin may have greater tissue penetration than carboplatin) and mitoxantrone.

Intralesional chemotherapy usually involves a suspension of a chemotherapeutic agent in a vehicle (the use of cisplatin or 5-fluorouracil in sterile sesame oil or bovine collagen matrix has been reported). The mixture should be injected into a tumor, creating high drug exposure to tumor cells. This involves minimal systemic drug levels, avoiding the risk of systemic toxicity. Intralesional chemotherapy is used to treat only small, easily accessible tumors.

Dosing

The initial treatment with an individual drug should be given at a dosage known to result in minimal toxicity in the majority of animals. Because the risk of toxicity is highest when an

animal receives a drug for the first time, the temptation may exist to begin with a low dose and increase the dosage incrementally after each administration that is toxicosis free. The logic of that approach is flawed, however, because the reduction in dose intensity can only reduce the chance for successful remission and accelerate the development of drug resistance. Effective treatment is more likely to result from the highest tolerated dosage, and prophylactic supportive strategies (see below) are preferable to an arbitrary reduction in the initial dosage.

The selection of drug dosage can also be influenced by organ function. Although no guidelines have been established, it may be safest to reduce the dosage of hepatically metabolized drugs by 50% if the serum bilirubin is greater than 1.5 mg/dL and by 75% if the serum bilirubin is greater than 3 mg/dL. Dosages can then be slowly increased after each cycle that occurs without toxicity.

Because carboplatin is renally excreted, carboplatin dosage ideally is based on the glomerular filtration rate (GFR). If the GFR cannot be estimated, an arbitrary dose reduction of 50% to 75% should be made for animals with renal azotemia; dosages then can be increased after each cycle that occurs without toxicity.

The frequency of drug administration is determined by the length of time required from administration of the drug to the recovery of normal tissues (bone marrow, gastrointestinal tract). For example, doxorubicin can be given every 2 weeks to most animals because neutropenia has usually completely resolved by this time. However, some individual patients may not be able to receive the drug any more often than every 3 weeks because of a neutrophil count that is still too low (see the section on monitoring, below). The drug that is the most common example of individual variability for dosing interval in veterinary medicine is carboplatin. In some animals (particularly cats), it may take 5 weeks or longer for hematologic parameters to recover to a level at which a subsequent dose can be delivered safely.

Drug Resistance

Chemotherapeutic drugs act through a multitude of mechanisms. Resistance to individual drugs may occur at the cellular level (e.g., altered target) or as a result of host factors (e.g., antibody formation to L-asparaginase). When combination chemotherapy is used, cross-resistance between different classes of agents is a serious threat to successful treatment. In particular, multiple drug resistance (MDR) due to a transmembrane efflux pump protein (gp170) can reduce intracellular levels of vinca alkaloids, anthracyclines, and other "naturally" derived chemotherapeutics to nontoxic levels. Because these drugs are often used in the treatment of lymphoma, it is wise *not* to overly rely on them in the rescue stage, but rather to use them in combination for first-line therapy. Interestingly, drugs classified as alkylating agents are not susceptible to the MDR mechanisms. There is very little cross-resistance, even between different alkylating agents. This may explain the successful strategy of using alkylating agents as rescue therapy for animals with lymphoma. It is also possible that the use of alkylating agents in combination with MDR-type drugs during the early phases of treatment (induction) may slow the onset of resistance. Trials of agents that competitively block MDR have not yet led to practical veterinary treatment strategies.

Drug Combinations

Combination chemotherapy has two major aims. The first is to slow the onset of drug resistance in tumor cells. As mentioned above, the use of agents with differing targets and mechanisms of action is most likely to provide long-term tumor control. In particular, the use of alkylating agents may slow the development of MDR (e.g., adding cyclophosphamide or the combination of mechlorethamine, vincristine (Oncovin), procarbazine, and prednisone [MOPP] to a chemotherapy protocol for lymphoma rather than using doxorubicin alone). The second aim of combination chemotherapy is to maximize tumor cell kill while minimizing toxicity. The combination of drugs that are myelosuppressive with drugs that are minimally myelosuppressive may fulfill this aim (e.g., cyclophosphamide and vincristine; doxorubicin and cisplatin). It is important that combinations comprise *effective* drugs; there is little use to using a nontoxic combination if one of the drugs has not been shown to be efficacious against the particular tumor type. Combinations, therefore, use drugs that have shown activity as single agents.

Some combinations may result in altered toxicity due to changes in the way a drug is metabolized or excreted. For example, L-asparaginase is thought to slow hepatic metabolism of drugs such as vincristine and doxorubicin, thereby increasing the risk of myelosuppression.

It is recommended that practitioners use only combinations for which published efficacy and toxicity data are available.

MONITORING OF ANIMALS WITH CANCER

History

Before chemotherapy is administered, drug dosages and toxicities, as well as the administration schedule, must be reviewed with the owner. After the chemotherapeutic treatment, the pet should be monitored at home for gastrointestinal or other toxicoses. In general, the use of antiemetics and appetite stimulants can prevent mild toxicities; diarrhea may be treated with dietary management or with sulfasalazine or metronidazole, as long as specific causes have been eliminated. Gastrointestinal toxicity usually occurs in the 4 to 5 days after treatment.

Chemotherapeutic doses should be reduced if the pet requires hospitalization for gastrointestinal signs or if such signs are unacceptable to the owner. A dose reduction of 25% for all subsequent administrations of that drug is a good rule of thumb, because with this reduction, it is unlikely that subsequent chemotherapy administration will be associated with toxicity. Supportive care, as both treatment and further prophylaxis, is mandatory.

Complete Blood Count

Neutropenia is a toxicity of many chemotherapy agents, and the nadir (lowest point) generally occurs 5 to 10 days after administration. A complete blood count (CBC) should be obtained 7 days after most treatments. Monocytosis on a CBC often predicts imminent neutrophil recovery, because monocytes have one fewer maturation step than granulocytes and therefore are released from the bone marrow earlier.

Neutrophil recovery is usually rapid; however, a nadir of less than 1000/μL should prompt a 25% dosage reduction for all subsequent administrations of that drug. It is not necessary to reduce the dosage of other myelosuppressive drugs, because they may not cause the same degree of suppression. Each drug should be assessed individually. If a dosage reduction is made, the nadir should again be assessed.

Neutropenia at the time of the next chemotherapy treatment is a reason to delay administration of a myelosuppressive drug (but not of a nonmyelosuppressive drug, such as L-asparaginase or prednisone). In general, a neutrophil count of less than 3000/μL requires a delay in chemotherapy, usually of 1 week, before the CBC is rechecked. If the pet takes a long time to recover (as occurs for many cats and some dogs after receiving carboplatin), it may be necessary to reduce the dosage so that the optimal intertreatment interval and dose intensity can be maintained.

Thrombocytopenia may be dose limiting for select chemotherapy agents (carboplatin, cumulative for CCNU), but is rarely clinically significant for other drugs. Platelet nadirs occur later than neutrophil nadirs, but are rarely as severe and recovery is slower but complete. Thrombocytopenia in a pet due to receive CCNU should prompt a dose reduction or discontinuation.

Serum Chemistry Profile

Renal function should be assessed by serum creatinine and urine specific gravity determinations prior to administration of nephrotoxic drugs (cisplatin in dogs; doxorubicin in cats) or renally excreted drugs (carboplatin). The dosages of these drugs should be adjusted as described above under Dosing.

Liver enzyme serum activity (alanine aminotransferase [ALT]) should be assessed prior to administration of lomustine. Irreversible hepatic toxicity can result if lomustine therapy is continued despite increases in serum ALT activity.

Increases in serum bilirubin should prompt dose reductions in hepatically metabolized drugs. Guidelines are provided under Dosing, above.

THERAPEUTIC SUPPORT OF ANIMALS WITH CANCER

In order that pets maintain the highest quality of life, and that chemotherapy dosages be maintained at the highest level, the veterinarian should, whenever possible, use prophylactic strategies to circumvent common toxicities.

Antiemetics

The recent introduction of serotonin antagonists such as ondansetron (Zofran) and dolasetron (Anzemet) has markedly altered toxicity patterns for animals treated with many drugs. Vomiting and nausea, leading to inappetence and weight loss, are common after treatment with drugs such as cisplatin (in dogs) and doxorubicin (in cats and dogs). Anzemet, given intravenously once at a dosage of 0.5 to 1 mg/kg or given orally once 20 to 30 minutes prior to treatment may markedly reduce the risk of this toxicity.

Appetite Stimulants

Anorexia is a common side effect of chemotherapy in cats (particularly doxorubicin or vincristine). Cyproheptadine (Periactin; 0.35 to 1 mg/kg given orally in cats and 0.1 to 0.2 mg/kg given orally in dogs) may stimulate appetite. The drug may be dosed every 12 hours, or less frequently if inappetence is mild. Megestrol acetate is an effective appetite stimulant in cats at a dosage of 0.25 to 0.5 mg/kg per day given orally for 3 to 5 days, then every 2 to 3 days. In humans, megestrol acetate not only improves appetite but also enhances the enjoyment of food.

Vincristine may result in intestinal ileus in cats and less commonly in dogs. Prokinetic drugs such as metoclopramide may act to reverse this toxicity. Some practitioners recommend prophylactic use of metoclopramide to reduce the risk of inappetence caused by vincristine or doxorubicin (perhaps by central action to reduce nausea). For prophylactic purposes, treatment is started at the time of chemotherapy and continued for 4 to 5 days. Prior to administering strong emetogens (e.g., cisplatin), owners should withhold food, because this reduces the risk of vomiting and may prevent future "aversion" to that food.

Antidiarrheal Drugs

The pet's diet should remain as stable as possible during chemotherapy to avoid exacerbation of gastrointestinal damage. Prophylactic absorbents (e.g., Kaopectate) may reduce the risk of diarrhea. If diarrhea occurs, a bland diet should be offered; if the diarrhea persists, and causes such as parasitism in these often immunosuppressed patients have been eliminated, sulfasalazine or metronidazole may reduce the severity. Prophylactic trimethoprim-sulpha (TMPS) antibiotics should be considered (see below).

Urothelial Bladder Wall Protection

Cyclophosphamide and ifosfamide are hepatically metabolized to their active forms and also to compounds that can cause bladder wall damage (acrolein). Prolonged contact time between the bladder wall and acrolein results in hemorrhagic cystitis. Furosemide, given as a single dosage (2 mg/kg either IV or PO) at the time of cyclophosphamide administration, almost completely abrogates this toxicity and is recommended even in dogs receiving prednisone concurrently. Allowing ample opportunity for the dog to void urine is equally important, and cyclophosphamide is preferably administered in the morning rather than late in the day. Mesna is a thiol drug that is active only in urine; it binds to acrolein, preventing the toxicity of urothelial damage. Because mesna is expensive, its use usually is limited to dogs receiving ifosfamide that have a high risk of urothelial damage.

Treatment of hemorrhagic cystitis includes the use of antiinflammatory drugs (e.g., piroxicam, 0.3 mg/kg given orally once a day); with prolonged cases, intravesicular dimethyl sulfoxide (DMSO) may accelerate recovery. Most cases resolve with time, but because the condition may require several weeks to subside, it is a toxicity best prevented. Sterile hemorrhagic cystitis is extremely rare in cats.

Prevention of Neutropenic Sepsis

Neutropenia is a common side effect of many chemotherapeutics and may occasionally be severe (e.g., neutrophil count less than 500/μL at the nadir). The risk of sepsis is low in animals receiving antibiotics concurrently, because the nadir rarely persists longer than a couple of days. Many oncologists recommend prophylactic use of a broad-spectrum, oral antibiotic (e.g., TMPS) in animals receiving a myelosuppressive agent for the first time. If the nadir is greater than 1000/μL, subsequent administrations may be given without prophylactic antibiotics.

Administration of TMPS to dogs for 14 days from the day of treatment with doxorubicin markedly reduced the likelihood of gastrointestinal toxicity (vomiting or diarrhea), hospitalization, and reduced quality of life (Karnovsky score). These effects, most marked in dogs with lymphoma, may be due to reduced bacterial translocation in damaged intestinal epithelial layers.

When a pet is severely neutropenic, it is tempting to use recombinant granulocyte-colony stimulating factor (G-CSF). Neutropenic dogs should have high endogenous G-CSF and are unlikely to benefit from exogenous administration. Also, the available human recombinant product (hr-G-CSF [Neupogen, Amgen]) carries a risk of induction of neutralizing and cross-reacting antibodies. Appropriate use of hr-G-CSF would be in cases in which an inadvertent and potentially lethal chemotherapy overdose has been delivered. For such a patient, hr-G-CSF therapy from the time of chemotherapy administration to beyond the neutrophil nadir has the best chance of preventing sepsis and death.

SPECIFIC CHEMOTHERAPEUTIC AGENTS

Commonly Used Alkylating Agents

Commonly used alkylating agents are listed in Table 179-1. Cyclophosphamide (Cytoxan) is used primarily for the treatment of lymphoma in dogs and cats. Chlorambucil (Leukeran) is used primarily for the treatment of chronic lymphocytic

leukemia or low-grade lymphoma in dogs and cats and as a substitute for cyclophosphamide if hemorrhagic cystitis occurs. Melphalan (Alkeran) is used primarily in combination with prednisone for the treatment of multiple myeloma in dogs and cats.

Less Commonly Used Alkylating Agents

Less commonly used alkylating agents are listed in Table 179-1. Mechlorethamine (Mustargen) is used in the MOPP protocol for lymphoma in dogs and cats. Procarbazine (Matulane) is used in the MOPP protocol for lymphoma in dogs and cats. Dacarbazine (DTIC) is used in combination with doxorubicin for the treatment of lymphoma, and some anecdotal activity has been indicated for melanoma. Lomustine (CCNU, Ceenu) is used for the treatment of lymphoma, mast cell tumors, brain tumors (response in gliomas and meningiomas) and possibly histiocytosis. Ifosfamide (Ifex) is active against lymphoma and soft tissue sarcomas, particularly in cats.

ANTITUMOR ANTIBIOTICS

Antitumor drugs act by interfering with topoisomerases, deoxyribonucleic acid (DNA) intercalation, and other mechanisms. These drugs usually exhibit cross-resistance with others in their class and with drugs in other classes, such as vincristine, paclitaxel, and etoposide. This resistance is mediated by the MDR glycoprotein.

Commonly Used Antibiotics

Commonly used antibiotics are listed in Table 179-2. Doxorubicin (Adriamycin; generic form) is the most active single agent in the treatment of lymphoma in dogs and is highly effective in combinations for lymphoma treatment in dogs and cats. It has broad-spectrum efficacy in the treatment of solid tumors, particularly osteosarcoma, and in combination with cyclophosphamide. Low-dose doxorubicin may be used for "sensitization" of tumor cells to radiation therapy. Mitoxantrone (Novantrone) shows moderate efficacy against lymphoma in dogs but low efficacy in cats. It also has low efficacy in the treatment of carcinomas and sarcomas. However, in combination with radiation therapy it may be efficacious for oral squamous cell carcinoma (SCC) in cats and in combination with piroxicam for transitional cell carcinoma in dogs. Dactinomycin (Actinomycin-D, Cosmegen) is a low-cost alternative to doxorubicin for canine lymphoma. However, it has low efficacy in the treatment of carcinomas and sarcomas.

Less Commonly Used Antibiotic

Bleomycin (Blenoxane) is a less commonly used antitumor antibiotic (Table 179-2). Its possible efficacy in the treatment of squamous cell carcinoma and lymphoma is unproven.

PLATINUMS

Cisplatin (Platinol) has efficacy in the treatment of canine osteosarcoma and many carcinomas. It is not for use in cats. Carboplatin (Paraplatin) has efficacy similar to cisplatin with no apparent renal toxicity (Table 179-3).

ENZYME

The enzyme L-asparaginase is used primarily for lymphoma in dogs (Table 179-4).

Table • 179-1

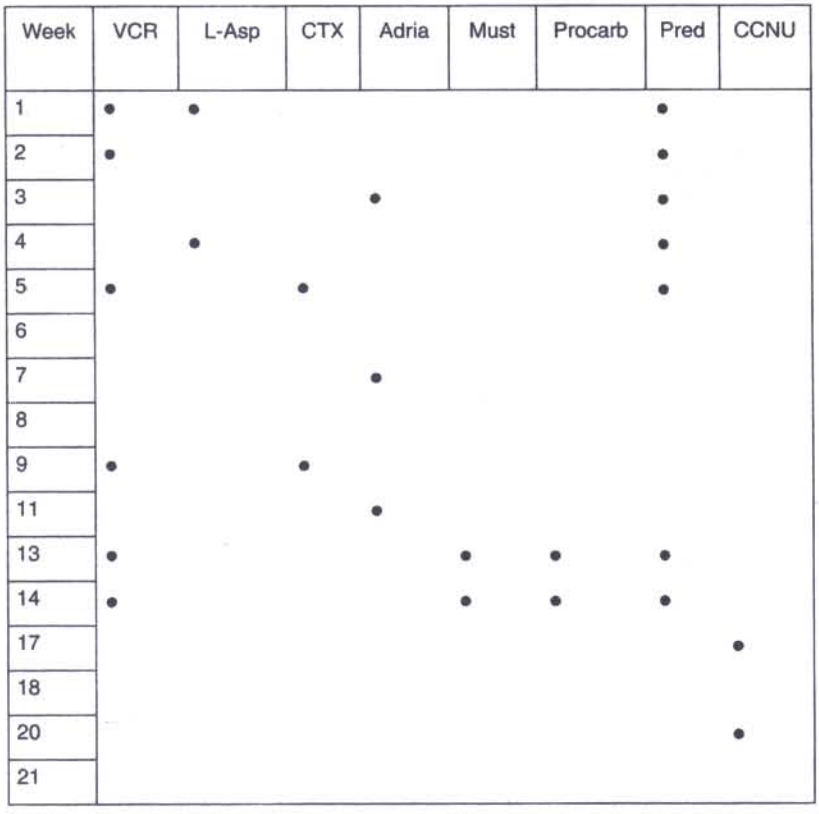
Commonly Used Alkylating Agents

DRUG	FORM	POTENTIAL SIDE EFFECTS	REGIMEN
Cyclophosphamide (Cytoxan)	25, 50 mg tablets; 500 mg vials	Myelosuppression Hemorrhagic cystitis	250 mg/m² PO 200 mg/m² IV q3wk 50 mg/m² PO every other day
Chlorambucil (Leukeran)	2 mg tablets (refrigerate)	Mild myelosuppression	2-8 mg/m² PO every other day 14 mg/m² PO daily for 4 days q3wk
Melphalan (Alkeran)	2 mg tablets (refrigerate)	Myelosuppression	1.5 mg/m² PO daily for 10 days, then a 10-day "rest"
Less Commonly Used Alkylating Agents			
Mechlorethamine (Mustargen)	10 mg vials	Myelosuppression Extravasation reaction	In MOPP: 3 mg/m² IV weekly
Procarbazine (Matulane)	50 mg capsules	Nausea, anorexia, diarrhea Myelosuppression	In MOPP: 50 mg/m² PO daily (dogs); 10 mg/cat PO daily
Dacarbazine (DTIC)	200 mg vials	Myelosuppression Anorexia, vomiting, diarrhea (Anzemet is used prior to treatment.)	800 mg/m² q3-4wk
Lomustine (CCNU; Ceenu)	10, 40, and 100 mg capsules	Myelosuppression, neutropenia, and delayed thrombocytopenia in dogs; delayed neutropenia in cats Irreversible renal and liver toxicity (uncommon)	70-90 mg/m² PO q4-6wk (dogs) 50 mg/m² PO q6wk (cats)
Ifosfamide (Ifex)	1 g with mesna (1 g) vials	Myelosuppression Hemorrhagic cystitis (must be given with mesna and diuresis protocol) Renal toxicity in cats	375 mg/m² IV (dogs) 900 mg/m² IV (cats) Given q3wk in 0.9% NaCl with mesna

Table • 179-2

Commonly Used Antibiotics

DRUG	FORM	POTENTIAL SIDE EFFECTS	REGIMEN
Doxorubicin, (Adriamycin; generic)	200 mg	Myelosuppression Cumulative cardiotoxicity Anorexia, vomiting, diarrhea Allergic reaction (infusion rate should not exceed 2 mg/min) Possible renal toxicity in cats Extravasation reaction	30 mg/m² IV (large dogs) 25 mg/m² or 1 mg/kg IV (cats and small dogs) Given q2-3wk
Mitoxantrone (Novantrone)	20 mg	Myelosuppression GI effects (uncommon)	6 mg/m² IV (dogs) 6.5 mg/m² IV (cats) Given q3wk
Dactinomycin (Actinomycin-D, Cosmegen)	0.5 mg (extravascular) vials	Myelosuppression Diarrhea, vomiting Requires slow infusion rate Extravasation reaction	0.7-1 mg/m² IV (not used in cats to date) Given q3wk
Less Commonly Used Antibiotic			
Bleomycin (Blenoxane)	15 IU (15 mg) vials	In humans: allergic reaction, pulmonary fibrosis	0.3-0.5 IU/kg IV or SQ weekly



VCR = vincristine, L-Asp = L-asparaginase, CTX = cyclophosphamide, Adria = doxorubicin, Must = mechlorethamine, Procarb = procarbazine, Pred = prednisone.

Figure 179-1 Tufts VELCAP-SC protocol for treatment of lymphoma in dogs. Patients are induced over 11 weeks with a combination of vincristine (0.75 mg/m² IV), L-asparaginase (10,000 IU/m² SQ, maximum dose 10,000 IU), doxorubicin (<1 m² = 1 mg/kg IV, >1 m² = 30 mg/m² IV), cyclophosphamide (250 mg/m² PO), and a tapering dose of prednisone starting at 40 mg/m² PO daily. All dogs in complete remission (CR) at week 13 receive consolidation treatments of MOPP (mechlorethamine [3 mg/m² IV], vincristine [0.75 mg/m² IV], procarbazine [50 mg/m² PO once a day for 14 days], and prednisone [40 mg/m² PO once a day for 14 days]) at weeks 13 and 14, followed by CCNU (90 mg/m² PO) at weeks 17 and 20. The protocol is reinstituted if clinical relapse is noted. The total cumulative dosage of doxorubicin should not exceed 180 mg/m². Dogs that are in CR by week 21 discontinue chemotherapy. Dogs receiving cyclophosphamide are treated concurrently with furosemide, 2 mg/kg PO once.

Table • 179-3

Platinums Used as Chemotherapeutic Agents

DRUG	FORM	POTENTIAL SIDE EFFECTS	REGIMEN
Cisplatin (Platinol)	50 mg (aqueous) vials	Renal toxicity Vomiting and (less commonly) diarrhea Myelosuppression Fatal pulmonary edema in cats	50-70 mg/m² IV with 0.9% saline diuresis q3-4wk
Carboplatin (Paraplatin)	50 mg, 150 mg vials	Myelosuppression	250-300 mg/m² IV q3-4wk

Table • 179-4

Enzyme Used as a Chemotherapeutic Agent

DRUG	FORM		REGIMEN
L-asparaginase (Elspar)	10,000 IU vials	Anaphylaxis	10,000 IU/m² SQ or IM weekly

MITOTIC INHIBITORS

Mitotic inhibitors act to inhibit assembly (vinca alkaloids) or disassembly (paclitaxel) of the mitotic spindle. Paclitaxel is rarely used in veterinary medicine, and dosages have not been published.

The commonly used mitotic inhibitor vincristine (Oncovin; generic form) is curative for canine transmissible venereal tumor. It also is very effective in combination chemotherapy for lymphoma in dogs and cats. It is included in some combinations for the treatment of sarcomas. Vinblastine (Velban) is effective in combination chemotherapy against lymphoma in dogs and cats; however, it is seldom used because of its myelosuppressive effect, which makes it more problematic than vincristine to include with other drugs. Vinblastine also appears to have efficacy for mast cell tumors in dogs (Table 179-5).

Table • 179-5

Commonly Used Mitotic Inhibitors

DRUG	FORM	POTENTIAL SIDE EFFECTS	REGIMEN
Vincristine (Oncovin; generic)	1 mg vials	Mild myelosuppression (dose related) Anorexia in cats, rarely dogs (dose related) Peripheral neuropathy (rare) Extravasation reaction	0.5-0.75 mg/m² IV weekly
Vinblastine (Velban)	10 mg vials	Myelosuppression Peripheral neuropathy (very rare) Extravasation reaction	2-2.5 mg/m² IV weekly

CHAPTER • 180

Practical Radiation Therapy

Alain P. Théon

Radiation therapy is the use of ionizing radiation for local and regional treatment of patients with malignant tumors and, occasionally, selected benign diseases. In veterinary medicine, it is a consultative discipline in which veterinary radiation oncologists see animals referred by other veterinarians. The objective of radiation therapy is eradication of a tumor with preservation of normal tissue structure and function.

The availability of appropriate equipment and the evolution of veterinary oncology into a multidisciplinary specialty have led to an increasingly important role for radiation therapy in the management of cancer in small animals. New developments in radiation therapy technology permit treatment of arbitrary tumor volumes anywhere in the body. Radiation therapy can be used alone or in combination with surgery or chemotherapy. The increase in the use of radiation therapy has led to a progressive decrease in the need for radical surgery as the sole treatment for many common cancers.

BIOLOGIC PRINCIPLES OF RADIATION THERAPY

Biological Effect of Radiation

The radiation used in radiation therapy is called *ionizing radiation* because it is sufficiently energetic to cause ionization and excitation of atoms and molecules in cells, resulting in a variety of short-lived ions and chemically unstable free radicals that cause molecular damage. With therapeutic radiation doses, the molecular damage most detrimental to cell survival is that involving the structure and function of genomic deoxyribonucleic acid (DNA).[1] Most of the damage to DNA results indirectly from interaction of DNA with free radicals derived from the ionization of cellular water molecules, the most common molecule in cells. Ionizing radiation produces many types of DNA damage, including single-strand breaks (SSB), double-strand breaks (DSB), base damage, and DNA-DNA or DNA-protein crosslinks. During the processing and enzymatic repair of the damage or during DNA replication, DNA damage may be completely repaired or may become irreversible. Radiation repair is usually more efficient in normal cells than in tumor cells. Although the majority of DNA damage can be repaired, heterologous DNA double-strand breaks are most often irreparable. Irreversible damage to the DNA results in chromosomal aberrations, gene mutations, cell degeneration, and cell death.

At clinically achievable doses, the damage induced by radiation results in cell death or terminal growth arrest.[2] Depending on the cell type and numbers and the kind of DNA damage, cell death occurs through two distinct pathways, proliferative cell death (mitotic cell death) and programmed cell death (apoptosis).[3] Mitotic cell death is the main form of cell death induced by ionizing radiation. It occurs during postirradiation mitosis in proliferating cells entering mitosis with unrepaired DNA damage. Mitotic cell death is selective for cells engaged in the mitotic cycle. This form of cell death is particularly relevant to radiotherapy of tumors, because one of the most important characteristics of a tumor is its ability to divide indefinitely. The difference in proliferative activity in normal cells and tumor cells accounts in part for the selective cytotoxic effects of radiation against tumors. Mitotic cell death is not immediate, but rather occurs after the cell passes through one or more consecutive aberrant mitoses, during which the number of chromosomal aberrations and genomic dysfunctions increases, leading to metabolic failure and cell death.[1] This mechanism of cell death leads to cell necrosis and results in local inflammation.

Cell death through apoptosis is a normal, noninflammatory physiologic process that occurs spontaneously or in response to cellular stress, including ionizing radiation. Apoptosis occurs regardless of the cell cycle and does not require cell division. Susceptibility to radiation-induced apoptosis is cell type specific and is most prominent in hematopoietic or lymphoid cells, but not in stromal- or epithelial-derived tissues. Apoptosis requires intact cellular mechanisms that are often compromised in tumor cells. The tumor suppressor gene protein p53 plays a pivotal role in radiation-induced apoptosis. Its mutation, which is common in some cancers, results in a decreased contribution from apoptosis to the overall cell death in different cell types.

While mitotic cell death and apoptosis kill and eliminate cancer cells, radiation-induced terminal growth arrest irreversibly prevents further tumor evolution. Terminal growth arrest is a process similar to senescence in which the cells remain physiologically active but have lost their ability to proliferate. This cytostatic effect on tumor cells results in a delayed tumor response to irradiation.

Tissue Response

The degree and speed of tumor regression after therapeutic irradiation is determined by several factors, including the susceptibility to ionizing radiation related to tumor type and the contribution of inhibition of cell proliferation and cell death; tumor cell kinetics (i.e., the rate of cellular proliferation, cell death, and cell loss); the proportion of clonogenic cells; and the amount of vasculoconnective tissue in or around the tumor.[4]

Tumor response during or shortly after treatment is not a reliable index of tumor curability, but slow regression of a tumor type that usually regresses quickly is often associated with an unfavorable prognosis. Tumors that regress quickly and completely (e.g., mast cell tumors in dogs and oral squamous cell carcinomas in cats) may also recur quickly. Incomplete tumor regression at the completion of treatment does not necessarily indicate treatment failure. Some soft tissue sarcomas, meningiomas, and pituitary adenomas may remain detectable for weeks or even months after the course of radiotherapy is finished and yet ultimately disappear and never recur. Tumor disappearance may also be delayed when bony changes associated with bone invasion are present. Anatomic deformity caused by tumors with an abundant intercellular stroma may be slow to resolve, which may be interpreted as a treatment failure. Slowly regressing oral

epulides in dogs are in fact one of the few highly curable tumors with radiation therapy. A practical implication of the complex reasons for different rates of tumor response is that only persistent or continual growth is a reliable sign of treatment failure. Therefore, as long as a tumor is regressing after radiotherapy, biopsy is contraindicated. A prematurely positive result from a biopsy specimen may lead to unnecessary salvage surgery, and repeated biopsies interfere with the healing of normal tissues.

The effects of radiation on normal tissues are restricted to the treatment site. Chronologically, the clinical effects of irradiation are subdivided into *acute effects*, which occur during or immediately after treatment (during the first 3 months) and *late effects*, which occur months to years after completion of treatment. The rate of appearance of injury depends not only on the proliferative activity of the stem cells but also on the lifetime of the differentiating progeny of these cells.

Acute effects result primarily from radiation-induced stem cell depletion, which exceeds cell production in actively proliferating parenchymal tissues. The most common acute radiation reactions involve the skin and mucous membranes and result from stem cell proliferation that is inadequate to maintain the epithelial surface. The acute effects of radiation therapy always accompany curative radiotherapy, because to some extent they mirror the damage done to tumor tissue. Although acute effects may be temporarily painful and require supportive therapy, they are not complications but normal tissue reactions, which are usually self-limited and resolve naturally after treatment. Acute reactions of the skin (skin desquamation and epilation) and oral mucosa (mucositis) may be lessened by cleansing the tissue with a 1:1 solution of hydrogen peroxide and normal saline and using topical ointments, systemic antibiotics, and corticosteroids to minimize infection and inflammation.[5]

Late effects are considered complications of radiation therapy. They are caused primarily by damage to the vasculoconnective stroma and slowly proliferating parenchymal tissues, such as the kidneys, cartilage, bone, or lungs. Clinically, radiation complications appear to be less severe in cats than in dogs. In cats, feline immunodeficiency virus (FIV) infection may be associated with a higher risk of radiation complications. Unlike acute effects, radiation complications are not self-limited and tend to be progressive. They are usually irreversible. In practice, with appropriate treatment techniques, the risk of severe complications is low and should be weighed against the probability of tumor control.[6] Radiation complications are usually managed conservatively. Occasionally, severe complications, including chronic ulcers, radionecrosis of soft tissues or bone, intestinal or rectal stenosis, or cystitis may require surgical resection of the involved tissue or organ (Table 180-1).

Text continued on p. 725.

Table • 180-1

Role of Radiation Therapy in the Treatment of Specific Neoplastic Diseases

ANATOMIC SITE	ROLE OF RADIOTHERAPY	RESULTS	ACUTE REACTIONS	COMPLICATIONS
Skin and Subcutaneous Tissues				
Squamous cell carcinoma	Curative treatment alternative to surgery for carcinomas not invading bone; treatment of choice for lesions of eyelids and nasal plane in cats and over cartilage; performed preoperatively for advanced tumors; palliative treatment with modest increase in survival for carcinoma of nasal plane in dogs.	*Nasal plane in cats:* 2-yr LCR: 77% for lesions <2 cm; 37% for advanced lesions[16]; comparable results for tumors of pinnae and forehead.	Erythema, moist desquamation, epilation; rarely, ulceration	Permanent epilation, skin atrophy, subcutaneous fibrosis; rarely, soft tissue necrosis
Mast cell tumor (dogs)	Primary treatment for small lesions; used postoperatively for microscopic or gross residual disease; adjuvant postoperative treatment for completely resected grade II/III lesions; preoperative treatment for unresectable tumors; low histologic grade and location on an extremity are favorable prognostic factors; used in combination with surgery and chemotherapy in dogs with regional metastasis.	2-yr LCR: 70%-92% for postoperative microscopic disease; 50%-85% for lesions <2 cm; 20%-58% for large tumor and gross residual tumor[11,12,36]; 60% for postoperative locoregional irradiation for node-positive dogs.[37]	Same as for squamous cell carcinoma	Same as for squamous cell carcinoma
Soft tissue sarcomas	For operable tumors: postoperative treatment when risk of surgical complication exists due to tumor size or location; preoperative treatment when increased risk of radiation complications exists due to radiosensitive normal	*Dogs:* 2-yr LCR: 33% for primary radiotherapy of all histologic types and sizes[15]; 40%-50% for hemangiopericytoma (HPA)[18,38] and 30% for fibrosarcoma (FSA)[18]	Same as for squamous cell carcinoma	Same as for squamous cell carcinoma

Continued

Table • 180-1

Role of Radiation Therapy in the Treatment of Specific Neoplastic Diseases—cont'd

ANATOMIC SITE	ROLE OF RADIOTHERAPY	RESULTS	ACUTE REACTIONS	COMPLICATIONS
	tissue (brain, spinal cord, lung, guts) in treatment field. For advanced inoperable lesions: primary treatment followed by limited resection if lesion rendered operable.	after subtotal resection; 85% for postoperative radiotherapy of all histologic types; 76% for FSA and 100% for HPA after microscopically incomplete resection[18]; 40 months median survival for postoperative irradiation of infiltrative lipomas.[39] *Cats with cutaneous FSA at vaccination sites:* 2-yr LCR: 55% with preoperative treatment,[29] 30% with postoperative treatment.[40]		
Perianal gland	Postoperative treatment for adenocarcinomas and regional irradiation to local lymph nodes for high-risk or node-positive dogs; primary treatment for large adenomas.	Median survival: 12-18 months for perianal adenomas/ carcinomas with postoperative irradiation.[41,42]	Same as for squamous cell carcinoma ADD: diarrhea and bleeding	Same as for squamous cell carcinoma ADD: Stenosis
Head and Neck				
Oral cavity	*Dogs:* Curative radiotherapy for small, caudally located squamous cell carcinoma (SCC),mycosis fungoides (MF), fibrosarcoma (FSA) of the gingiva/palate, buccal mucosa; alternative to surgery for small, rostrally located SCC, plasmacytoma of the gingiva/ palate and floor of the mouth, and epulides; used postoperatively for advanced resectable SCC and FSA; used alone or with chemo-therapy to improve survival for advanced unresectable lesions; palliative for advanced melanomas (MMA) and tumors of the base of the tongue and tonsils. *Cats:* Curative for odontogenic tumors and epulis; palliative for SCC with modest increase in survival.	*Dogs:* 2-yr LCR for lesions <2 cm : 100% for epulides; 74% for SCC; 67% for FSA; 54% for MMA[25]; comparable results for postoperative treatment of advanced resectable (2-4 cm) epulides, SCC, and FSA. Prolongs survival in advanced SCC (median survival, 7.5 months) and FSA (median survival, 7.1 months); palliative for symptoms of advanced MMA (median survival, 7-8 months).[14,23] *Cats:* 2-yr LCR : 100% for postoperative irradiation of odontogenic tumors.[43]	Painful mucositis, resulting in dysphagia, xerostomia, and weight loss	Persistent xerostomia, dental decay; rarely, fistulas, bone exposure, and osteoradio-necrosis of mandible and maxilla
Nasal cavity/ paranasal sinuses	Primary treatment to improve survival for carcinomas and sarcomas; combination with surgery or chemotherapy may not increase survival. Curative alone or in combination with chemotherapy for localized lymphoma.	*Dogs:* Median survival for nonlymphoproliferative tumors: 10-13 months (all tumors)[17,44]; 12-14 months for carcinomas[14,45]; 15 months for chondro-sarcomas.[14] *Cats:* Median survival for nonlymphoproliferative tumors: 12 months (all tumors)[46]; 28 months for lymphoma.[47]	Nasal and oral mucositis; conjunctivitis ± keratitis for eye in radiation field; skin epilation	Loss of smell, chronic keratitis, cataract, kerato-conjunctivitis; rarely, bone necrosis

Continued

Table • 180-1

Role of Radiation Therapy in the Treatment of Specific Neoplastic Diseases—cont'd

ANATOMIC SITE	ROLE OF RADIOTHERAPY	RESULTS	ACUTE REACTIONS	COMPLICATIONS
Ear canal	Primary treatment alternative to surgery for small ceruminous adenocarcinoma or squamous cell carcinomas; used postoperatively for advanced lesions.	2-yr LCR: 56%[48]	Otitis, dysphagia	Damage to middle and inner ear and cranial nerves (Horner's syndrome)
Thyroid	*Dogs:* Irradiation used alone or as a postoperative treatment with subtotal resection of adenocarcinomas; used preoperatively for inoperable lesions, followed by limited resection if lesion is rendered operable. *Cats:* Primary treatment with radioiodine for functional adenomas and adeno-carcinomas; used as postoperative treatment with subtotal resection for carcinomas.	*Dogs with carcinomas treated with teletherapy:* 2-yr survival rate: 50% after irradiation alone[49]; 66% after subtotal resection in dogs with no evidence of metastasis.[50] *Cats treated with radioiodine:* 2-yr cure rate for adenomas: 92%[51]; >50% for carcinomas given postoperative treatment.[52]	Teletherapy: Skin epilation, dysphagia (esophagitis), hoarseness, cough (tracheitis)	Teletherapy: Subcutaneous fibrosis; rarely, spinal cord damage
Central Nervous System				
Pituitary gland	Effective in controlling signs of mass effects, in dogs with macroadenoma/carcinomas and no/mild neurologic signs; used in combination with medical treatment for pituitary-dependent hyperadrenocorticism (PDH). Ineffective for dogs with severe neurologic signs.	*Dogs with Cushing's disease:* 2-yr survival: No neurologic signs, 100%[53]; mild to moderate neurologic signs, 45%[54]; median survival in dogs with severe neurologic signs, 4 months.[54] *Cats with acromegaly:* Median survival, 15 months [55,56]	Hair loss, skin erythema, otitis, dullness (brain edema)	Hearing loss, cataract formation if eye is in the field; rarely, brain necrosis
Intracranial meningioma	Postoperative irradiation after incomplete resection for cure and primary radiation therapy (RT) for inoperable lesions.	Postoperative irradiation 2-yr LCR: 70%[20]; median survival in dogs with inoperable tumors: 9 months.[34]	Exacerbation of neurologic signs dullness	Somnolence, Seizure, behavioral modification, local motor or sensory signs
Spinal cord	Postoperative treatment to improve neurologic signs and survival.	Median survival for postoperative irradiation of meningiomas: 17 months.[57]	Subtle exacerbation of Neurologic signs	Decrease in sensation or motor weakness pain; rarely, irreversible spinal cord myelopathy
Bone				
Primary bone tumors	For appendicular osteosarcomas: preoperative treatment combined with chemotherapy (cisplatin/carboplatin) for limb-sparing procedure; palliative treatment as alternative to amputation or for pain relief in advanced disease.	Median survival of dogs with osteosarcoma (OSA) treated with limb-sparing surgery, irradiation, and cisplatin: 9 months[33]; treated with	Skin erythema, dry/moist desquamation	Subcutaneous fibrosis, ankylosis, distal edema; rarely, bone/soft tissue necrosis

Continued

Table • 180-1

Role of Radiation Therapy in the Treatment of Specific Neoplastic Diseases—cont'd

ANATOMIC SITE	ROLE OF RADIOTHERAPY	RESULTS	ACUTE REACTIONS	COMPLICATIONS
	For axial and skull tumors: postoperative irradiation concurrent with chemotherapy.	irradiation and cisplatin: 5 months[34]; treated with palliative irradiation alone: 2-4 months.[58]		
Metastatic bone tumors	Palliative local treatment or systemic administration of bone-seeking radioisotopes for pain relief.	Mean survival in dogs treated with radioactive Sm-153: 8 months.[9]	Depression of platelet and white blood cell count	

The local control rate (LCR) is provided as a cure rate; the median survival or local control is provided if a cure rate has not been determined or if it cannot be computed because of small sample size.

Radiocurability

The radiation doses delivered and the volume of tissue treated in clinical radiotherapy are determined as much by the tolerance of normal tissue that is included in the irradiated volume as they are by the tumor being treated. Normal tissue in the radiation field is said to be dose limiting with respect to the maximum dose that can be safely administered. Therefore tumors are typically treated within a narrow range of doses, thus commonly achieving a narrow range of tumor control rates. Maximal doses are therefore limited even for tumors with high local failure rates. This is true in spite of the fact that one can confidently assume that a sufficient dose of radiation will control virtually any localized tumor. Thus a radiocurable tumor is one that can be eradicated by a dose of radiation that is well tolerated by the surrounding normal tissues. A practical implication of this is that a tumor that is curable in one anatomic site may not be curable in another. The art of clinical radiotherapy is to find the right balance between tumor control and injury to normal tissues, to achieve what is called *uncomplicated cure*. A curative dose of radiation is a dose that will potentially cure or control the disease and result in a probability of serious complications of less than 5% for bone or soft tissue necrosis and less than 1% for spinal cord injury.

Because curative radiation doses are often by necessity close to the maximum dose tolerated by normal tissues, the radiation dose must be planned and delivered accurately to the tumor with as little radiation dose to the uninvolved normal structures as possible. Accurate tumor localization with modern imaging technology (computed tomography [CT] and magnetic resonance imaging [MRI]) and optimum use of the radiation therapy techniques allow delivery of a high radiation dose to the tumor relative to the surrounding normal tissue. The choice of a treatment technique depends on the location, size, and extension of the tumor and adjacent normal structures. Each technique exploits the specific differences in patterns of dose distribution in tissues according to the type (photons versus electrons) and energy of radiation and the distance from the source of radiation to the lesion to be treated.

In *teletherapy* (also called *external beam therapy*), the distance between the source of radiation and the patient (50 to 100 cm) allows delivery of a relatively uniform dose of radiation to a large volume of tissue. The higher the energy of the radiation, the more significant the sparing of superficial structures (skin and subcutaneous tissues) and the greater the penetration of the beam. Medium energy x-rays (200 to 300 kV) produced by orthovoltage units are useful for the treatment of superficial tumors because their limited penetration in tissue minimizes the radiation dose to deeper, uninvolved tissues. High energy radiation (greater than 1 MV [1 MV = 1 million electron-volt]), including x-rays produced by linear accelerators and gamma rays produced by telecobalt units, are used for the treatment of large and deep-seated tumors. The availability of high energy radiation therapy units in veterinary medicine has expanded the number and types of cancers that can be cured with irradiation. High energy electrons produced by a linear accelerator have a tissue penetration range of a few centimeters, which allows complete sparing of the underlying tissues. Electron beams are useful in the treatment of superficially located tumors or those overlying radiosensitive normal tissue (spinal cord, brain, lung, and gastrointestinal tract).

Brachytherapy is a technique in which sealed radioactive sources are applied directly to the area to be treated. The short distance between the source of irradiation and the tumor provides a rapid decrease in dose as distance from the radiation source increases. This allows delivery of a high radiation dose to the tumor-bearing structures while sparing uninvolved adjacent normal tissues. When radioactive sources (usually iridium-192) are implanted directly into the tissues (Figure 180-1), the technique is called *interstitial brachytherapy* or *curietherapy*. It is used for small lesions that cannot be completely excised and for operable cutaneous tumors with indistinct margins for which there is a high probability of recurrence.[7] It may also be used in combination with teletherapy to boost the radiation dose to a specific area. When radioactive sources (usually strontium-90) are applied to the tumor's surface (Figure 180-2), the technique is called *surface brachytherapy* or *plesiotherapy*. Treatment is curative for superficial lesions of the skin, including carcinoma in situ and early squamous cell carcinoma (SCC) lesions less than 2 mm thick. Surface brachytherapy may also be used as primary or ancillary treatment for superficial fibrovascular infiltrates of the cornea that are not responsive to medical treatment. The shortest distance between the radiation source and the tumor cells is achieved by use of organ-seeking radiopharmaceuticals that are administered systemically. Irradiation is then selective to the tissue that concentrates the radioisotope. Clinical applications of systemic radiotherapy include radioactive iodine-131 for the treatment of feline hyperthyroidism and functional thyroid cancer in dogs and cats; phosphorus-32 for myeloproliferative and lymphoproliferative diseases, such as polycythemia vera and essential thrombocythemia[8]; and samarium-153 or strontium-89 for metastatic bone tumors.[9]

Another way to achieve uncomplicated cure with radiation therapy is to divide the dose into a series of equal-sized fractions

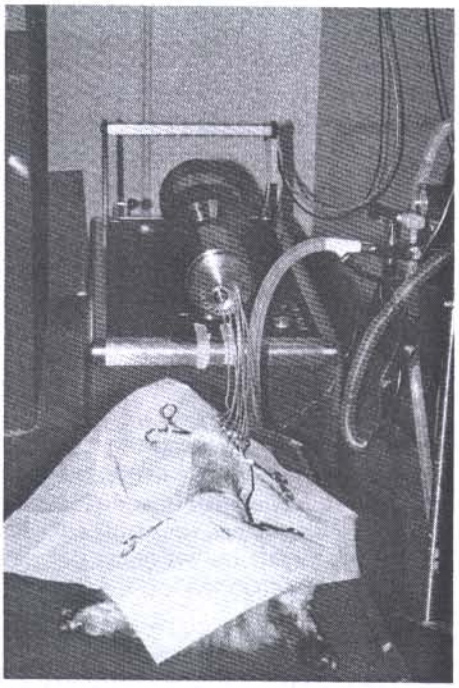


Figure 180-1 Setup for interstitial brachytherapy using a remote afterloader for postoperative irradiation of an interscapular fibrosarcoma in a cat. The technique is ideal for this location because a high radiation dose can be delivered, yet dose-limiting normal tissue, including the spinal cord and lungs, is spared. The treatment is done on an outpatient basis and poses no radiation hazard to personnel. The head of the remote afterloader (Gammamed Iii; RTS Technology, North Andover, Massachusetts), which contains a radioactive source (10 Ci, iridium-192) in a shielded container, is connected by source guide tubes to plastic needles implanted in the tumor bed below the skin. After all personnel have left the treatment room, the afterloader is activated from a shielded control room, and the radioactive source is driven through the array of applicators to deliver the planned dose. When treatment is complete, the radioactive source returns to the shielded container, and personnel can safely enter the treatment room.

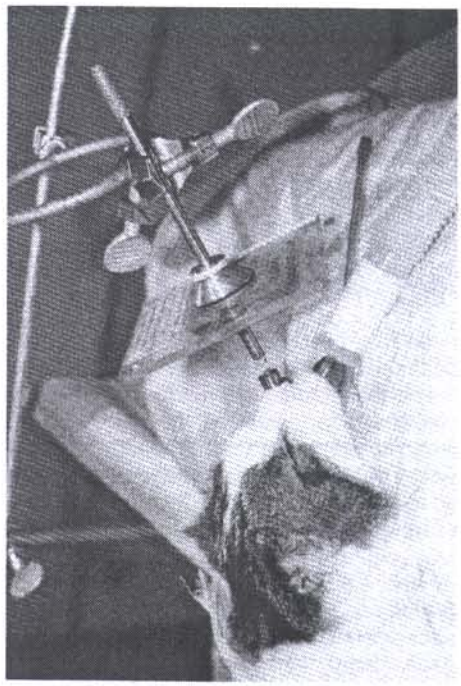


Figure 180-2 Cat undergoing surface brachytherapy for early-stage squamous cell carcinoma of the nasal plane. The strontium-90 radioactive source at the tip of the applicator is a fission byproduct (half-life, 30 years) that produces an electron beam (2.3 MeV maximum energy). Electrons have shallow penetration in tissues, which allows delivery of high radiation doses to the tumor without exposure to the underlying normal tissues. The dose is 100% at the surface and decreases rapidly with depth: 40% at 1 mm, 20% at 2 mm, and less than 1% at the surface of the nasal cartilage. The applicator is carefully positioned directly on the surface of the lesion. The Lucite shield protects the operator's hands from scattered electrons. Because each treatment takes 3 to 4 minutes, the applicator is held with a stand to minimize radiation exposure to personnel. The surface dose ranges from 200 to 250 Gy. Usually one treatment is sufficient.

given over several weeks, a process called *fractionation*. Fractionated irradiation allows selective regeneration of normal tissues due to their greater ability to repair radiation injury between treatments and to repopulate during the course of radiotherapy relative to the majority of tumors. As a result, curative treatment may be given while not exceeding the tolerance of the surrounding normal tissues. Clinical data, essentially in people, indicate that large doses per fraction are preferentially damaging to slowly proliferating tissues responsible for radiation complications. As a rule, when the dose of radiation per fraction decreases, the risk of radiation complications decreases, which allows the use of higher total doses and inclusion of a larger volume of normal tissues.

In people, the standard fractionation for external beam therapy includes daily (5 days a week) dose fractions of 1.8 to 2.0 Gy (Gray [1 Gy=100 rad]). In teletherapy, various treatment schedules have evolved over the years, with dose fractions decreasing from 4 Gy given on an alternate-day schedule (Monday-Wednesday-Friday) to 3 Gy given on a daily schedule (5 days a week), and total radiation doses have increased from 40 to 60 Gy. The current recommendation for curative treatment is delivery of daily radiation doses (5 days a week) of 3 Gy or less in an overall treatment time that is as short as is consistent with acute reactions (over 3 to 4 weeks). Longer overall treatment times or intertreatment times (three fractions/week) increase the risk of "tumor escape" through accelerated repopulation. The benefit of daily treatment compared with alternate-day treatments has been shown in cats with oral carcinomas[10] and dogs with mast cell tumors.[11] In addition, in people, treatment prolongation caused by interruptions due to severe acute reactions, intercurrent illness, public holidays, or machine breakdown has been shown to have a negative influence on the outcome. The detrimental effect of treatment interruptions increases as treatment progresses. An early interruption in the treatment course is less detrimental for the patient than a late interruption.

Because brachytherapy is used to treat smaller target volumes and the volume irradiated outside the target volume is minimized, the potential for complications is lower than with teletherapy. As a result, dose fractionation with large doses per fraction may be used for interstitial brachytherapy (five doses of 5 to 7.5 Gy given once a week) or plesiotherapy (one or two doses of 150 to 200 Gy) without increasing the risk of serious complications.

CLINICAL RADIATION THERAPY

The basic principle of clinical radiation therapy is that treatment should always benefit the patient, even though the treatment

outcome may not be entirely predictable. The selection of patients for radiation therapy should involve consultation with a radiation oncologist, preferably in a multidisciplinary clinic setting, and should include consideration of all aspects of the individual patient. The only contraindication for radiation therapy in dogs and cats is inability to tolerate the multiple episodes of anesthesia necessary for positioning and immobilization during treatment. Concurrent disease, particularly of the heart and liver, may be more limiting to survival than cancer.

Treatment Goals

After the extent (staging) and pathologic characteristics of the tumor have been evaluated, the objective of radiation therapy must be determined based on the likelihood of tumor spread, the expected cure rate, and treatment morbidity. The treatment goal should be defined at the onset of formulation of the therapeutic strategy, because it affects the selection of the appropriate treatment modalities (irradiation alone or in combination with other modalities) and the radiation treatment plan (technique and target volume). A correct assessment of the treatment goal is one of the most important decisions in radiation therapy. Overly aggressive treatment plans can expose animals that are not curable to needless morbidity, prolonged and expensive treatment, and unnecessary radiation effects. On the other hand, therapeutic decisions that are too pessimistic deprive the animal of a small but real chance for cure.

Curative Radiotherapy

Radiation therapy is most commonly used with curative intent when there is no evidence of widespread dissemination of metastases. Animals are treated with curative intent when it is expected that a finite probability exists that the tumor will be destroyed after adequate therapy, even if that chance is low. Radiation therapy given with curative intent is called *definitive therapy* if it is used for a localized, primary tumor that has been biopsied or incompletely resected. Radiation therapy is called *adjuvant therapy* if it is applied to a primary tumor or to sites of potential spread when the malignant cell burden is microscopic or below the level detectable by current imaging methods. Local and regional tumor control is an absolute necessity for cure of a patient with a solid tumor. *Tumor control* refers to complete eradication of the tumor at the primary site and in adjacent involved tissues and lymphatics. Failure to achieve control results in an increased likelihood of metastases and death. Tumors that are diagnosed and treated at an early stage, before distant metastases have occurred, are often curable by radiation therapy. Tumors arising from or involving organs highly vulnerable to radiation injury and tumors with a high propensity to develop distant metastases are rarely cured with radiation therapy alone.

The probability of tumor control depends on several clinical factors, including the tumor's size, extent, histologic grade, proliferative activity, and location and whether there is a history of previous treatment. Other factors, such as the patient's species, gender, age, and performance status, also may affect tumor control. One of the most important factors influencing the probability of local control is the tumor's size and extent. An inverse relationship between the probability of local control and tumor volume has been shown for mast cell tumors,[12] oral tumors (squamous cell carcinomas, fibrosarcomas, melanomas, and epulides),[13,14] and soft tissue sarcomas[15] in dogs; squamous cell carcinomas of the nasal plane in cats[16]; and intranasal tumors (carcinomas, chondrosarcomas) in dogs.[17] Although invasion of bone or cartilage is not a contraindication to irradiation, local control rates are higher when the tumor is confined to the site of origin.

Histologic identification and grading of tumors are useful pretreatment predictors of biologic behavior. In practice, some tumors (e.g., round cell tumors) are easily controlled with low radiation doses, but most of the common tumors that can be cured with radiation (carcinomas, soft tissue sarcomas) require high doses. A few tumor types (e.g., glial tumors) are rarely cured, even with high doses. Usually, microscopic tumor deposits of any histologic type can be cured with moderate doses of radiation.[18] Histologic grading and tumor cell kinetics have been shown to be prognostic factors. High histologic grades are associated with a poorer prognosis after irradiation for mast cell tumors[12] and soft tissue sarcomas.[19] A high tumor growth fraction is associated with a poorer prognosis for SCC of the nasal plane, meningiomas in dogs, and oral SCC in cats.[10,16,20]

Tumors of similar histologic types arising from different anatomic sites have different biologic characteristics. In some instances, cancers arising from sites only 1 or 2 cm apart show markedly different responses that are not explainable by current knowledge. For example, in cats, squamous cell carcinoma of the facial skin is curable with radiation therapy alone, but squamous cell carcinoma of the oral cavity is rarely controlled. Paradoxically, in dogs, squamous cell carcinoma of the oral cavity is radiocurable, but squamous cell carcinoma of the nasal plane cannot be controlled with irradiation.

Palliative Radiotherapy

The goal of palliation is to relieve pain or other complications resulting from an incurable tumor but not to prolong life. Although life may be prolonged through the use of palliative irradiation, this is not the primary goal. For pets with extensive and rapidly progressive tumors and anticipated short survival, radiation therapy may be used to slow local progression of the disease and relieve distressing symptoms. Palliative radiation therapy offers an opportunity for rapid improvement in the quality of a pet's life. In this setting, the treatment course is as short as possible, using a few larger dose fractions and lower total doses. However, the use of large dose fractions is associated with a high risk of complications, and palliative treatment regimens should not be used for animals with a life expectancy greater than 6 to 12 months. Administration of palliative versus curative treatment for purposes other than alleviating pain or suffering amounts to substandard care. Palliation is acceptable for animals with a short life expectancy because the probability of developing late complications is limited. Palliative irradiation is not a less expensive, less complicated alternative treatment for pets that would benefit from treatment given with curative intent. The use of palliative radiation therapy has been investigated for management of selected tumors, including thyroid tumors,[21] pituitary tumors,[22] oral melanomas,[23] and nasal tumors[24] in dogs and oral squamous cell carcinomas in cats.[25] Tumor control duration has proved to be inferior compared with that obtained with standard fractionation and is associated with significant risk of complications in animals surviving longer than 6 months.

Palliative radiation therapy is useful to relieve discomfort associated with both skeletal tumors (primary and metastatic bone lesions) and soft tissue tumors. Pain, compression of vital structures such as the brain, ulcerating skin lesions, and bone tumors or bone metastases in weight-bearing bones susceptible to fracture can be managed effectively with palliative radiation. Dogs with appendicular osteosarcomas that are not candidates for amputation may benefit from palliative radiation therapy. Treatment consists of three to four weekly large-dose fractions (8 to 10 Gy). Pain relief occurs in 75% to 90% of these dogs, with the period of pain control lasting 2 to 3 months.[26,27] The duration of pain relief may be slightly longer for appendicular than for axial bone tumors and may be increased by use of higher radiation doses and concurrent use of platinum-based chemotherapy.[26,27]

Clinical Role of Radiation Therapy

Ideally, the radiation oncologist should be involved at the time of diagnosis and initial decision making so that if and when radiation therapy is used, the oncologist will be knowledgeable about all the factors involved in the treatment planning. Seeing the intact, untouched lesion before surgery can be of immense help in planning definitive treatment. The best results are achieved by an initial integrated treatment plan with combined modalities tailored to the particular pet's cancer rather than by ad hoc attempts to salvage the failures of another modality. Treatment of localized tumors often involves the use of surgery or radiation therapy or a combination of the two (Figure 180-3). Treatment of tumors with a high probability or evidence of metastasis at the time of diagnosis involves a combination of local treatment and systemic chemotherapy.

Primary Radiation Therapy

Radiation therapy plays an important role in the curative treatment of small malignant solid tumors. It is also used in the management of benign tumors, including adenomas of the pituitary and perianal glands and oral epulides in dogs and thyroid adenomas in cats. Surgery is essentially a local treatment, whereas radiotherapy offers locoregional treatment covering a wider area, less constrained by anatomic boundaries and surgical techniques. Local control rates for radiation therapy are equivalent to those for surgery for small, localized tumors (2 to 4 cm) in many sites, and irradiation has the advantage of controlling the disease in situ, thus avoiding disruption of anatomic structure and preserving function. In practice, radiation therapy is used for lesions that are technically difficult to completely resect without excessive functional and cosmetic mutilation. Radiation therapy is particularly well suited for lesions of the facial skin, including carcinomas of the nose, eyelids, ear canals, or pinnae, and certain more extensive lesions of the forehead and cheeks. Radiation therapy may be preferred at specific sites on the trunk or extremities for tumors that have extended near or around critical structures such as the spinal cord, nerves, large vessels, or tendons. For certain early-stage lesions in less strategic locations, surgery can be carried out expediently and effectively and therefore is preferred. For example, surgery is preferred for oral tumors that are rostrally located, where a wide excision is possible. Radiation therapy is preferred, on the other hand, for caudally located tumors when a high risk of oral incompetence is anticipated after radical excision or when regional lymph node involvement is observed or anticipated.

Less frequently, primary radiotherapy is used for tumors that are highly radiocurable or that are technically unresectable. Tumors of any size, including transmissible venereal tumors at all sites, localized mycosis fungoides of the oral mucosa in dogs, and extranodal solitary lymphomas (stage I), can be cured with radiation therapy alone. Radiation therapy is the mainstay of treatment for central nervous system (CNS) and intranasal tumors because most such lesions are inoperable.

Radiation therapy is also used as primary treatment for control of invasive and inoperable cancers. The goal is not to cure the pet, because extensive disease or potential distant metastases obviate this goal, but to prolong survival. This setting is different from palliative radiation therapy, in which the quality, rather than the duration, of survival is of utmost importance. Many animals may live for long periods in comfort with residual tumor or metastasis. Some animals have good prospects of prolonged survival with inoperable regional disease without demonstrable metastases. The goal of radiation therapy in this situation is to achieve lasting local control and improve the duration and quality of survival. Here, control indicates that the local disease can be kept within bounds for extended periods. In dogs with large intracranial tumors (gliomas, pituitary adenomas, meningiomas) or inoperable soft tissue sarcomas, the treatment goal is to control the growth of the tumor and extend the dog's survival. Thus the radiation therapy technique and dose are similar to those used in curative radiation therapy.

Reirradiation of recurrent tumors that are unresectable because of their strategic location may be used in selected cases to prolong survival.[28] Because of the poor radiation tolerance of previously irradiated adjacent normal tissues, recurrences are best managed by resection.

Combinations of surgery and radiation therapy may be used for advanced locoregional disease.

Radiation therapy and surgery may be "equally" beneficial for the treatment of small lesions, but they also can be mutually beneficial in the treatment of advanced tumors. The goals of a combined approach are to preserve function and cosmetic appearance and to reduce the chance of local failure when the probability of cure by either modality alone is low.

The timing and dose of radiotherapy and its sequencing with surgery depend on (1) the tumor's resectability (preoperative irradiation may be used if complete resection is not feasible); (2) the dose desired (high doses must follow surgery); and (3) the extent of the planned surgery (extensive procedures must precede radiotherapy). The interval between the application of each treatment method should be planned to minimize additive complications without losing any advantage in tumor control.

The main combinations of surgery and radiation therapy involve preoperative and postoperative radiation therapy. The optimal sequencing depends on the tumor's size, location, and histologic characteristics. The best interval between preoperative radiation and surgery or between surgery and postoperative radiation has not been clearly established. When radiation therapy is given preoperatively, the optimal interval between irradiation and surgery is usually 3 to 4 weeks. This allows acute radiation reactions to resolve before fibrosis begins to develop. When radiation therapy is given postoperatively, an interval of 2 to 3 weeks after surgery usually allows satisfactory wound healing.

Postoperative radiation therapy. Radiation therapy may be used postoperatively as an adjuvant treatment for control of postoperative microscopic disease or with curative intent for control of residual gross disease. The advantages of postoperative irradiation are that the entire surgical specimen is available for review for exact histopathologic classification; the extent of microscopic tumor can be assessed directly; and a high dose of radiation can be given without increasing surgical morbidity. In wounds that are healing poorly, such as those with postoperative infection or dehiscence, irradiation will further hinder healing. In pressing instances, irradiation may be given to animals with an open wound. Depending on the size of the wound, this may be accomplished without complication; however, the wound may have difficulty healing by secondary intention and may require skin grafting or plastic reconstructive techniques.

Adjuvant radiation therapy is used to improve local control and functional results for treatment of operable tumors. A tumor is considered operable if it is anticipated to be highly likely that all gross disease can be resected, leaving at most microscopic disease. Operable tumors include accessible, medium-sized or advanced tumors in locations where wide resection is possible. Adjuvant radiation therapy is used to improve local control and functional results. In this setting, clinically apparent disease is surgically resected and irradiation is given to eliminate tumor microextension present at the periphery of the gross tumor and in regional lymph nodes. In clinical practice, animals with resectable tumors are treated with postoperative irradiation when histopathologic evidence of microscopic residual disease is present (close to or positive for tumor

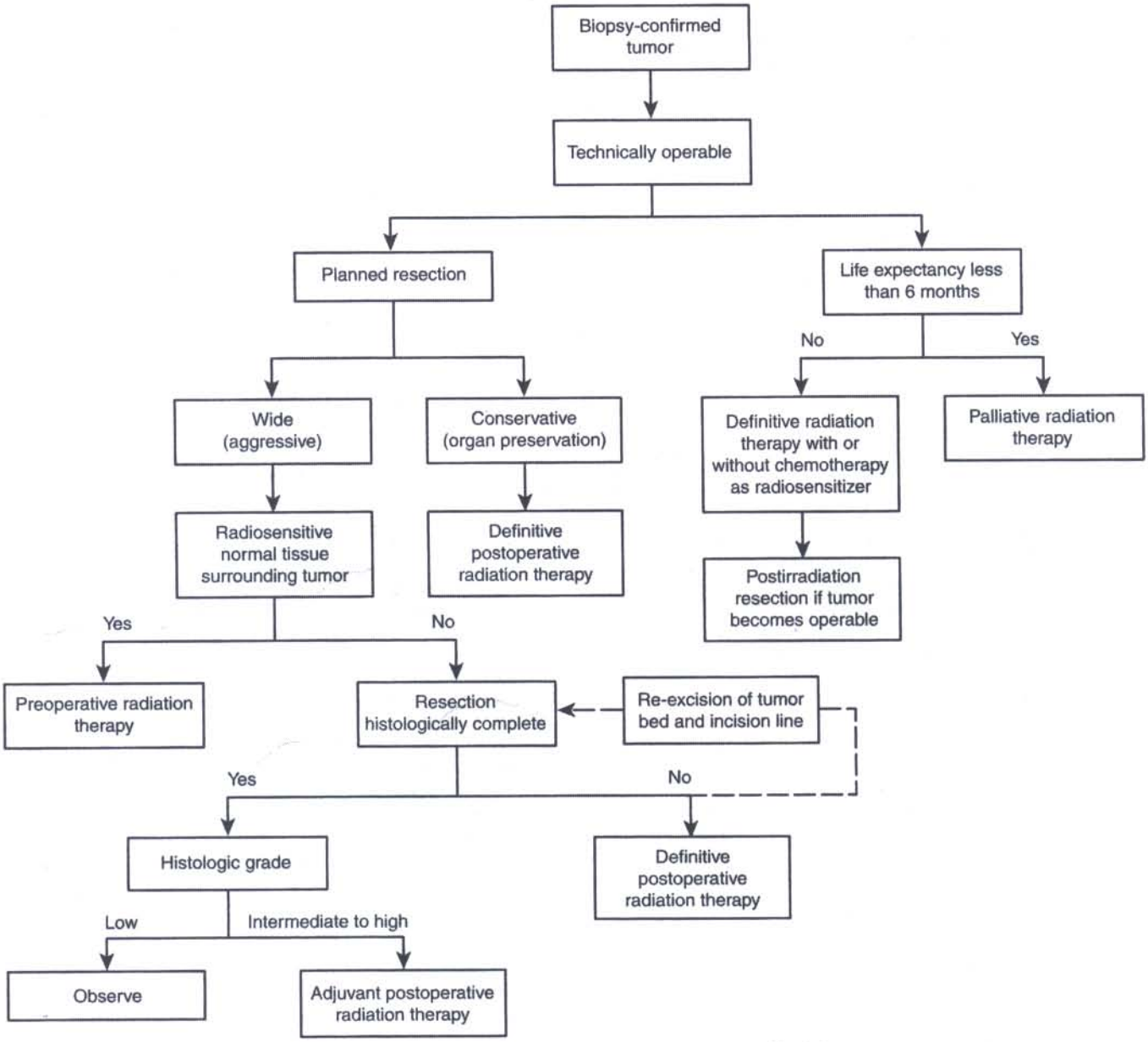


Figure 180-3 Integration of radiation therapy in the management of solid tumors in patients with no evidence of systemic disease. The term *definitive radiation therapy (RT)* refers to therapy given at full dose when gross disease is present; *adjuvant RT* refers to radiation therapy given at moderate dose for treatment of microscopic or subclinical disease.

at surgical margins) or when the risk of local recurrence is high after surgery because of extensive tumor invasion and high histologic grade. Clean surgical margins are not a guarantee that all tumor cells have been removed, because cell aggregates greater than $10^6/cm^3$ or higher are required for histopathologic detection. Aggressive intermediate or high-grade fibrosarcomas, hemangiopericytomas, cutaneous hemangiosarcomas, infiltrative lipomas and liposarcomas, myxosarcomas, synovial cell sarcomas, and mast cell tumors resected with clean surgical margins benefit from adjuvant postoperative irradiation.

Unfortunately, radiation therapy is too frequently used after a partial resection in which gross residual disease is present. This is the setting in which the treatment combination is the least effective. Irradiation is most effective for treatment of microscopic or subclinical residual disease.[18] Partial removal of gross disease (surgical debulking) provides little therapeutic advantage. For example, a surgical excision that removes 99% of a tumor containing 10^{10} cells (about 10 g of tissue) leaves 10^8 tumors cells. In fact, subtotal resection may lessen the chance of cure by irradiation in some situations, because tumor cells may be disseminated throughout the surgical bed and may be implanted in relatively hypoxic scar tissue, where they are less sensitive to irradiation. In addition, reduction of tumor volume may result in a compensatory burst of accelerated regrowth of residual tumor cells, which can decrease the efficacy of radiation therapy.

Preoperative irradiation. Advantages of preoperative radiation are that it can eradicate subclinical or microscopic disease beyond the margins of the surgical resection; it may theoretically diminish tumor implantation within the operative field; and it can decrease the potential for dissemination of tumor cells that might produce distant metastases. In some cases it may convert a nonresectable tumor into one that can be resected.

Preoperative irradiation is more "dose effective" than postoperative radiotherapy; that is, a lower dose is needed preoperatively to reduce rates of local recurrence to the same extent as postoperative radiation. Although radiation doses are lower and radiation treatment fields are smaller than those used with postoperative radiation therapy, preoperative treatment may be associated with an increased risk of surgical morbidity. The decision to accept increased short-term morbidity from wound healing complications with preoperative radiation therapy must be balanced against the potential effects of larger radiation doses and larger treatment volumes associated with postoperative radiotherapy. Practical measures have proved useful in avoiding treatment complications. At the time of surgery, it is extremely important to handle irradiated tissues with care. Whenever possible, the fascia and underlying muscle should be left attached to the skin and subcutaneous tissue as they are reflected from the tumor. Potential dead spaces should be avoided, and wounds should be drained and closed without tension. Seromas and hematomas should be drained, because they are likely to increase the incidence of late wound breakdown and subsequent infection, thus delaying the administration of radiation therapy.

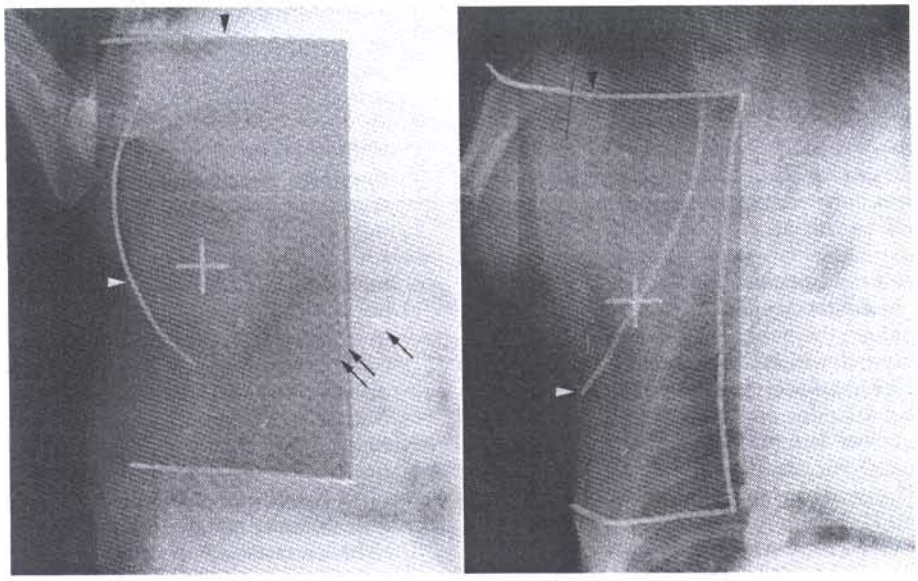
For large operable tumors with anticipated extensive regional microextensions or for those that arise from or are located close to radiosensitive normal tissue (brain, spinal cord, lung, abdominal cavity), there is an advantage in using adjuvant preoperative irradiation. In contrast to postoperative irradiation, preoperative treatment can be given to a smaller treatment volume with lower radiation doses. Although there is a potential increase in postoperative morbidity, the risk of long-term, radiation-induced complications is reduced. In this setting, irradiation is followed by wide-margin surgical resection according to the original extent of the disease. This treatment combination is effective for most operable cutaneous soft tissue sarcomas in dogs and cats. The benefit of this approach has been demonstrated for the treatment of feline fibrosarcomas at vaccination sites overlying the spinal cord and lungs.[29]

Sequential combination of surgery and radiation therapy. A subset of animals with advanced, incompletely resectable cancer may be treated with definitive irradiation followed by surgery if the tumor undergoes significant regression and becomes resectable. In this setting, the timing between irradiation and surgery is longer (8 to 10 weeks) to allow tumor shrinkage and normal tissue recovery than in planned preoperative irradiation. This approach requires careful monitoring of tumor response after irradiation while planning the surgery. This treatment combination is different from that in which surgery is used for attempted salvage of those that experience a locoregional recurrence after definitive irradiation.

In clinical practice, the sequential combination of irradiation followed by surgery is reserved for situations in which either the tumor is initially thought to be unresectable or the original boundaries are obscured. In this setting, a definitive dose of radiation is used, followed by limited surgical resection to eliminate the residual gross disease that has not been sterilized by irradiation. This approach has been found effective, with minimal surgical morbidity in expert hands, for advanced lesions arising from the head (carcinomas and soft tissue sarcomas of the face and oral cavity) and neck region (thyroid carcinomas) and the extremities (fibrosarcomas, hemangiopericytomas, and mast cell tumors).

Surgical procedures helpful for radiation therapy. Because the most common treatment combination is irradiation given after surgery, the surgeon plays a critical role in treatment. Unless the primary tumor can be removed in *toto*, it usually is preferable to perform a biopsy of the site, visualize the extent of the tumor, and then end the procedure. The treatment options can then be reconsidered. This approach is better than performing heroic surgical procedures that will compromise the efficacy of radiation therapy. Because the radiation treatment field must incorporate all areas that have potentially been contaminated by surgical dissection, single incisions, rather than multibranched ones, should be made. Drain sites should be positioned close to the wound to be included in the treatment field. Good communication between the radiation oncologist and the surgeon is imperative. Information regarding the total extent of tissue involvement, the estimated volume of residual tumor, and the quality of the surgical margins is required for radiation treatment planning. To excise the tumor and then refer the pet for radiation therapy treatment imposes a severe handicap on the therapist and the pet. The location of the cutaneous surgical scar, the palpable postoperative induration, the owner's recollection, and the surgical notes are usually inadequate to determine the location of the tumor bed. Radiation treatment fields devised primarily on the location of the skin incision are associated with a risk of geographic treatment miss. For the radiation dose to be delivered precisely to the tumor confines, as identified at the surgical procedure, the walls of the excision cavity must be marked with radiopaque markers (i.e., steel or titanium surgical hemostatic clips or wire) to document the boundaries of the tumor bed and residual disease.

Radiographic documentation of the clips is used to localize the entire tumor volume for treatment planning and to verify that the treatment setup provides adequate coverage of the entire tumor volume (Figure 180-4). If markers are not present for guidance, the radiation oncologist must use larger than usual fields to decrease the likelihood of inadequate coverage, with subsequent increased risk of complications.



A B

Figure 180–4 Dog with a mast cell tumor in the axillary region treated postoperatively with two orthogonal radiation fields: **A,** Lateral view. **B,** Dorsoventral view. The tumor bed is defined by radiopaque surgical hemostatic clips. The clinical setup was based on the location of the scar and surgical induration, the surgeon's recollection of the tumor location, and the surgical report, which provided anatomic landmarks (rib number) and measurements of tumor extension. Postoperative portal films were done to verify the treatment setup. The radiation fields marked with solder wire *(black arrowhead)* taped on the skin were determined clinically (*X* at center of treatment field). Although the skin incision was made almost directly over the tumor, the location of the skin incision marked with solder wire *(white arrowhead)* was not immediately above the tumor because the position of the underlying tissues was different on the treatment table than that on the operating table. The dorsoventral radiation field **(B)** was barely adequate. The lateral field **(A)** was clearly inadequate because surgical clips *(black arrows)* extended outside the dorsal border of the radiation field. Correction of the treatment setup would not have been possible without demarcation of the tumor volume with surgical clips. The geographic treatment miss would have resulted in tumor recurrence.

Integration of Radiation Therapy, Surgery, and Chemotherapy for Inoperable or Metastatic Disease

The use of combinations of radiation therapy and chemotherapy has increased. Radiation therapy alone or in combination with surgery is usually directed at primary tumor masses and involved regional nodes, whereas systemic treatment is aimed at distant metastases.

Radiation therapy and chemotherapy play important roles in the management of metastases that are either documented (radiographically, histopathologically, or cytologically) or suspected (subclinical disease). Radiation therapy is effective for the treatment of subclinical disease in the regional lymphatics and in the treatment of clinically positive lymph nodes. For tumors with a high potential for regional spread (invasive tumors with intermediate to high histologic grades), a large treatment field is used to include the first-echelon lymph nodes along with the primary lesion. The benefit of large-field irradiation can be demonstrated by the lower rate of metastasis observed in dogs with malignant oral tumors treated with irradiation when compared with dogs treated with surgery.[14] When clinically positive nodes are present, the radiation field includes the gross disease (primary and positive nodes) and contiguous nodes that are at risk. In this setting, radiation therapy is often used with palliative intent.

Adjuvant chemotherapy is used for treatment of subclinical disease after effective local treatment (surgery and/or irradiation) has been completed. The initial decision to use local treatment alone or both a local and systemic approach depends on the risk of occult distant disease and the availability of effective chemotherapy. As local treatment becomes more effective, animals live longer and a higher number develop metastasis. This pattern of failure is seen with some tumors that previously had the reputation of low metastatic rates, including squamous cell carcinomas of the oral cavity, fibrosarcomas in any location, and hemangiopericytomas. As a result, chemotherapy may have a bigger part to play as an adjuvant to local treatment. Adjuvant chemotherapy with cisplatin, carboplatin, or doxorubicin is indicated for control of subclinical disease in tumors with a high risk of distant failure, including osteogenic sarcomas and high-grade soft tissue sarcomas. Preliminary data on the use of chemotherapy to prevent metastasis for oral melanoma[23] and mast cell tumors[30] in dogs and vaccine-associated sarcomas[29] and oral carcinomas[25] in cats have failed to show a therapeutic benefit.

For the treatment of locally advanced, unresectable disease, concomitant chemoradiotherapy is the most promising approach. Schedules of concomitant chemoradiotherapy can be synchronous, with the two modalities administered close together, or alternating, with the treatments administered in a nonoverlapping fashion. Administration of radiotherapy and chemotherapy concomitantly is a dose-intensive approach that exploits the independent, complementary activity of radiotherapy locally and chemotherapy distantly (spatial cooperation). In cats with mediastinal lymphoma and severe respiratory compromise secondary to pleural effusion, radiation therapy may be used along with induction chemotherapy

to improve the likelihood of rapid and complete remission. The beneficial effects of concurrent chemotherapy and radiation therapy result from the added toxic effects of the two modalities in the treatment field, with less than additive effects against dose-limiting normal tissues. Cisplatin and carboplatin are ideal agents for concomitant chemoradiotherapy. They have established single-agent activity, as well as synergistic interaction but nonoverlapping toxicities with radiotherapy. The drugs may be used as a systemic cytotoxic agent in addition to irradiation or as a radiosensitizer administered as small, frequent doses systemically[31] or intratumorally.[32] Several clinical trials are underway to test the efficacy of irradiation combined with carboplatin and mitoxantrone for the treatment of advanced tumors in dogs and cats. The benefit of adding chemotherapy to irradiation has been shown with cisplatin in dogs with appendicular osteosarcomas, regardless of whether they are resectable, and for carboplatin in dogs with intranasal carcinomas.[33-35]

ROLE OF RADIATION THERAPY IN THE MANAGEMENT OF CANCER PATIENTS

Radiation therapy can be used in the clinical management of virtually every type of solid tumor in dogs and cats. Table 180-1 outlines the role of radiotherapy for specific tumors, the results obtained, and the possible treatment complications that should be discussed with owners before treatment. This table is not intended for use as a manual of radiation therapy. Most of the results are given as local control rates at 2 years because in general, the risk of local failure 2 years after irradiation is low in animals that have survived disease free. As a result, the 2-year local control rate represents a reliable estimate of the cure rate in dogs and cats that have no evidence of metastasis before treatment. The local control rates given here represent a lower limit, because they were obtained with treatment protocols that may not have been optimum. It is anticipated that the current use of higher radiation doses given with effective fractionation schemes and optimum irradiation techniques will result in higher local control rates. Specific results according to tumor size, location, and other prognostic factors are given in the other chapters of this text.

A great improvement in the treatment of cancer could be achieved immediately if all animals received what is currently acknowledged as the best available treatment. This requires that individual veterinarians appreciate the potential of available treatment modalities, especially the advantage of multidisciplinary consultation, at the time of initial diagnosis and treatment.

The role of radiation therapy for the treatment of brain tumors and in combination with surgery for mammary and salivary gland adenocarcinomas, thymomas, and intra-abdominal carcinomas (prostate, bladder, and rectum) needs to be established in animals because of its important role in people.

CHAPTER • 181

Hematopoietic Tumors

David M. Vail
Douglas H. Thamm

LYMPHOMA

Lymphoma (lymphosarcoma [LSA]) is the most common hematopoietic tumor affecting dogs and cats. It is defined as a proliferation of malignant lymphoid cells affecting primarily the lymph nodes or solid visceral organs, such as the liver or spleen. The management of LSA initially is quite gratifying in both species, because response rates approach 90% in dogs and 70% in cats treated with multiagent chemotherapeutic approaches. Unfortunately, most animals eventually succumb to relapse of chemotherapy-resistant, disseminated disease.

Etiology

The etiology of LSA in companion animals is for the most part unknown. Although certain varieties of LSA in cats have been directly and indirectly associated with feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV), respectively, no strong evidence exists as yet of a retroviral etiology in dogs. A weak to moderate association between canine LSA and the use of herbicides, exposure to strong magnetic fields, or residence in industrial areas has been observed in preliminary epidemiologic studies,[1-5] and a recent study found a meaningful association between environmental tobacco smoke exposure and the risk of feline gastrointestinal LSA.[6] More thorough studies are necessary to evaluate these associations further. Both somatic and germ line mutations in the tumor suppressor gene p53 have been reported in some cases of canine LSA,[7] and occasional clustering of LSA in related dogs has suggested a heritable component in limited instances.[8]

Classification of Lymphoma

Various classification schemes for LSA have been evaluated, including those based on the anatomic site, the World Health Organization (WHO) clinical stage (Table 181-1), the histologic/cytologic phenotype, and the immunophenotype.

Canine Classification

In the dog, 80% to 85% of cases are the multicentric anatomic type and present as WHO stage III or IV.[9-13] Alimentary (~7%), cutaneous (~6%), mediastinal (~3%) and miscellaneous extranodal sites (central nervous system [CNS], bone, heart, nasal cavity, and primary ocular locations) are less frequently encountered. Regardless of the histologic classification scheme used (e.g., Kiel, NCI-Working Formulation), most cases (80%) equate to medium- or high-grade non-Hodgkin's LSA in humans.[14-16] Most canine LSA is of the

Table • 181-1

World Health Organization Clinical Staging for Domestic Animals With Lymphoma

STAGE	CRITERIA
I	Single lymph node
II	Multiple lymph nodes in a regional area
III	Generalized lymphadenopathy
IV	Liver and/or spleen involvement (with or without stage III)
V	Bone marrow or blood involvement and/or any nonlymphoid organ (with or without stages I to IV)
Substage a	Without clinical signs of disease
Substage b	With clinical signs of disease

World Health Organization: TNM Classification of Tumors in Domestic Animals. World Health Organization, Geneva, 1980.

B-cell immunophenotype, with approximately 20% to 30% being of T-cell derivation.[9,14-16]

Feline Classification

In the cat, a definite and repeatable shift in anatomic type, immunophenotypic derivation, and retroviral association has occurred concomitant with the initiation of widespread FeLV testing and vaccination programs over the past 15 to 20 years.[17-19] Studies prior to this era reported that the mediastinal and multicentric forms of LSA predominated and that these represented younger, FeLV-positive cats. Contemporary reports document that currently, LSA primarily affects older, FeLV-negative cats and that the alimentary form predominates (Table 181-2). Only 10% to 20% of cases are now associated with FeLV antigenemia, compared with the 60% to 70% figure published before FeLV testing and vaccination became available.

Along with a shift away from FeLV antigen–associated tumors has come an alteration in the traditional signalment and relative distribution of anatomic sites. The median age of 9 to 10 years now reported is considerably higher than the 4- to 6-year medians reported prior to this era. The median age of cats within various anatomic tumor groupings has not changed, however, and sites traditionally associated with FeLV (i.e., mediastinal and multicentric locations) still occur primarily in younger, FeLV-antigenemic cats. Similarly, the alimentary form occurs most often in older, FeLV-negative cats. It is unclear whether this change in the epidemiology of LSA in cats is due to FeLV vaccination itself or whether the procedure of FeLV antigen testing before vaccination has allowed separation of potentially infective cats from the susceptible population. Either situation would result in a reduction in the number of FeLV-positive LSA cases. Recently, European oncologists have reported mediastinal LSA in young, Oriental breed cats that are uniformly FeLV negative.[19]

A distinct class of LSA in cats has more recently been reported.[20-23] This lesion, a granulated, round cell tumor, has been termed either *globule leukocyte tumor* or *large granular lymphocyte LSA*, although these are likely variations of the same disease. The tumor usually involves the intestinal tract and abdominal viscera, with systemic involvement being the norm. Affected cats are generally FeLV negative. A series of cats with LSA resembling human Hodgkin's disease also has been recently reported.[24]

Clinical Presentation and Signs

Canine Multicentric Lymphoma

LSA affects primarily middle-aged to older dogs. No sex predilection is observed, and many different breeds are represented. Only 10% to 20% of dogs are clinically ill (WHO substage b) at presentation,[9-13] therefore most cases present as healthy dogs with incidental generalized lymphadenopathy. In dogs with substage b disease, the clinical signs are nonspecific and can include inappetence, weight loss, and lethargy. Paraneoplastic hypercalcemia may result in presentation for polyuria and polydipsia. In stage V disease, if bone marrow involvement is marked, peripheral cytopenias may result in presentations reflecting neutropenic sepsis, thrombocytopenic hemorrhage, or anemia.

Canine Lymphoma of Other Sites

The presentation and associated clinical signs of LSA reflect the anatomic form present in each individual case. Alimentary forms present with signs specific to the gastrointestinal tract, including vomiting, diarrhea (with or without blood), weight loss, and inappetence. Mediastinal forms may present with respiratory signs, including dyspnea and muffled heart sounds. Mediastinal LSA may also present with precaval syndrome, characterized by pitting edema of the head, neck, and forelimbs secondary to tumor compression of the cranial vena cava (Figure 181-1). Nearly half of mediastinal LSA cases are associated with paraneoplastic hypercalcemia,[25] therefore polydipsia and polyuria are common presenting complaints for this anatomic form.

Cutaneous LSA has been called the "great imitator" because of its ability to present in many varying forms. Single or multiple cutaneous lesions can occur, which may appear as mild, eczematous plaques or more impressive nodular tumors (Figure 181-2).

Table • 181-2

Characteristics of Feline Lymphoma by Anatomic Site

ANATOMIC SITE	RELATIVE FREQUENCY	AGE	T CELL ASSOCIATION	FeLV POSITIVE
Alimentary	50%-70%	~10-14 yr	High	Low (5%)
Multicentric	10%-25%	Depends on feline leukemia virus (FeLV) status*	Depends on FeLV status*	Approximately one third
Mediastinal/thymic	10%-20%	Young	High	High (>80%)
Nasal	~10%	Aged	Low	Low
Renal	5%-10%	Middle-aged	Low to moderate	Low to moderate
Other	5%-25%	Mixed	Mixed	Mixed

*FeLV-positive cats tend to be younger, and the cancer is more commonly of T cell derivation.

Figure 181-1 Precaval syndrome in a dog with mediastinal lymphoma. Pitting edema of the head and neck are noted.

Lesions may or may not be pruritic and can occur anywhere on the skin and in the oral cavity.

Miscellaneous sites of disease result in signs attributable to the location (i.e., lameness for bone lesions, neurologic compromise for CNS lymphoma).

Feline Lymphoma

No breed or sex predilections have been identified. Age and its association with FeLV status have been discussed previously. In general, cats are more likely than dogs to present with clinical illness; 75% or more present with substage b signs.[17,18] The clinical presentation of LSA in cats depends on the anatomic sites involved. Cats with alimentary LSA or large granular lymphocyte LSA present with varying degrees of weight loss, unkempt haircoat, inappetence, chronic diarrhea, and vomiting. Cats with mediastinal disease are often in severe respiratory distress due to the effects of an intrathoracic mass or the presence of significant pleural effusion. Cats with renal LSA may present with polyuria/polydipsia secondary to renal failure. In the case of nasal LSA, sneezing, chronic serosanguineous nasal discharge, exophthalmos, and facial deformity are common presentations. Cats with FeLV-associated LSA are more likely to present with pale mucous membranes as a result of anemia.

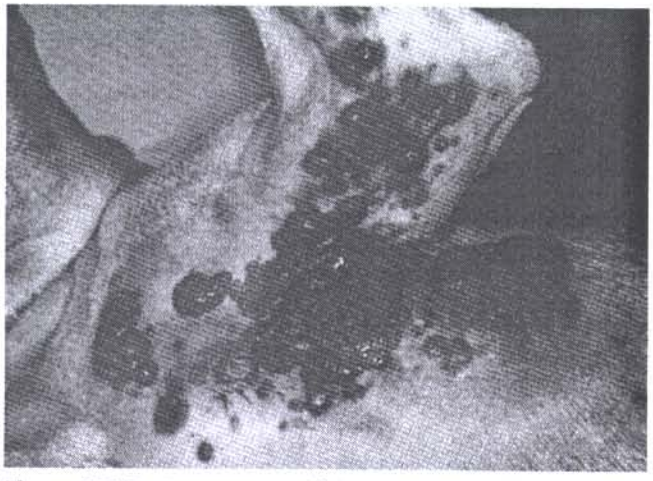


Figure 181-2 Cutaneous T-cell lymphoma (mycosis fungoides) in a dog.

Diagnosis

Physical Examination

A thorough physical examination should include palpation of all assessable lymph nodes and a rectal examination in the dog. The clinician should inspect the mucous membranes for pallor or petechiae indicative of anemia or thrombocytopenia secondary to myelophthisis and should look for evidence of major organ failure, including the presence of icterus or uremic ulcers. Abdominal palpation may reveal organomegaly, intestinal wall thickening, or mesenteric lymphadenopathy. The presence of a mediastinal mass and/or pleural effusion may be suspected based on thoracic compression in cats and auscultation in both dogs and cats. An ophthalmic examination, including funduscopic assessment, may reveal abnormalities (e.g., uveitis, retinal hemorrhage, ocular infiltration) in approximately one third to one half of dogs with LSA.[26]

Hematologic Abnormalities

A complete blood count (CBC), including a numeric platelet count, is a necessary part of any evaluation of dogs or cats suspected of having LSA. Hematologic abnormalities occur in most cases of multicentric LSA.[27] Anemia, when present, is usually normocytic, normochromic, and nonregenerative, reflecting anemia of chronic disease. Regenerative anemias may reflect concomitant blood loss or hemolysis. Cats with FeLV-associated disease may have a macrocytic anemia. If significant myelophthisis is present, the anemia may be accompanied by thrombocytopenia and leukopenia. Circulating atypical lymphocytes may be indicative of bone marrow involvement and leukemia. It is important to differentiate multicentric LSA with bone marrow involvement (i.e., stage V disease) from primary lymphoblastic leukemia (discussed later in this chapter), because these two diseases have entirely different prognoses. Hypoproteinemia is more commonly observed in animals with alimentary LSA.

Bone marrow aspiration cytology is recommended for staging because of the prognostic significance of marked marrow involvement; it is also recommended for cases in which LSA is suspected but has not yet been documented.

Serum Biochemical Abnormalities

The serum biochemical abnormalities seen in LSA often reflect the anatomic site involved. In addition, approximately 15% of dogs with LSA (40% of dogs with mediastinal involvement) are hypercalcemic, often owing to the ectopic production of parathyroid hormone–related peptide.[25,27,28] In cases of hypercalcemia of unknown origin, LSA should always be considered high on the differential disease list, and diagnostics directed at this possibility should be undertaken. In addition, the presence of hypercalcemia can serve as a marker for response to therapy. Elevations in blood urea nitrogen and serum creatinine can occur secondary to renal infiltration with tumor, hypercalcemic nephrosis, or dehydration. Liver-specific enzyme or bilirubin elevations may result from hepatic parenchymal infiltration. Serum globulin elevations, usually monoclonal, occur infrequently with B cell–derived LSA.

Retroviral Status

In the cat, retroviral screening (i.e., FeLV and FIV) is important from diagnostic, prognostic, and husbandry standpoints.

The relative frequency of FeLV associations is presented in Table 181-2.

Imaging

Imaging (radiographic, ultrasonographic, or computed tomography [CT]) may be important for diagnosis, especially in cases lacking peripheral lymphadenopathy. Imaging is equally important for clinical staging (i.e., determining the extent of disease), because results may significantly affect the overall prognosis and alter the caregiver's willingness to pursue therapy.

Abnormalities on thoracic radiographs are noted in approximately two thirds to three fourths of dogs with LSA[29,30]; these include one third with evidence of pulmonary infiltrates (Figure 181-3) and two thirds with thoracic lymphadenomegaly. It is important to note that 20% of dogs present with cranial mediastinal lymphadenopathy, which correlates negatively with both remission and survival duration.[29]

Abdominal radiographs or ultrasound may reveal evidence of sublumbar/mesenteric lymph node, spleen, or liver involvement in approximately 50% of dogs. Abdominal ultrasound is most important in cats when intestinal LSA is suspected.

Special studies, including contrast studies of the gastrointestinal tract, CT or myelographic studies of the central nervous system, and skeletal radiograpic/scintigraphy surveys are reserved for cases in which involvement of the appropriate anatomic site is suspected.

In the authors' practice, for the typical cases of canine multicentric LSA, imaging is limited to thoracic radiographs, because there is no prognostic difference between dogs with stage III and stage IV disease (i.e., liver/spleen involvement); however, the presence of cranial mediastinal lymphadenopathy is of prognostic significance.[29]

Cytologic and Histopathologic Diagnosis

Microscopic conformation of LSA is the cornerstone of diagnosis in both cats and dogs. Fine needle aspirate (FNA) cytologic assessment by a skilled clinical pathologist is often adequate to make a diagnosis of LSA in dogs; however, conclusive histologic conformation is the gold standard. The predominance of a homogenous population of immature lymphoid cells is suggestive of LSA (Figure 181-4), although small cell variants do exist. Avoidance of nodes draining reactive areas (e.g., submandibular nodes in the presence of periodontal disease) is recommended, because reactive hyperplasia may mask (or mimic) the true neoplastic condition.

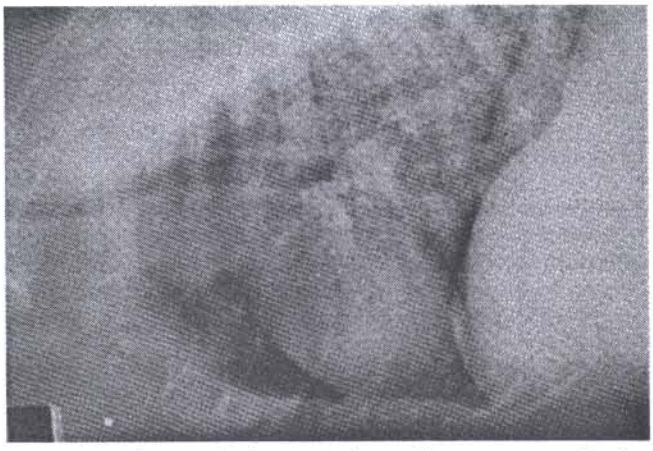


Figure 181-3 Lateral thoracic radiographic projection of a dog illustrating interstitial pulmonary infiltration with tumor typical of lymphoma at this site.

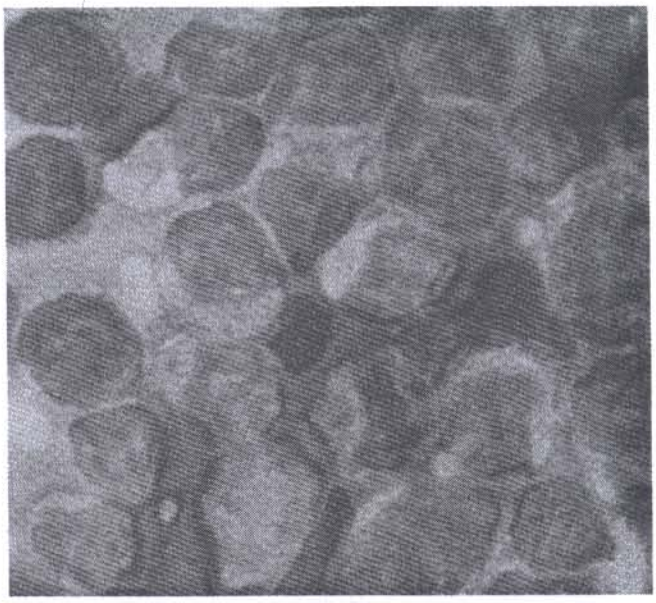


Figure 181-4 Fine needle aspirate cytology (Wright-Giemsa stain, ×1000) of a peripheral lymph node in a dog with high-grade lymphoma. The node is effaced with an homogenous population of immature lymphoid cells.

In the cat, FNA assessment alone is not sufficient in most cases because of the difficulties encountered in distinguishing LSA from benign hyperplastic lymph node syndromes unique to the species. These syndromes include idiopathic peripheral lymphadenopathy, plexiform vascularization of lymph nodes, and peripheral lymph node hyperplasia of young cats.[31-34] In these cases, whole lymph node excision is preferred, because evaluation of orientation, invasiveness, and architectural abnormalities may be necessary for diagnosis.

Besides their role in confirming a diagnosis of LSA, histologic and cytologic samples can be analyzed by various histochemical and immunohistochemical techniques to determine the immunophenotype (B cell versus T cell), tumor proliferation rates (e.g., Ki-67, proliferating cell nuclear antigen [PCNA], argyrophilic nucleolar organizer regions [AgNOR]), and histologic subtype (high-, intermediate-, or low-grade tumors).[9,15,16,35-38] The availability of such analysis is increasing; however, currently only immunophenotype in dogs is consistently predictive of prognosis. Histologic assessment of markers of multidrug resistance and apoptotic pathways (e.g., P-glycoprotein, p53) are currently being evaluated in dogs and cats with LSA, but their significance requires further evaluation.[7,37,39-43]

Additional site-specific cytologic or histologic assessments may be warranted when extranodal sites are suspected. Thoracocentesis followed by cytologic evaluation of pleural fluid is often diagnostic in cats with mediastinal LSA but is less likely to be of value in dogs with effusions secondary to mediastinal involvement. Conversely, cerebrospinal fluid (CSF) analysis is more commonly helpful in dogs than cats with CNS LSA because the more common spinal form of LSA in cats is generally extradural.[44,45] In cats suspected of having CNS LSA, bone marrow and renal involvement are often present, and cytologic assessment of these organs is generally more easily attainable than CNS sites.

Differential Diagnosis

The differential diagnoses for LSA, which vary with the anatomic form of the disease, are presented in Table 181-3.

Table • 181-3

Common Differential Diagnoses for Lymphoma

ANATOMIC FORM	DIFFERENTIAL LIST
Generalized lymphadenopathy	• Disseminated infections (e.g., bacterial, viral, rickettsial, parasitic, and fungal) • Immune-mediated disorders (e.g., lupus, polyarthritis, vasculitis, dermatopathy) • Other hematopoietic tumors (e.g., leukemia, multiple myeloma, malignant or systemic histiocytosis) • Tumors metastatic to nodes • In cats, many benign reactive hyperplastic syndromes (see text)
Alimentary	• Infiltrative enteritis (e.g., lymphocytic, plasmacytic enteritis) • Nonlymphoid intestinal neoplasms • Granulomatous enteritis • Granulated round cell tumors in cats • Gastrointestinal mast cell tumors in cats
Cutaneous	• Infectious dermatitis (e.g., advanced pyoderma) • Immune-mediated dermatitis (e.g., pemphigus) • Other cutaneous neoplasms
Mediastinal	• Thymoma • Heart base tumor (chemodectoma) • Ectopic thyroid tumor • Pulmonary lymphomatoid granulomatosis • Granulomatous disease (e.g., hilar lymphadenopathy with blastomycosis)

Therapy

Untreated dogs and cats live an average of 4 to 6 weeks once a diagnosis has been established. In general, LSA is a systemic disease and requires a systemic approach to therapy (i.e., chemotherapy). Exceptions to this occur in cases of solitary site or extranodal LSA, for which local therapy involving either surgery or radiotherapy may be indicated.

Systemic Chemotherapy in Dogs with Lymphoma

There are almost as many chemotherapy protocols for dogs with LSA as there are veterinary oncologists. This likely reflects our inability to achieve cure in the majority of cases. LSA in the dog can be an initially gratifying disease to treat, because remission rates approach 80% to 90% with available combination chemotherapy protocols, and quality of life is generally excellent during the period of remission.[46] However, the majority of dogs eventually succumb to drug-resistant recurrence of the disease, on average, 1 year after diagnosis.

Due to the large and ever increasing number of available chemotherapeutic protocols, several factors should be considered and discussed with caregivers when choosing a protocol, which can be done on a case-by-case basis. These factors include the cost, time commitment involved, efficacy, toxicity, and experience of the clinician with the protocols in question. With the availability of generic drugs, chemotherapy protocols are becoming affordable to a larger segment of veterinary clientele. In general, more complex combination chemotherapy protocols are more expensive, more time-consuming (i.e., requiring repeated office visits and closer monitoring), and more likely to result in toxicity than are simpler, single-agent protocols. However, as a general rule, more complex combination protocols result in longer remission and survival durations than do single agent protocols.

A complete listing of all available chemotherapy protocols for dogs with LSA is beyond the scope of this review, therefore the reader is referred to a recent review and other reports.[11,16,46] This discussion presents an example of the combination protocol used by the authors and the most widely used single agent protocol. Most complex combination protocols are modifications of CHOP protocols initially designed for human oncologic use. The CHOP protocol represents combinations of cyclophosphamide *(C)*, doxorubicin (hydroxydaunorubicin *[H]*), vincristine (Oncovin *[O]*), and prednisone *(P)*. Regardless of which CHOP-based protocol is used, the overall median remission and survival times are approximately 8 and 12 months, respectively.[12,13,46,47] Approximately 20% to 25% of treated dogs are alive 2 years or longer after initiation of these protocols. Response rates and the length of response vary, depending on the presence or absence of prognostic factors discussed under Prognosis. Historically, the treatment protocol begins with an intensive *induction phase*, during which drugs are given weekly; this is followed by a *maintenance phase*, during which treatment intervals are slowly spread out and the drugs are given less frequently.

An important question is how long chemotherapy should be continued beyond the point at which complete remission has been achieved; that is, how long should the maintenance phase last or, for that matter, should maintenance therapy be used at all? In most human LSA protocols, after a 6-month induction phase, no benefit has been shown with continued maintenance therapy, therefore no further therapy is given until recurrence is observed. Recent evidence suggests that use of a DOX-containing, multiagent protocol (Table 181-4) for 6 months, followed by monthly re-evaluation, results in remission and survival times similar to those achieved with protocols involving a prolonged maintenance phase.[12,13]

The most effective and commonly used single agent chemotherapy protocol available for dogs with LSA is DOX.[11,48-50] DOX is administered at a dosage of 30 mg/m^2 given intravenously every 3 weeks for five treatments. Response is observed in 75% to 80% of cases, and median remission and survival durations of approximately 5 and 7 months, respectively, are reported. The advantages of this single agent protocol are that it is less time-consuming and expensive, and fewer hospital visits are required. Because only one drug is used, any side effects encountered are attributable to that drug.

If financial or other client concerns preclude the use of more aggressive systemic chemotherapy, prednisone therapy alone (2 mg/kg given orally daily) often results in short-lived remissions of approximately 1 to 2 months. In these cases, it is advisable to inform clients that if they should decide to pursue more aggressive therapy at a later date, dogs with prior prednisone therapy may be more likely to have drug-resistant disease and to experience shorter remission and survival durations with subsequent chemotherapy protocols. This is especially true after long-term prednisone use or in dogs that have experienced a recurrence while receiving prednisone.[51]

Modifications in the chemotherapy dose and/or frequency may be necessary under conditions of excess toxicity, as discussed in Chapters 178 and 179. When hypercalcemia is present, if the dog has substage A disease and continues to eat and drink, ancillary therapy for the hypercalcemia is usually

Table • **181-4**

University of Wisconsin–Madison Combination Chemotherapy Protocol for Dogs With Lymphoma

TREATMENT WEEK	DRUG, DOSAGE, AND ROUTE	TREATMENT WEEK	DRUG, DOSAGE, AND ROUTE
1	Vincristine: 0.5-0.7 mg/m² IV[a] L-asparaginase: 400 U/kg SC[b] Prednisone: 2 mg/kg PO[c]	11	Vincristine: 0.5-0.7 mg/m² IV
2	Cyclophosphamide: 250 mg/m² IV Prednisone: 1.5 mg/kg PO	13	Cyclophosphamide: 250 mg/m² IV
3	Vincristine: 0.5-0.7 mg/m² IV Prednisone: 1 mg/kg PO	15	Vincristine: 0.5-0.7 mg/m² IV
4	Doxorubicin: 30 mg/m² IV Prednisone: 0.5 mg/kg PO	17	Doxorubicin: 30 mg/m² IV
6	Vincristine: 0.5-0.7 mg/m² IV	19	Vincristine: 0.5-0.7 mg/m² IV
7	Cyclophosphamide: 250 mg/m² IV	21	Cyclophosphamide: 250 mg/m² IV
8	Vincristine: 0.5-0.7 mg/m² IV	23	Vincristine: 0.5-0.7 mg/m² IV
9*	Doxorubicin: 30 mg/m² IV	25†	Doxorubicin: 30 mg/m² IV

*If the patient is in complete remission at week 9, treatment continues to week 11.
†If the patient is in complete remission at week 25, therapy is discontinued and the dog is rechecked monthly for recurrence.
NOTE: A CBC should be performed before each chemotherapy treatment. If the neutrophil count is less than 2000 cells/μL, the clinician should wait 5 to 7 days and then repeat the CBC; the drug is administered if the neutrophil count has risen above the 2000 cells/μL cutoff.

unnecessary, because initiation of chemotherapy results in eucalcemia within a few days. If the animal is ill, azotemic, or showing signs attributable to hypercalcemia, therapy directed specifically at hypercalcemia (see Chapter 237) concurrent with the initiation of systemic chemotherapy is warranted.

Systemic Chemotherapy in Cats with Lymphoma

Several combination chemotherapy protocols for cats have been reported and reviewed previously.[17-19,52] It has become clear that the addition of DOX to COP-based protocols (C, cyclophosphamide; O, Oncovin [vincristine]; *P*, prednisone) is superior to COP alone in the cat.[17,52] However, in one European study, cats receiving COP experienced remission and survival durations comparable to cats treated with CHOP protocols in North America.[19] In contrast to dogs, DOX does not appear to be as effective single agent for feline LSA.[53] In general, cats do not enjoy as high a response rate or as long remission and survival durations as dogs with LSA. Complete response rates vary between 50% and 75%, and overall median remission and survival durations are approximately 4 to 8 and 6 to 8 months, respectively.[17,19,54] However, a larger proportion of cats (30% to 40%) that achieve a complete response with combination chemotherapy enjoy more durable overall remission and survival times (i.e., 2 years) than that seen in dogs. Response rates and length of response vary according to the presence or absence of prognostic factors discussed under Prognosis. The modified CHOP-based protocol preferred by the authors for cats is represented in Table 181-5.

A recent preliminary report suggests that cats with low-grade gastrointestinal LSA may respond favorably and enjoy comparably long survival times using a protocol of oral chlorambucil (15 mg/m² given daily for 4 days, repeated every 3 weeks) and prednisone.[55]

Cats with large granular LSA or globule leukocyte tumors tend to respond more poorly to chemotherapy, although durable responses have been reported.[20]

Reinduction or Rescue Therapy

Ultimately, most dogs and cats with LSA successfully treated with chemotherapy relapse. This often represents a recrudescence of the tumor in a more drug-resistant form. Evidence suggests that recurrent LSA in dogs is more likely to express the gene encoding the P-glycoprotein transmembrane drug pump that is often associated with multiple drug resistance.[39-41] At the first recurrence of LSA, it is recommended that reinduction first be attempted by repeating of the induction protocol that was initially successful. In general, the likelihood of a response and the length of the response are half those seen with the initial therapy; however, a subset of animals will enjoy long-term reinductions. Recently it was shown that dogs that reached the observation phase using a no-maintenance protocol had a very high likelihood of a second response to the identical protocol.[13]

If reinduction fails or if the patient does not respond to the initial induction, so-called rescue agents or rescue protocols can be utilized. These drugs or drug combinations typically are not found in the standard CHOP protocol and are withheld for use in drug-resistant cases. A number of rescue protocols have been reported in the veterinary literature and have previously been reviewed.[46] The most common protocols used in dogs include single agent use or combination use of Actinomycin-D, mitoxantrone, lomustine (CCNU), DOX (if DOX was not part of the original induction protocol), DOX/dacarbazine combination, D-MAC (*D*, dexamethasone; *M*, melphalan; *A*, Actinomycin-D; C, cytosine arabinoside) and MOPP (*M*, methclorethamine; O, Oncovin; *P*, procarbazine; *P*, prednisone). Mitoxantrone, DOX, and MOPP have also been advocated in cats with resistant relapse. In general, overall rescue response rates of 25% to 50% are reported; however, these responses are usually not durable. Median response durations of 1.5 to 2 months are the norm. A small subset of animals will enjoy longer remission durations.

Therapy for Extranodal Lymphoma

If extranodal involvement is part of a more generalized or multicentric disease process, the systemic therapies previously discussed should be instituted. Conversely, if the extranodal site is solitary and not part of a multicentric presentation, local therapy may be performed without institution of systemic chemotherapy. In these latter cases, strict adherence to staging diagnostics, including bone marrow evaluation and radiographic/ultrasonographic imaging of the thorax and

Table • 181-5

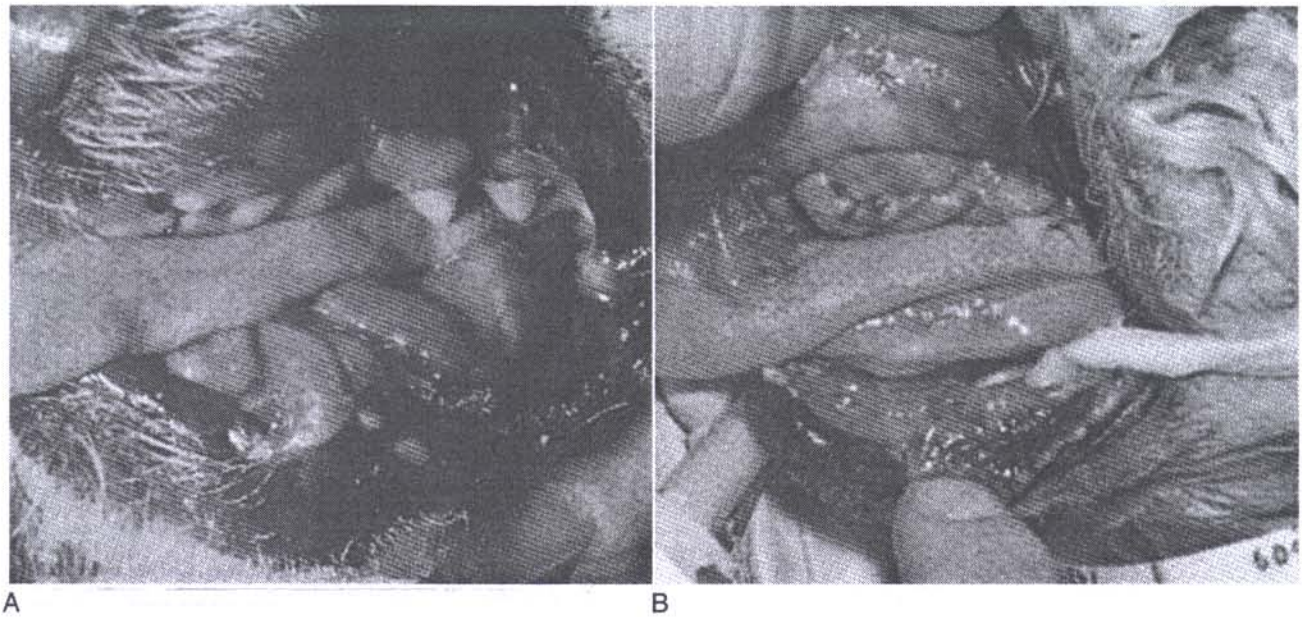
University of Wisconsin–Madison Combination Chemotherapy Protocol for Cats With Lymphoma

TREATMENT WEEK	DRUG, DOSAGE, AND ROUTE	TREATMENT WEEK	DRUG, DOSAGE, AND ROUTE
1	Vincristine: 0.5-0.7 mg/m² IV L-asparaginase: 400 U/kg SC Prednisone: 2 mg/kg PO	11	Vincristine: 0.5-0.7 mg/m² IV
2	Cyclophosphamide: 200 mg/m² IV Prednisone: 2 mg/kg, PO	13†	Cyclophosphamide: 200 mg/m² IV
3	Vincristine: 0.5-0.7 mg/m² IV Prednisone: 1 mg/kg PO	15	Vincristine: 0.5-0.7 mg/m² IV
4	Doxorubicin: 25 mg/m² IV Prednisone: 1 mg/kg, PO*	17	Doxorubicin: 25 mg/m² IV
6	Vincristine: 0.5-0.7 mg/m² IV	19	Vincristine: 0.5-0.7 mg/m² IV
7†	Cyclophosphamide: 200 mg/m² IV	21†	Cyclophosphamide: 200 mg/m² IV
8	Vincristine: 0.5-0.7 mg/m² IV	23	Vincristine: 0.5-0.7 mg/m² IV
9‡	Doxorubicin: 25 mg/m² IV	25§	Doxorubicin: 25 mg/m² IV

*Prednisone (1 mg/kg, PO) is continued every other day from this point on.
†If renal or CNS lymphoma is present, substitute cytosine arabinoside (600 mg/m² SC bid over 2 days) at these treatments.
‡If the patient is in complete remission at week 9, continue to week 11.
§If the patient is in complete remission at week 25, therapy is discontinued and the cat is rechecked monthly for recurrence.
NOTE: A CBC should be performed before each chemotherapy treatment. If the neutrophil count is less than 2000 cells/μL, the clinician should wait 5 to 7 days and then repeat the CBC; the drug is administered if the neutrophil count has risen above the 2000 cell/μL cutoff.

abdomen, are warranted to ensure that the process is localized. If the disease is confined, local surgery and/or radiotherapy is often effective (Figure 181-5). Clients should be informed that systemic LSA is likely to occur months to years later, and a regular recheck schedule should be instituted. It is the authors' opinion that systemic therapy should be withheld until systemic disease has been documented.

In cases in which CNS involvement is part of a more generalized process, penetration by chemotherapeutic drugs through the blood-brain barrier (BBB) may be a concern, and additional therapies are recommended. In standard CHOP protocols, only prednisone consistently penetrates the BBB. The addition of cytosine arabinoside, which achieves therapeutic CSF levels, to a CHOP-based protocol is recommended in such cases. Radiotherapy can also be effective, directed either to the entire neural axis (multifocal CNS lymphosarcoma) or to specific CNS locations (solitary central or spinal LSA). Cytoreductive surgery has been attempted in a



A B

Figure 181-5 A, Solitary gingival lymphoma in a dog staged negative for systemic involvement. B, The same dog 6 months after external beam radiation therapy (48 Gy total dose). A complete response and long-term survival were achieved.

small number of cases of extradural LSA in both cats and dogs, with mixed results.[44-46]

Cutaneous LSA in solitary sites has been effectively treated with local surgery or radiotherapy, but the likelihood of ultimate systemic involvement is high. Multiple cutaneous lesions are more commonly encountered (see Figure 181-2), and systemic therapy is necessary. In general, cutaneous LSA tends to be less responsive to chemotherapy than multicentric LSA, and clinical signs can wax and wane considerably over time. Responses have been reported with oral cis-retinoic acid therapy (Accutane®, 1 to 3 mg/kg given orally twice a day), Doxil® (a liposome encapsulated form of DOX), L-asparaginase, dacarbazine, lomustine, topical nitrogen mustard, and standard CHOP-based protocols.[57-60] Response rates are approximately 40% to 50%, and long-term survival is uncommon.

Prognosis

Prognostic Factors in Dogs

A list of factors known or suspected to affect remission rates and/or remission and survival durations in dogs with LSA is presented in Table 181-6. Age and breed do not affect the duration of remission or survival, and most studies fail to correlate the clinical stage to the prognosis except in dogs with marked stage V disease; that is, if bone marrow is heavily infiltrated, if overt leukemia is present, or if peripheral cytopenias exist secondary to myelophthisis. The two factors that most consistently correlate with the prognosis in dogs with LSA are the immunophenotype and the WHO substage.[9-14,16,29] Many reports have confirmed that dogs with CD3 immunoreactive tumors (i.e., T cell derived) have significantly shorter remission and survival durations (Figure 181-6). Similarly, dogs presenting with substage b disease (i.e., clinically ill) do poorly compared with dogs with substage a disease (Figure 181-7).

Other factors reported to correlate with the prognosis are less consistent; that is, they are not found to correlate in all studies, are preliminary reports, or contradictory reports exist in the literature. Some correlate after univariate analysis; however, when scrutinized by multivariate analysis (in which all factors are considered together), they are no longer significant. An example is the presence of hypercalcemia. In several reports, the presence of hypercalcemia is associated with a poor prognosis; however, if multivariate analysis is performed, hypercalcemia is no longer predictive, primarily because dogs with hypercalcemia are more likely to have T cell–derived LSA, which is a much stronger prognostic factor.

Prognostic Factors in Cats

Unlike in the dog, CD3 immunoreactivity has not been established as a negative prognostic factor in the cat.[17] This may reflect the wider variations in frequency of the different anatomic forms of LSA encountered in cats and the difficulty of distinguishing differences. Factors most strongly associated with a more positive prognosis in cats appear to be complete response to therapy (which unfortunately cannot be determined prior to treatment), negative FeLV status, early clinical stage, substage a disease, and the addition of DOX to the treatment protocol.[17,19,52,54,61] Early reports may contradict more recent studies, partly because FeLV associated LSA is declining, and early literature may not equate to more recent populations studied.[19] In general, FeLV-negative cats that achieve a complete response on CHOP-based protocols have a high likelihood of long-term survival, with approximately 35% alive at 1.5 years after diagnosis. Cats with nasal LSA, overall, have the best prognosis, because local radiotherapy (or chemotherapy, if radiotherapy is not available) results in excellent control, with median survival times approaching 1.5 years.

The Future of Lymphoma Therapy

Based on the similarity of results achieved using the many and varied combination chemotherapy protocols, it is unlikely that currently available chemotherapeutics will significantly improve the outcome in dogs and cats with LSA. All combination protocols reported to date stop short of the same 10- to 12-month median survival "brick wall." Advances in remission and survival durations await the development of new agents

Table • 181-6

Factors Known or Suspected to Affect the Prognosis in Dogs With Lymphoma

FACTOR	STRENGTH OF ASSOCIATION	COMMENTS
World Health Organization (WHO) clinical stage	Weak	This factor is likely predictive of the outcome only in stage V disease with marked marrow involvement.[16]
WHO substage	Strong	Dogs with substage b disease have shorter remission and survival durations.[9,10,11,13,14]
Immunophenotype	Strong	Dogs with T-cell lymphoma have shorter remission and survival durations than dogs with B-cell tumors.[9,14,16,19,29]
Hypercalcemia	Moderate	Poorer prognosis is not independent; rather, it is more likely due to T-cell association.[10,11]
Prolonged steroid pretreatment	Moderate	Most studies show previous steroid use shortens response durations.[9,10,29,113]
Sex	Weak	Some studies report that males have shorter remission and survival durations; other reports are contradictory.[9,35]
Proliferation rate	Weak	Reports are contradictory.[25,29]
Cranial mediastinal lymphadenomegaly	Moderate to strong	Large compilation of cases shows association with shorter remission and survival durations; other reports are contradictory.[16]
Histologic grade	Moderate	Low-grade tumors are less likely to respond to chemotherapy; however, patients may live longer despite this.[40,41]
P-glycoprotein expression	Moderate	This factor is associated with poor response rates and shorter remission and survival durations.

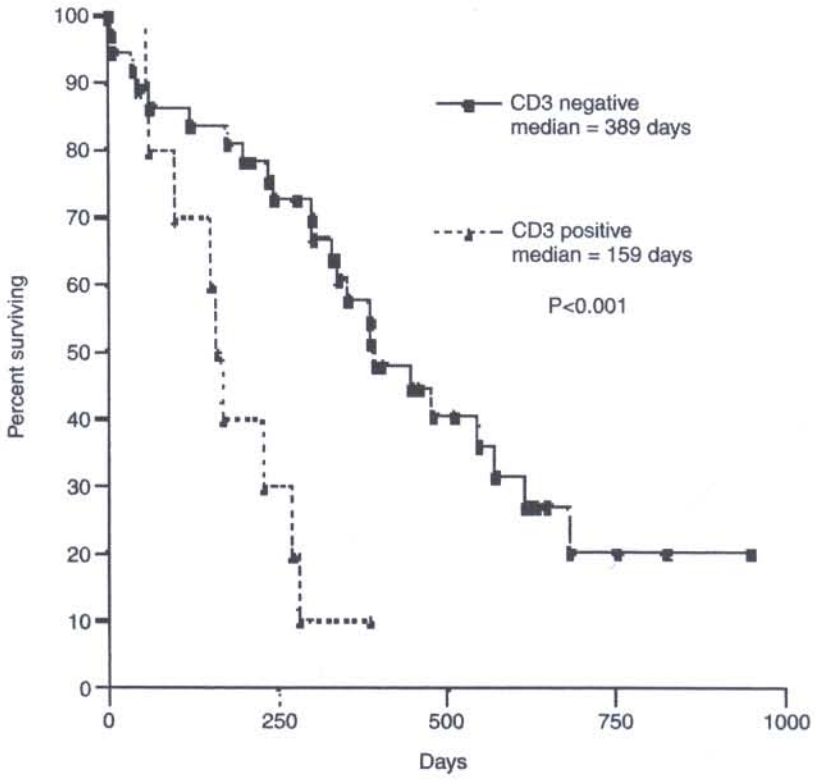


Figure 181-6 Kaplan-Meier survival duration estimates for a group of 55 dogs with lymphoma treated with an identical CHOP-based combination chemotherapy protocol at the University of Wisconsin. Dogs with CD3 immunoreactive (T-cell) lymphoma had significantly shorter survival durations.

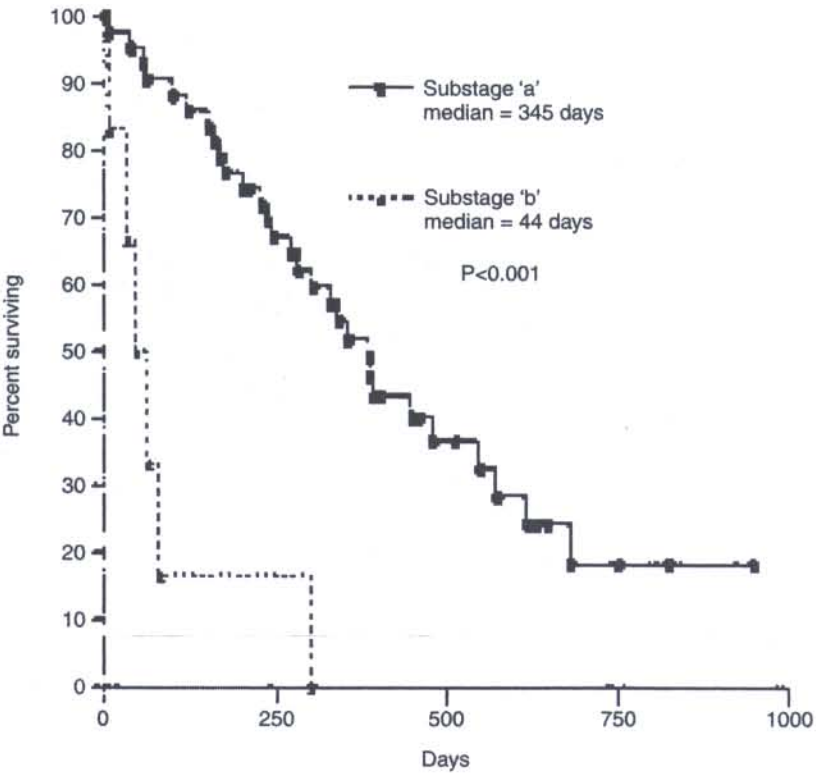


Figure 181-7 Kaplan-Meier survival duration estimates for a group of 55 dogs with lymphoma treated with an identical CHOP-based combination chemotherapy protocol at the University of Wisconsin. Dogs with substage b disease (i.e., those that were clinically ill) had significantly shorter survival durations.

or novel treatment modalities. Mechanisms of avoiding or abrogating multidrug resistance, enhancing tumor apoptosis (programmed cell death), utilization of chemotherapy/radiotherapy combinations, and novel immunomodulatory therapies (e.g., antibodies, vaccination strategies) are all active areas of investigation in both human and veterinary oncology. As practitioners who experience both the gratification that comes with high initial response rates and the frustration of equally high relapse rates, we eagerly await the advancement of these treatment modalities.

LYMPHOID LEUKEMIA

Leukemia is defined as a proliferation of neoplastic cells in the bone marrow. An important distinction is that by definition, the malignant cells may or may not be present in the peripheral blood circulation. Categorization of lymphoid leukemia into acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL) is important from a diagnostic, prognostic, and therapeutic standpoint (Figure 181-8). Both forms are relatively rare in companion animals.[62-66]

Acute Lymphoblastic Leukemia

ALL is characterized by proliferations of morphologically immature lymphoblasts in the bone marrow or peripheral blood. ALL may be confused with multicentric LSA in dogs that also have advanced stage V disease (i.e., secondary bone marrow infiltration). However, the primary component of ALL is leukemia. The clinical course is rapid, progressive, and poorly responsive to therapy.[62,64]

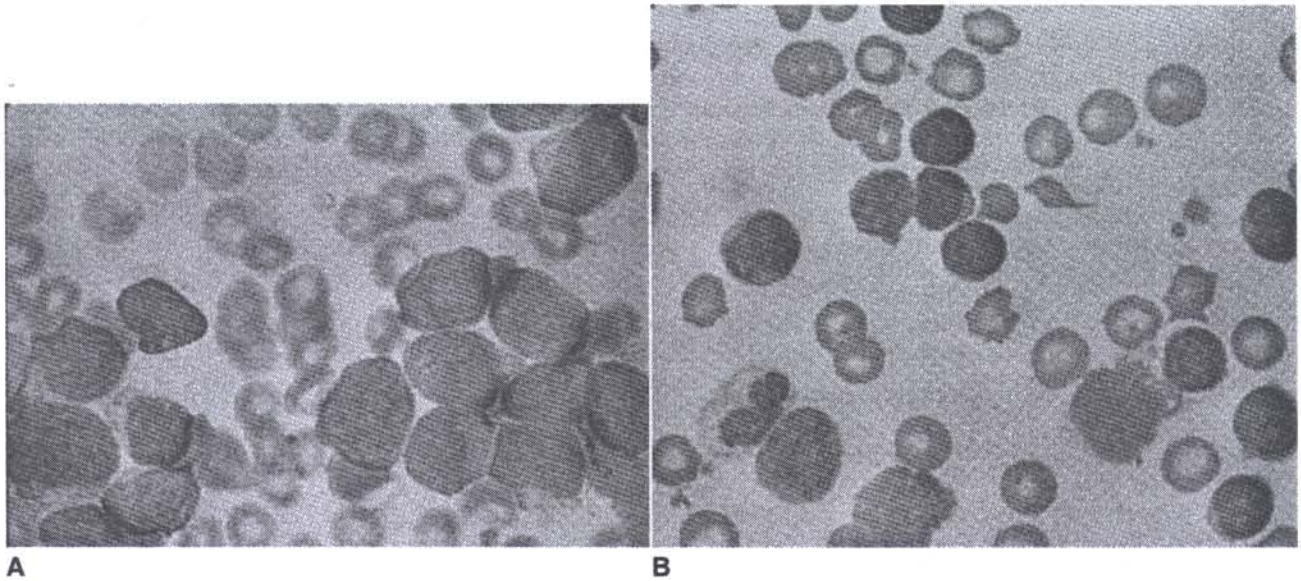
No breed or sex predilection exists for dogs with ALL. Middle-aged to older dogs are typically affected. Cats with ALL are usually younger and are often FeLV antigenemic.[66] Presentations are nonspecific and commonly include lethargy, weight loss, intermittent pyrexia, hepatosplenomegaly, and nonspecific abdominal pain. Neurologic signs, both central and peripheral, have been reported. The majority of affected animals are anemic, and varying degrees of thrombocytopenia and leukopenia are commonly present.

The diagnosis is confirmed by documentation of marked lymphoblast proliferation in the bone marrow or peripheral blood. Bone marrow aspirate or core biopsy and a complete blood count are usually all that are required for diagnosis. Aspiration cytology of lymph node and involved organs and conformation of retroviral status in cats may be contributory. The presence of 30% or more lymphoblasts in the bone marrow is considered diagnostic. Approximately 10% of cases are classified as "aleukemic" leukemia because bone marrow infiltration is present but peripherally circulating lymphoblasts are absent. ALL may be further differentiated clinically from stage V multicentric LSA by its more rapid progression, lack of significant lymphadenopathy in approximately 50% of cases, poor chemoresponsiveness, and short survival times.

The prognosis is generally poor for dogs and cats with ALL.[62,64-66] Combination chemotherapy protocols designed to treat LSA result in remission in approximately 25% of cases, but remission durations are usually quite short, and survival times of more then a few months are rare. A short-term response to low-dose cytosine arabinoside (10 mg/m^2 given subcutaneously twice a day) has been reported in a cat.[67]

Chronic Lymphocytic Leukemia

CLL is characterized by the proliferation of phenotypically mature lymphocytes rather than lymphoblasts. Interestingly, recent immunophenotypic and clonotypic analysis has shown that the majority of CLL cases in dogs arise from CD8+ T cells, many of which show a large granular lymphocytic morphology.[68] CLL is reported primarily in older dogs and cats. The clinical presentation is nonspecific and may include lethargy, organomegaly, pyrexia, polyuria/polydipsia, hemorrhage (from thrombocytopenia), intermittent lameness, and collapse.[63] Most dogs present with mild to moderate lymphadenopathy, splenomegaly, and pale mucous membranes. However, asymptomatic lymphocytosis may be detected on routine geriatric or preanesthetic screening in some animals.



A B

Figure 181-8 A, Peripheral blood smear (Wright-Giemsa stain, ×1000) from a dog with acute lymphoblastic leukemia (ALL). Note the morphologically immature lymphoblasts characteristic of ALL. B, Peripheral blood smear (Wright-Giemsa stain, ×1000) of a dog with chronic lymphocytic leukemia (CLL). Note the morphologically mature lymphocytes characteristic of CLL. (Courtesy Dr. Karen Young, University of Wisconsin—Madison.)

A normocytic, normochromic, nonregenerative anemia usually accompanies a marked mature peripheral lymphocytosis, which may range from 10,000 to 300,000/μL or more. Thrombocytopenia and neutropenia may be present as a result of myelophthisis. Although a minority of cases present with hyperglobulinemia, after immunoelectrophoresis, approximately half have evidence of a monoclonal gammopathy, often with Bence Jones proteinuria. No association with FeLV infection has been documented in the cat. Unlike ALL, CLL can have a protracted clinical course and is usually initially responsive to chemotherapy.[63] Treatment is not instituted unless significant clinical signs, organomegaly, or peripheral cytopenias (anemia, neutropenia, thrombocytopenia) are present that affect or threaten the animal's quality of life. Cases of CLL have been followed for many months without the necessity for therapy. If therapy is indicated, chlorambucil (*dogs:* 0.2 mg/kg given orally daily for 10 days, then 0.1 mg/kg/day; *cats:* 2 mg/cat given orally every other day) is combined with prednisone (2 mg/kg given orally daily). The dosage is adjusted based on the response. Approximately 75% of animals respond and enjoy a normal quality of life, with a median survival time of approximately 1 year. Although the prognosis is good in the short term, eventually CLL becomes resistant to therapy or progresses to ALL. When this happens, lymphoblasts replace mature lymphocytes as the abnormally proliferating population, and survival is short.

NONLYMPHOID LEUKEMIAS AND MYELOPROLIFERATIVE DISORDERS

Myeloproliferative disorders (MPDs) are defined as a group of nonlymphoid bone marrow cell disorders in which proliferation of one, several, or all of the marrow cell lines occurs. The disorders may represent preneoplastic or neoplastic conditions that may have a benign or malignant course. These are rare conditions in companion animals. With few exceptions (see Polycythemia Vera [Primary Erythrocytosis], p. 743), the veterinary literature on MPDs is sparse at best and is composed almost entirely of single case reports. Our experience with MPDs, therefore, is almost exclusively anecdotal, and specific characterizations and therapeutic recommendations are lacking.

Classification

In general, MPDs are classified first on the basis of the derivation of the cell in question and second on the degree of cellular differentiation. If the proliferating cell population is mature or microscopically typical of a well-differentiated bone marrow cell line, the disorder is classified as chronic; if an immature or poorly differentiated cell line is present, the disease is classified as acute. Table 181-7 lists the MPDs reported in the veterinary literature. Because pluripotent bone marrow stem cells are involved, one MPD may evolve into another, and more often than not, more than one cell line is involved in the same disorder.

Clinical Presentation

Animals with a chronic MPD may have no clinical signs until organ involvement or bone marrow myelophthisis results in systemic disease. Clinical signs in dogs with late-stage chronic MPD or acute MPD are generally nonspecific and can include organomegaly, pallor, sepsis, and hemorrhage from thrombocytopenia. Most MPDs have been associated with FeLV infection in cats.

Diagnosis

The diagnosis of MPD is based on demonstration of the proliferating cell line in the absence of non-neoplastic diseases associated with bone marrow hyperplasia or hypoplasia. Differential diagnoses therefore include chronic inflammatory diseases (e.g., ehrlichiosis), multicentric LSA, estrogen toxicity, lead poisoning and, in the case of essential or primary thrombocytosis, iron deficiency. Because many of the acute MPDs are poorly differentiated and/or represent combinations of cell lineages, light microscopic morphology often is insufficient to determine the specific cellular derivation. Histochemistry, immunohistochemistry, and flow cytometric analysis are ultimately necessary in many instances for precise classification. Several private and academic laboratories perform these analyses. A complete listing of available tests is beyond the scope of the present chapter; these have been reviewed elsewhere.[95,96]

Therapy

The acute MPDs are generally poorly responsive to single agent or combination chemotherapy protocols, therefore their prognosis is grave. Several agents and combinations have been tried,

Table • 181-7

Myeloproliferative Disorders Reported in Dogs and Cats

CLASSIFICATION	CELL LINEAGE	SELECTED REFERENCES
Acute Myeloproliferative Disorders		
Acute myelogenous leukemia (AML)	Myeloblasts	64-66
Acute myelomonocytic leukemia (AMML)	Myeloblasts/monoblasts	64-66, 69-71
Acute monocytic leukemia (AmoL)	Monoblasts	64-66, 72
Acute megakaryoblastic leukemia (AmkL)	Megakaryoblasts	73-79
Erythroleukemia	Erythroblasts	66, 80
Chronic Myeloproliferative Disorders		
Chronic myelogenous leukemia (CML)	Neutrophils, late precursors	82-84
Primary thrombocythemia	Platelets	84, 85
Basophilic leukemia	Basophils and precursors	86, 87
Eosinophilic leukemia	Eosinophils and precursors	88, 89
Polycythemia vera	Erythrocytes	84, 90-94

including DOX, cytosine arabinoside, 6-thioguanine, and CHOP-based protocols.[64-66,76] Response rates are low, and overall survival times are generally short. If chemotherapy is pursued, aggressive supportive therapy is usually necessary and may include whole blood or blood-component therapy to address cytopenias secondary to myelophthisis, antibiotic support, and aggressive fluid therapy.

Chronic MPDs carry a guarded prognosis; however, initial durable responses to therapy are more likely than with an acute MPD. Therapy is not required until clinical signs or significant peripheral cytopenia develops. Hydroxyurea has been used successfully in the treatment of several types of chronic MPD, particularly polycythemia vera (see below), essential thrombocythemia, basophilic leukemia, and chronic myelogenous leukemia (CML).[81,85-87,97,98] In dogs with CML, hydroxyurea is administered at an initial dosage of 20 to 25 mg/kg given orally twice daily. This dosage is continued until the leukocyte count drops to less than 20,000 cells/μL, at which time the dosage is reduced to 10 to 15 mg/kg daily or switched to 50 mg/kg given orally once every 2 to 3 weeks. A common side effect of hydroxyurea therapy in dogs is onychomadesis (sloughing of the claw or toenail). In dogs that respond to hydroxyurea therapy, survival times of many months have been reported. Ultimately, many of the chronic MPDs shift into a terminal phase or *blast crisis*, in which a fatal acute leukemic phase is observed.

Polycythemia Vera (Primary Erythrocytosis)

Polycythemia vera (PV) is defined as an abnormal proliferation of erythroid precursors in the bone marrow; this occurs independent of erythropoietin (EP), and the cells follow a normal, orderly pattern of maturation. The result is an abnormally elevated packed cell volume, erythroid count, and blood hemoglobin level. PV must be differentiated from so-called relative polycythemia or secondary polycythemia. Relative polycythemia is a result of hemoconcentration secondary to severe dehydration, body fluid shifts, or acute splenic contraction in dogs. It is readily corrected with fluid-based therapies. Secondary polycythemia is defined as EP-mediated erythrocytosis. Conditions associated with secondary polycythemia include right-to-left cardiac shunts, congestive heart failure, severe chronic pulmonary disease, some forms of renal disease, and neoplasms that secrete EP or EP-like substances.

Middle-aged dogs and cats are typically affected.[84,90-94] Clinical signs and physical findings associated with PV include hyperemic mucous membranes, injected scleral and retinal vessels, weakness, exercise intolerance, frank hemorrhage (epistaxis, hematuria, melena), neurologic signs (dementia, seizures, paralysis, ataxia), and occasional splenomegaly. Cardiac or renal compromise may also be present. The majority of signs reported occur secondary to hyperviscosity syndrome, discussed at length in the plasma cell tumor portion of this chapter.

The diagnosis is made by documentation of significant erythrocytosis (60% to 75% hematocrit) with normal to decreased serum EP levels and the absence of conditions associated with relative or secondary polycythemia. Thoracic and abdominal radiographs, abdominal ultrasound, arterial blood gas determinations, bone marrow aspirate testing, and serum EP levels should be procured to rule out differentials. Erythroid hyperplasia with relatively normal patterns of maturation is found on bone marrow cytology. Radioactive chromium determinations of red blood cell mass may contribute to the diagnosis.

Therapy for PV involves reduction of the red blood cell mass and suppression of erythroid production in the bone marrow. Reduction of the red blood cell mass can easily be achieved by phlebotomy (15 to 20 cc/kg body weight) and reinfusion of the patient's plasma after removal of the red blood cells.[91-93] Several techniques can be used to suppress erythrocyte production, including the use of radioactive phosphorous (^{32}P) or, more commonly available, chemotherapy.[84,97] The antineoplastic drug of choice is hydroxyurea, although alkylating agents such as melphalan, cyclophosphamide, and busulfan have also been used, with mixed results. Hydroxyurea therapy is instituted at a dosage of 20 to 25 mg/kg given orally twice a day in dogs (10 to 15 mg/kg in cats). Once the hematocrit is below 60%, hydroxyurea is given every other day. Complete blood counts must be carefully monitored for potential myelosuppression of other cell lineages. Most cases of PV respond to therapy, and survival times of a year or longer are the norm. Progression to leukemia is reported in some humans with the disease.

PLASMA CELL NEOPLASMS

Plasma cell neoplasms are defined as neoplastic proliferations of cells of the B-lymphocyte plasma cell lineage. This population is believed in most instances to be monoclonal (i.e., derived from a single cell), because it typically produces homogenous immunoglobulin. Plasma cell neoplasms include multiple myeloma, IgM (Waldenstrom's) macroglobulinemia, and solitary plasmacytoma (including solitary osseous plasmacytoma and extramedullary plasmacytoma). Multiple myeloma is the most important plasma cell neoplasm based on incidence and severity.

Multiple Myeloma

Multiple myeloma (MM) is responsible for approximately 8% of all canine hematopoietic tumors.[99] The true incidence of MM in the cat is unknown; however, it is much less common than in the dog.[100] In MM, malignant plasma cells produce an overabundance of a single type, or component, of immunoglobulin, which is referred to as the M-component. Rarely, biclonal immunoglobulin production has been reported.[101] The M-component may represent any class of immunoglobulin or only a portion of the molecule, such as the light-chain (Bence Jones protein) or heavy chain (heavy chain disease) of the molecule.

Etiology

The etiology of MM is for the most part unknown. Genetic predispositions, viral infections, chronic immune stimulation, and exposure to carcinogens have all been suggested as contributing factors.[102-104] MM has not been associated with either FeLV or FIV infection.

Pathophysiology

A wide array of pathologic abnormalities and related clinical syndromes can occur as a result of tumor infiltration of various organ systems, the presence of high levels of circulating M-component, or a combination thereof.

Hyperviscosity syndrome (HVS) represents one or a constellation of clinicopathologic abnormalities resulting from greatly increased serum viscosity. The magnitude of HVS is related to the type, size, shape, and concentration of the M-component in the blood. It is more common with IgM macroglobulinemias because of their high molecular weight; however, IgA- and IgG-associated HVS can occur, albeit less frequently.[99,105,106] High serum viscosity occurs in approximately 20% of dogs with MM and can result in bleeding diathesis, neurologic signs (e.g., dementia, depression, seizure activity, coma), ophthalmic abnormalities (e.g., dilated and tortuous retinal vessels, retinal hemorrhage, retinal detachment), and increased cardiac workload with the potential for subsequent development of cardiomyopathy or congestive failure.[99,105-110] These consequences are thought to be a result of sludging of blood in small vessels, ineffective delivery of

oxygen and nutrients, and coagulation abnormalities. HVS is less common in cats but has been reported in association with IgG-, IgA-, and IgM-secreting tumors.[106,111-114]

Renal disease is present in 30% to 50% of dogs with MM.[99] This can occur as a result of Bence Jones (light chain) proteinuria, tumor infiltration into renal tissue, hypercalcemia, amyloidosis, diminished perfusion secondary to hyperviscosity syndrome, dehydration, or ascending urinary tract infection. Bence Jones proteinuria (BJP) occurs in approximately 25% to 40% of dogs with MM; the true incidence of BJP in cats is not well established.

Hypercalcemia occurs in 15% to 20% of dogs with MM and is thought to result primarily from the production of osteoclast-activating factor or other cytokines (e.g., interleukin-6) by neoplastic cells.[99,106] In two dogs with MM and hypercalcemia, serum elevations in circulating N-terminal parathyroid hormone–related protein were noted, although its relative contribution to hypercalcemia is unknown.[115] Hypercalcemia may be exacerbated by associated renal disease. Hypercalcemia is rare in cats with MM.[116,117]

Susceptibility to infection and immunodeficiency are often the ultimate causes of death in animals with MM. Normal immunoglobulin levels are usually severely depressed, and leukopenias may be present secondary to marrow infiltration (myelophthisis).

Variable cytopenias may be observed in association with MM. A normocytic, normochromic, nonregenerative anemia is encountered in approximately two thirds of dogs.[99,106] This can result from myelophthisis, blood loss from coagulation disorders, anemia of chronic disease, or increased erythrocyte destruction secondary to high serum viscosity. Similar factors lead to thrombocytopenia and leukopenia in 25% to 30% of affected dogs.

Bleeding diathesis can result from one or a combination of events. M-components may interfere with coagulation in a number of ways, including inhibition of platelet aggregation and the release of platelet factor-3, adsorption of minor clotting proteins, generation of abnormal fibrin polymerization, production of heparin-like anticoagulants, and a functional decrease in calcium.[118]

Cardiac disease, if present, is usually a result of excessive cardiac workload and myocardial hypoxia secondary to hyperviscosity. Myocardial infiltration with amyloid and anemia may be complicating factors.

Clinical Presentation and Signs

MM occurs in aged dogs and cats, and no breed or sex predilection has been consistently reported. Clinical signs are variable due to the wide range of pathologic effects possible and may be present up to one year prior to diagnosis.[99] The most common clinical signs in decreasing order of frequency are lethargy and weakness, lameness as a result of bone destruction, hemorrhage, polyuria/polydipsia, and neurologic deficits. Bleeding diathesis is usually represented by epistaxis and gingival bleeding. Central nervous system signs may include dementia, seizure activity, and deficiencies in midbrain or brain stem localizing reflexes secondary to HVS or extreme hypercalcemia. Signs reflective of transverse myelopathies secondary to vertebral column infiltration, pathologic fracture, or extradural mass compression can also occur.

In the cat, anorexia and weight loss are the most common clinical signs.[116,119,120] A history of chronic respiratory infections may be present. Skeletal lesions are uncommon in cats, but hepatosplenomegaly is more commonly seen due to organ infiltration.[116] Epistaxis, pleural and peritoneal hemorrhagic effusions, retinal hemorrhage, and central neurologic signs have been reported.[106,111-114,120] Polydipsia and polyuria can occur secondary to renal disease, and dehydration may develop. Hindlimb paresis secondary to osteolysis of lumbar vertebral bodies has been reported in a cat.[121]

Diagnosis

The diagnosis of multiple myeloma usually follows demonstration of bone marrow plasmacytosis and serum or urine myeloma proteins (M-component), as well as detection of osteolytic bone lesions (primarily in the dog). In the absence of osteolytic bone lesions, a diagnosis can be made if marrow plasmacytosis is associated with a progressive increase in the M-component.

All animals suspected of plasma cell tumors should receive a CBC, platelet count, serum biochemistry profile, and urinalysis. Particular attention is paid to renal function and serum calcium levels. Serum electrophoresis and immunoelectrophoresis are performed to detect a monoclonal spike (Figure 181-9) and to categorize the isotype of immunoglobulin involved. In the dog, the M-component is usually of the IgG or IgA class in nearly equal incidence.[99,106] If IgM constitutes the M-component, the term *macroglobulinemia* (i.e., Waldenstrom's macroglobulinemia) is used. Biclonal gammopathy has also

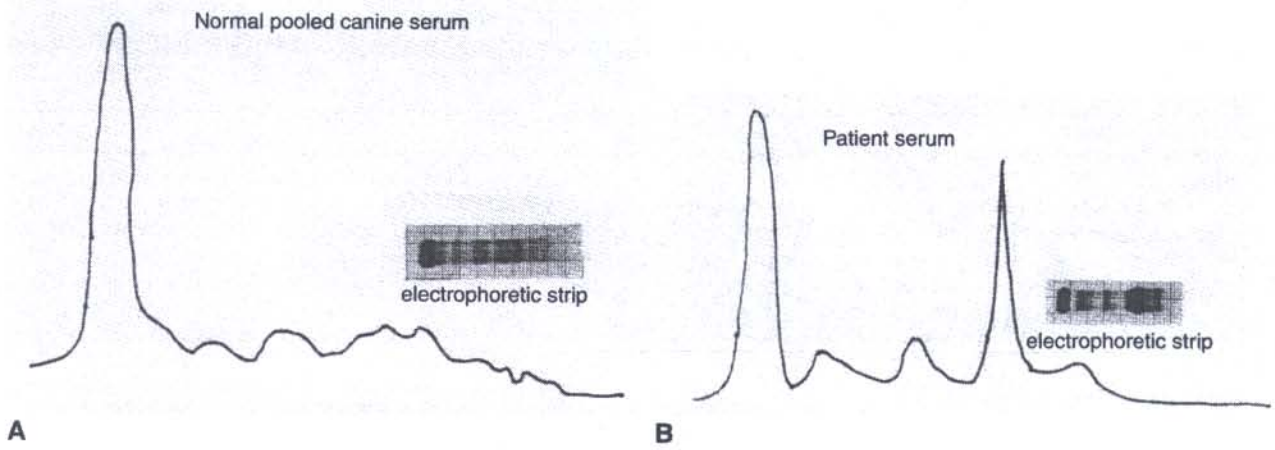


Figure 181-9 A, Serum protein electrophoresis from pooled normal dogs. Stained cellulose acetate electrophoretic strip with accompanying densitogram. B, Serum protein electrophoresis from a dog with multiple myeloma. Note the large M component spike (representing an IgA monoclonal gammopathy) in the gamma region.

been reported.[101,122] In the cat, MM is usually associated with IgG elevations; only a few cases of IgA or IgM gammopathies have been reported.[106,111-114,120,123] Occasionally, cryoglobulinemia has been reported in dogs and cats with MM.[106,124-126] Cryoglobulins are paraproteins that are insoluble at temperatures below 37° C and that require blood collection and clotting to be performed at 37° C before serum separation. If Bence Jones proteinuria is suspected, heat precipitation and electrophoresis of urine are necessary, because commercial urine dipstick methods are not capable of this determination. "Nonsecretory" varieties of multiple myeloma have been reported rarely in dogs.[127,128]

Definitive diagnosis usually requires a bone marrow aspirate or core biopsy. Normal marrow contains less than 5% plasma cells, whereas myelomatous marrow often greatly exceeds this level. Malignant plasma cells can have a varied microscopic appearance, ranging from that of normal plasma cells to early stages of differentiation.

Skeletal survey radiographs are recommended to determine the presence and extent of osteolytic lesions, which may have diagnostic, prognostic, and therapeutic implications. Rarely, biopsy of osteolytic lesions (i.e., Jamshidi core biopsy) is necessary for diagnosis. Bone lesions may be isolated, discrete lesions (including pathologic fractures) or diffuse osteopenias (Figure 181-10). Approximately 25% to 30% of dogs with MM have evidence of bony lysis or diffuse osteoporosis.[99,106] Bones engaged in active hematopoiesis are more commonly affected (e.g., vertebrae, ribs, pelvis, skull, and proximal long bones). Skeletal lesions are rare in cats with MM and in dogs with IgM (Waldenstrom's) macroglobulinemia.[106,119,120] In macroglobulinemia, malignant cells often infiltrate the spleen, liver, and lymphoid tissue rather than bone.[124,129]

If clinical evidence of hemorrhage is present, coagulation assessment (e.g., platelet count, prothrombin time [PT], and partial thromboplastin time [PTT]) and serum viscosity measurements should be undertaken. Nearly half of these patients have abnormal PT and PTT values.

All animals should undergo a careful funduscopic examination; abnormalities may include retinal hemorrhage, venous dilatation with sacculation and tortuosity, retinal detachment, and blindness.

Differential Diagnosis

Disease syndromes other than MM can be associated with monoclonal gammopathies and should be considered in any list of differential diagnoses. These disorders include other lymphoid tumors (LSA, CLL, and ALL), chronic infections (e.g., ehrlichiosis, leishmaniasis, feline infectious peritonitis [FIP]), and monoclonal gammopathy of unknown significance (MGUS). MGUS (i.e., benign, essential, or idiopathic monoclonal gammopathy) is a benign monoclonal gammopathy that is not associated with osteolysis, bone marrow infiltration, or Bence Jones proteinuria.[130,131]

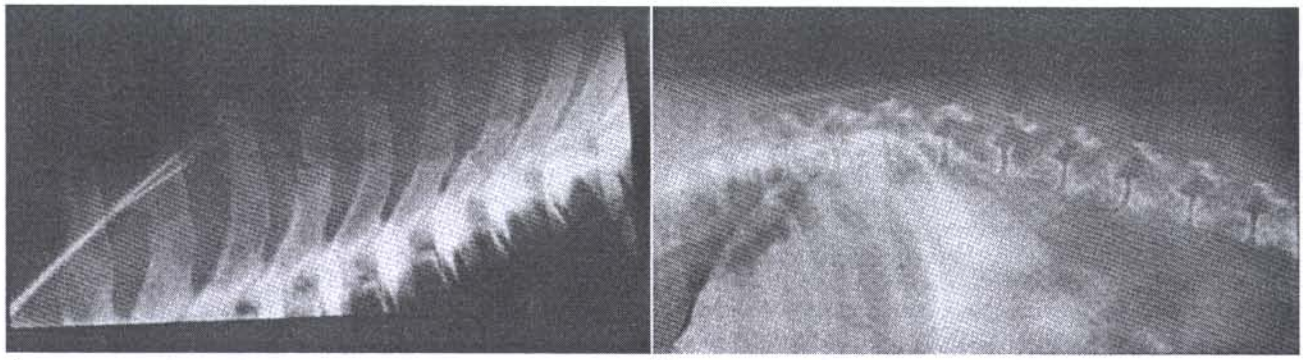
Treatment

Initial Therapy of Multiple Myeloma

Therapy should be directed at both the tumor cell mass and its secondary systemic effects. Chemotherapy is highly effective at reducing the myeloma cell burden, relieving bone pain, initiating skeletal healing, and reducing levels of serum immunoglobulins.[99,106] It significantly extends both the quality and length of most patients' lives. Complete elimination of neoplastic myeloma cells is rarely achieved, however, and although MM remains a gratifying disease to treat, eventual relapse is to be expected.

Melphalan, an alkylating agent, in combination with prednisone, is the treatment of choice. In the dog, the initial starting dose for melphalan is 0.1 mg/kg given orally once daily for 10 days; it is then reduced to 0.05 mg/kg given once daily continuously. Prednisone is initiated at a dosage of 0.5 mg/kg given orally once daily for 10 days, then reduced to 0.5 mg/kg every other day. Therapy continues until clinical relapse occurs or myelosuppression necessitates a dose reduction. The most clinically significant toxicity of melphalan is myelosuppression, particularly thrombocytopenia. Complete blood counts, including numeric platelet counts, should be performed biweekly for 2 months after initiation of therapy and monthly thereafter. If significant myelosuppression occurs, reduction of the dosage or the treatment frequency may be necessary. An alternative pulse dosing regimen for melphalan (7 mg/m^2 given orally daily for 5 consecutive days every 3 weeks) has been used successfully at the University of Wisconsin in a small number of cases in which myelosuppression limited more conventional continuous low-dose therapy. Melphalan and prednisone therapy can also be used in cats with multiple myeloma, although the results are generally less rewarding.

Cyclophosphamide can be used as an alternate alkylating agent, sometimes in combination with melphalan; however, there is no evidence to suggest that it is superior. In the authors' practice, cyclophosphamide is limited to cases presenting with severe hypercalcemia or widespread systemic involvement, in which a faster acting alkylating agent may



A B

Figure 181-10 A, Lateral thoracic radiographs of a dog showing multiple expansile, lytic lesions in the axial skeleton, most apparent in the spinous processes of the vertebrae, as can be seen with multiple myeloma. B, Lateral vertebral radiographs of a dog with multiple myeloma. Note the overall decreased opacity of the lumbar vertebrae secondary to diffuse marrow involvement with tumor, which causes a loss of bone trabeculae and thinning of the cortices. (Courtesy Dr. Lisa Forrest, University of Wisconsin—Madison).

more quickly alleviate the systemic effects of the disease. Cyclophosphamide is administered at a dosage of 200 mg/m² given intravenously once at the same time oral melphalan therapy is started. Chlorambucil, another alkylating agent, has been used successfully for the treatment of IgM macroglobulinemia in dogs at an initial dosage of 0.2 mg/kg given orally once daily.[106]

Evaluation of Response to Therapy

Response is based on improvement in clinical signs, clinicopathologic parameters, and radiographic improvement of skeletal lesions. Subjective improvement in bone pain, lameness, lethargy, and anorexia should be evident within 3 to 4 weeks. Objective laboratory improvement, including a reduction in serum immunoglobulin levels or Bence Jones proteinuria, is usually noted within 3 to 6 weeks. Radiographic improvement in osteolytic bone lesions may take months, and resolution may only be partial.

As previously discussed, complete resolution of multiple myeloma rarely occurs, and a good response is defined as a reduction in measured M-component (i.e., immunoglobulins or Bence Jones proteins) to at least 50% of pretreatment values.[106] For routine follow-up, quantitation of serum immunoglobulins via radial immunodiffusion or measurement of urine Bence Jones proteins is performed monthly until a good response is noted and then every 2 to 3 months. Repeat bone marrow aspiration is performed if warranted.

Therapy Directed at Complications of Multiple Myeloma

Long-term control of complications, including hypercalcemia, hyperviscosity syndrome, bleeding diathesis, renal disease, immunosuppression, and pathologic skeletal fractures, depends on control of the tumor mass. However, therapy directed more specifically at these complications may be indicated in the short term.

If hypercalcemia is marked and significant clinical signs exist, standard therapies are indicated (see Chapter 237). Moderate hypercalcemia typically resolves within 2 to 3 days of initiation of melphalan/prednisone chemotherapy.

Hyperviscosity syndrome is best treated in the short term by plasmapheresis. Whole blood is collected from the patient and centrifuged to separate plasma from packed cells. Packed red cells are resuspended in normal saline and reinfused into the patient. Bleeding diathesis usually resolves along with HVS; however, platelet-rich plasma transfusions may be necessary with thrombocytopenia.

Renal impairment may necessitate aggressive fluid therapy. Careful attention to secondary urinary tract infections and appropriate antimicrobial therapy are indicated. Patients with MM can be thought of as "immunologic cripples," and prophylactic antibiotic therapy in dogs with multiple myeloma has been advocated by some.[106] In humans, however, prophylactic antibiotic use is not superior to diligent monitoring and aggressive antimicrobial management when indicated.[132] Cidal antimicrobials with low potential for nephrotoxicity are preferred.

Pathologic fractures of weight-bearing long bones and vertebrae, resulting in spinal cord compression, may require immediate intervention in conjunction with systemic chemotherapy. Orthopedic stabilization of fractures should be undertaken and may be followed with external beam radiotherapy. Recently, inhibition of osteoclast activity by bisphosphonate drugs has been shown to reduce the incidence and severity of skeletal complications of MM in humans.[133] This class of drugs may hold promise for use in dogs and cats in the future.

Rescue Therapy

At the time of relapse or in cases initially resistant to melphalan, rescue therapy may be attempted. The authors have had success with a combination of DOX (30 mg/m² given intravenously every 21 days), vincristine (0.7 mg/m² given intravenously on days 8 and 15 of the cycle), and prednisone (1 mg/kg given orally daily) administered in 21-day cycles. Although most dogs initially respond to a rescue protocol, the duration of response tends to be short, lasting only a few months. High-dose cyclophosphamide (300 mg/m² given intravenously every 7 days) has also been used as a rescue agent, with limited success. A durable rescue with liposome-encapsulated DOX has been reported in a dog with MM.[134] In humans, the antiangiogenic and anticytokine drug thalidomide is an active agent in chemotherapy-refractory MM.[135] To the authors' knowledge, thalidomide has not been evaluated in veterinary MM patients.

Prognosis

The prognosis for dogs with MM is good for initial control of the tumor and a return to good quality of life. In a group of 60 dogs with MM, 43% achieved complete remission (i.e., serum immunoglobulins normalized) and 49% achieved partial remission (i.e., immunoglobulins less than 50% of pretreatment values); only 8% did not respond to melphalan and prednisone chemotherapy.[99] Long-term survival is the norm, with a median of 540 days reported. Hypercalcemia, Bence Jones proteinuria, and extensive bony lysis are known negative prognostic factors in the dog. The long-term prognosis for dogs is poor, because recurrence is expected. Eventually, the tumor no longer responds to available chemotherapeutics, and death follows from renal failure, sepsis, or euthanasia for intractable bone or spinal pain.

The prognosis for MM in the cat is not as favorable as in the dog.[112,116,119,120] Although most cats transiently respond to melphalan/prednisone or cyclophosphamide-based protocols, responses are not durable, and most patients succumb within 2 to 3 months. One long-term feline survivor has been reported.[117]

In nine dogs with IgM macroglobulinemia, response to chlorambucil occurred in the majority, and a median survival time of 11 months was reported.[106]

SOLITARY PLASMACYTOMA

Solitary collections of monoclonal plasmacytic tumors can originate in bone or soft tissues and are referred to as *solitary osseous plasmacytoma (SOP)* and *extramedullary plasmacytoma (EMP)*, respectively. The majority of SOPs eventually progress to systemic MM.[128,136] Cutaneous EMP, including oral cavity EMP, is typically a benign disorder in dogs.[137] Conversely, the natural behavior of noncutaneous EMP appears to be much more aggressive. Gastrointestinal EMPs have been reported to involve the esophagus, stomach, and small and large intestine.[138-143] Metastasis to associated lymph nodes is common in these cases, although bone marrow involvement and monoclonal gammopathies are less commonly encountered. One report exists of subcutaneous EMP in a cat with IgG gammopathy; the EMP progressed to lymph node disease and distant metastasis.[144]

Clinical Signs

Clinical signs associated with solitary plasmacytomas relate to the location of involvement; in rare cases with high levels of M-component, HVS may occur. SOP usually is associated with pain and lameness if the appendicular skeleton is affected or with neurologic signs if vertebral bodies are involved. Cutaneous EMP usually has a benign course with no related clinical signs. Gastrointestinal EMP, however, typically presents with relatively nonspecific signs that may suggest alimentary involvement. One case of ataxia and seizure activity in a dog with EMP secondary to tumor-associated hypoglycemia has been reported.[145]

Diagnosis
The diagnosis of SOP and EMP requires tissue biopsy. It is important to thoroughly stage such cases of SOP and noncutaneous EMP with bone marrow aspirate, serum electrophoresis, and skeletal survey radiographs to ensure that disease is confined to a local site prior to initiation of therapy. In the case of poorly differentiated solitary plasmacytic tumors, immunohistochemical studies, directed at detecting immunoglobulin light and heavy chains and thioflavin-T, may be helpful in confirming a diagnosis.

Therapy
Animals with solitary plasma cell tumors may be treated with local therapy in the absence of systemic chemotherapy, provided thorough clinical staging does not reveal systemic involvement. Effective local control has been achieved with surgical excision or external beam radiotherapy, alone or in combination. Most dogs with noncutaneous SOP and EMP eventually develop systemic myeloma, and there exists controversy among veterinary oncologists as to whether systemic chemotherapy should be initiated at the time of local therapy. Systemic dissemination may not occur for many months to years beyond diagnosis in humans, and studies in humans reveal no benefit from initiation of systemic chemotherapy prior to the documentation of subsequent systemic involvement.[132]

Long-term follow-up of patients with solitary plasmacytoma is indicated to detect both recurrence of disease and systemic spread.

Prognosis
Dogs with cutaneous plasmacytomas are usually cured by means of surgical excision. Dogs with SOP or EMP of the alimentary tract treated by surgical excision (in combination with systemic chemotherapy once systemic disease is documented) enjoy long-term survival in the majority of cases.

CHAPTER • 182

Tumors of the Skin

Kenneth M. Rassnick

The skin is the most common site of occurrence for neoplasms in the dog and the second most common site in the cat. Subcutaneous and cutaneous tumors together account for at least one third of all canine tumors. Approximately 20% to 30% are histologically malignant.[1] Mast cell tumors, perianal adenomas, lipomas, histiocytomas, sebaceous gland adenomas, and papillomas are the most common histologic types of canine tumors.[1-4] Skin and subcutaneous tissues account for approximately one fourth of all tumors in the cat, and 50% to 65% are histologically malignant.[1,2,5] The histologic appearance of malignancy does not necessarily correlate with the tendency to metastasize. The most common skin tumors found in cats include basal cell tumors, mast cell tumors, squamous cell carcinoma, and fibrosarcoma.[2,5,6]

Tumors of the skin and subcutis can be broadly classified histologically according to their tissue of origin: epithelial, mesenchymal, round cell, or melanocytic (Box 182-1). Tumors can be further classified according to individual cell of origin as long as sufficient differentiation is present. This chapter focuses primarily on tumors of epithelial origin, melanocytic tumors, and some of the round cell tumors.

GENERAL APPROACH TO SKIN TUMORS

History and Physical Examination
Because lesions and masses involving the skin are easily seen, they are common reasons for owners to seek veterinary care. General history taking should include duration and rate of tumor growth, change in appearance over time, response to previous treatments, and related medical problems. All tumors should be accurately reported in the medical record. Topographic maps are helpful in making this documentation a permanent part of the record. Three-dimensional caliper measurements and the actual anatomic locations of masses should be recorded. The record should also include gross appearance (color, alopecia, ulceration), consistency (firm, soft), borders (circumscribed, infiltrative), and attachments to underlying tissues (fixed, movable). In addition to a complete physical examination of the animal, lymph nodes draining a skin mass should always be thoroughly evaluated.

Diagnostics
The key to the appropriate management of skin tumors is a specific diagnosis. In many circumstances, diagnosis and characterization of a skin mass should be done before a definitive surgical excision. Knowledge of the tumor type allows the clinician to plan an appropriate surgical approach, make decisions about the need for adjuvant radiation therapy or chemotherapy, and discuss realistic outcomes of therapy and prognosis with clients. Figure 183-2 in Chapter 183 shows an approach to the diagnosis of superficial masses based on initial fine needle aspiration cytology and tissue biopsy.

Routine hematologic and biochemical analyses are rarely helpful in the diagnosis of cutaneous masses; however, some skin tumors may be associated with hematologic or paraneoplastic complications (see Chapter 189). "Screening" blood tests are recommended before a definitive procedure is planned.

Radiographs of the thorax are required in the clinical staging of malignant skin tumors, and ultrasound evaluation of abdominal organs may be useful in the assessment of potential sites of metastases for some tumors. For tumors that deeply attach to underlying tissues, imaging modalities such as radiographs, computed tomography (CT), or magnetic resonance imaging

Box • 182-1

Common Skin and Subcutaneous Tumors

Epithelial Tumors
Papilloma
Intracutaneous cornifying epithelioma
Squamous cell carcinoma
Basal cell tumors
Trichoepithelioma
Pilomatricoma
Trichoblastoma
Sebaceous gland tumors
Hepatoid gland tumors (perianal gland tumors)
Sweat gland tumors (apocrine gland tumors)
Ceruminous gland tumors
Anal sac apocrine gland tumors

Mesenchymal Tumors
Soft tissue sarcomas (see Chapter 183)

Round Cell Tumors
Plasmacytoma
Mast cell tumor (see Chapter 186)
Lymphoma (see Chapter 181)
Histiocytoma (see Chapter 187)
Transmissible venereal tumor (see Chapter 188)

Melanocytic Tumors
Melanoma

(MRI) may be helpful for delineating tumor borders prior to surgical excision.

Enlarged lymph nodes should always be evaluated cytologically or histologically. For some tumors (e.g., mast cell tumors), metastases may be present in lymph nodes that are palpably normal, therefore lymph node evaluation should be a routine part of the evaluation of an animal with a cutaneous mass.

Fine Needle Aspiration

Fine needle aspiration is easy and quick and often provides information about the neoplastic cell type. Fine needle aspiration cytology is most useful in the diagnosis of round cell tumors (e.g., mast cell tumors, cutaneous lymphoma) and for identifying benign skin tumors or papules, nodules, and masses that are non-neoplastic. When cytology is nondiagnostic, a biopsy should be performed. Likewise, when a cytologic diagnosis of neoplasia is obtained, a biopsy should always be done to confirm the diagnosis and assess important prognostic information, such as the degree of differentiation or the tumor grade, a description of vessel invasion, and an evaluation of tissue margins if an excisional biopsy is performed.

Biopsy

A number of biopsy techniques can be used, depending on the size and anatomic location of the mass. Incisional, needle core, or punch biopsies are indicated for large, infiltrative masses or for tumors in a difficult area for reconstruction (e.g., extremities, perineal or periocular regions). For superficial exophytic lesions, shave biopsies done with a scalpel blade may be adequate. For small, freely movable dermal masses, excisional biopsy can be both diagnostic and therapeutic. Even when the diagnosis is known prior to the excisional biopsy, the histopathology of the final specimen should also be determined because it may provide information useful for treatment planning.

When performing nonexcisional biopsies, clinicians should always carefully examine the region to be sampled. The biopsy site should be in an area that can easily be included in the definitive resection or, if indicated, radiation field. As a general rule, all biopsy incisions on extremities should be longitudinal along the axis of the limb. Injection of local anesthetics into cutaneous and subcutaneous tumors should be avoided. Tumor tissue is poorly innervated, and the mass itself does not require anesthesia. Local injections cause tissue distortion and make margin evaluation difficult. The biopsy should be taken deep enough to avoid superficial necrotic tissue and surrounding areas of inflammation. The biopsy procedure should never disrupt tissue planes. A biopsy that opens new and previously uninvolved tissue planes generally necessitates a wider surgical resection or radiation field to control local disease. Drain placement should be avoided, because it allows fluid that has been contaminated with neoplastic cells to contact all tissues through which the drain is placed. Similarly, formation of seromas or fluid pockets may allow tumor cells to invade previously uninvolved tissue planes.

An ideal histologic specimen should include the junction of the tumor with adjacent normal tissue. This allows the pathologist to assess the degree of invasiveness of the tumor. Sample size and consistency are important for obtaining accurate pathologic diagnoses. Most tumors are not homogenous, containing areas of inflammation, necrosis, and reactive tissue, and small samples may not be representative of the entire lesion. Samples smaller than 1 × 1 mm are usually inadequate. Needle core samples 1 mm wide and 5 mm long can be adequate. Samples that fall apart in formalin are often blood, mucus, or necrotic material and are not sufficient for a diagnosis. Large biopsy samples or multiple biopsy specimens from different areas of the tumor (collected through the same incision) can improve chances for an accurate diagnosis.

Cautery and radiofrequency surgical instruments should not be used during the biopsy procedure because they alter tissue and cellular morphology, which may complicate interpretation. Cautery for hemostasis may be used once the sample has been removed.

Finally, applying India ink or other marking dyes to the cut surfaces of excised tumors prior to fixation in formalin is an effective way to ensure that the pathologist can distinguish surgical margins from preparation artifacts.

EPITHELIAL TUMORS

Papilloma

Cutaneous papillomas are benign proliferations of the epidermis and are common in the dog but relatively rare in cats. Grossly, they are whitish or gray, pedunculated or cauliflower-like masses and are often referred to as *warts* or *verrucae*. Both viral and nonviral forms exist. The papillomaviruses are species-specific deoxyribonucleic acid (DNA) viruses. They are fairly stable in the environment and can survive for longer than 2 months at 4° to 8° C and for 6 hours at 37° C.[7] Papillomaviruses can be transmitted by direct and indirect (e.g., fomite) contact. In general, infection occurs in damaged skin, and incubation times vary from 1 to 2 months.[7]

Cutaneous papillomas occur in older dogs, and single or multiple lesions may be seen. They most commonly occur on the head, eyelids, and feet and are not associated with papillomavirus. *Canine oral papillomatosis* is a contagious disease of viral origin that often affects young or immunocompromised dogs.[8] Multiple lesions occur in the mouth, pharynx, face, and skin. *Cutaneous inverted papillomas*, cup-shaped lesions seen

in young dogs, are also caused by infection with a papillomavirus. They occur on the ventral abdomen and groin.[9] Rare cases of multiple, pigmented plaques, or *papular papillomas*, have been reported in dogs.[10]

In cats, most solitary cutaneous papillomas are not caused by papillomavirus. In contrast, papillomas that occur on the ventral tongue in cats are generally viral in origin, as are multiple cutaneous papillomas. These viral papillomas may be precursors to feline multicentric squamous cell carcinoma, or Bowen's disease (see Feline Squamous Cell Carcinoma, below).[11]

Surgical excision of solitary cutaneous papillomas is curative. Canine oral papillomatosis usually undergoes spontaneous regression within 3 months, and the dog is then immune to reinfection.[7] Oral administration of retinoids has been reported to be effective in the treatment of canine inverted papillomas,[12] and anecdotal reports indicate that interferon may be effective in the treatment of severe oral or cutaneous viral papillomatosis.[13]

Intracutaneous Cornifying Epithelioma

Intracutaneous cornifying epitheliomas (keratoacanthomas) arise from the outer portion of the hair follicle. They usually occur in relatively young, purebred dogs. Most are solitary, but generalized forms exist. Norwegian elkhounds and keeshonds are predisposed to the generalized form.[14] These tumors often have a central pore filled with inspissated keratinous material. Gentle digital pressure applied to the mass results in expulsion of a gray-white keratinous material.

Intracutaneous cornifying epitheliomas are benign and do not recur after adequate surgical removal. In the generalized form, new tumors may develop throughout a dog's life. Oral retinoids may be useful in the treatment of multiple intracutaneous cornifying epitheliomas. In one study of seven dogs, five complete remissions and two partial remissions occurred.[12] Spontaneous regression has also been reported to occur in a dog with the generalized form.[15]

Canine Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is a common malignant neoplasm in the dog. The etiology usually is not known. Tumors that develop in unpigmented or lightly pigmented skin, such as the abdomen and inguinal areas, are believed to be induced by ultraviolet radiation (sun damage).[16] Occasionally SCC may be caused by burns, chronic infectious or immune-mediated diseases, or progression from viral papillomas.[13,17] In an immunohistochemistry study of 40 dogs with SCC, 100% of lesions showed expression of cyclo-oxygenase-2 (COX-2).[18] COX-2 has been implicated in the oncogenesis of various human cancers, but the precise mechanisms leading to upregulation of COX-2 are not known.

SCC in the dog may be proliferative, ulcerative, or erosive. The clinical features and management of canine SCC are highly dependent on the anatomic location.

Canine Cutaneous Squamous Cell Carcinoma

Cutaneous SCC may first be diagnosed as a preneoplastic lesion, but it ultimately progresses to an invasive tumor. Rarely, metastases to regional lymph nodes and the lungs may occur.[19] Canine cutaneous SCC is best managed with adequate surgical excision. Preneoplastic lesions may be responsive to oral retinoids,[16] and intralesional therapy with sustained-release cisplatin, 5-fluorouracil, or carboplatin may have a role in the management of some dogs with superficial SCC.[20] Aggressive surgical excision is the treatment of choice for invasive cutaneous SCC. Radiation therapy for incompletely excised tumors and chemotherapy with platinum drugs or doxorubicin for metastatic tumors can be considered, but their efficacy is unproven.

Canine Nasal Planum Squamous Cell Carcinoma

Nasal planum SCC can be treated with aggressive surgical excision of the nasal planum and premaxilla, but the prognosis is extremely guarded. Case selection is important when this procedure is considered. In a study of six dogs treated surgically, two recurred in less than 2 months, probably because of incomplete resections.[21] The results of radiation therapy for SCC in this location have been largely disappointing. In one study, all seven dogs treated with radiation for incompletely excised tumors suffered recurrences in 8 to 12 weeks.[21]

Canine Digital Squamous Cell Carcinoma

SCC originates from the subungual epithelium or occasionally from other tissues of the digit and is the most common digital tumor in dogs. Approximately 80% of digital SCCs invade bony tissue of the third phalanx. Metastases are uncommon at initial diagnosis but may be diagnosed in as many as 30% of dogs after treatment. Rarely, dogs may develop SCC on multiple digits, either simultaneously or over time.[22] Wide amputation that includes disarticulation of the first phalanx and metacarpal or metatarsal bone is the treatment of choice. In one study, the 1- and 2-year survival rates were 95% and 74%, respectively, for 19 dogs with SCC arising from the subungual epithelium; the rates were 60% and 40%, respectively, for 10 dogs with SCC arising from other parts of the digit.[22]

Feline Squamous Cell Carcinoma

As with dogs, SCC in cats occurs most frequently in sun-damaged skin and is usually preceded by actinic (solar) keratosis.[13] Viruses may also be underlying etiologies for feline SCC. In one study, 24% of cats infected with feline immunodeficiency virus (FIV) developed SCC.[23] It is unclear whether a direct causal relationship exists, or whether the condition is due to outdoor sunlight exposure in these cats. Papillomavirus has been identified in lesions of multicentric SCC in situ (Bowen's disease).[11]

Feline Cutaneous Squamous Cell Carcinoma

Cutaneous SCC in the cat usually starts as a crusted area that eventually develops into an erosive or ulcerative lesion. The most common sites are unpigmented areas exposed to sunlight, including the external nares, pinnae, eyelids, and lips. Multiple lesions occur in approximately 45% of affected cats.[24] Metastases are rare.

Several treatment options exist for feline cutaneous SCC, including aggressive surgical excision ("pinnectomy," "nosectomy"), cryotherapy, external beam radiation, strontium-90 plesiotherapy, photodynamic therapy, and intralesional chemotherapy. These treatments are most successful in small (less than 5 cm), superficial lesions, therefore early diagnosis and prompt therapy are essential. Small, minimally invasive SCC lesions can be controlled for longer than 1 year in most cats, and long-term control (e.g., 2 to 7 years) is possible in 10% to 60%. Treatment of larger (greater than 5 cm) or more invasive tumors is disappointing, with control times generally less than 2 years.[24-28] In all cats, avoidance of sunlight is important to prevent additional lesions.

Feline Multicentric Squamous Cell Carcinoma in Situ (Bowen's Disease)

Bowen's disease is a condition of small, plaquelike, crusted SCC lesions that histologically do not invade the basement membrane. Unlike solar-induced SCC, multicentric SCC in situ is found in haired, pigmented areas and may be caused by infection with a papillomavirus.[11] Lesions are multifocal over the head, neck, thorax, abdomen, and limbs. Occasionally focal areas of invasive SCC may be present. When possible, surgical excision is the treatment of choice. Strontium-90 plesiotherapy may be effective for lesions less than 5 mm in diameter.[11] Therapy with oral retinoids is variably successful.[11]

Basal Cell Tumors

Basal cell tumors are benign neoplasms that arise from the basal cells of the epidermis. They are the most common skin tumor affecting the cat.[29] The tumor previously classified as basal cell tumor in the dog has been reclassified as trichoblastoma. Basal cell tumors are usually solitary, firm, rounded, and well circumscribed. Occasionally they may be cystic. Basal cell tumors are often pigmented, which can lead to a clinical misdiagnosis of melanoma. Adequate surgical excision is the treatment of choice.

Basal Cell Carcinoma

Basal cell carcinomas are usually solitary and similar to basal cell tumors; they are often pigmented brown/black. This tumor is locally invasive, therefore clinical management should include wide surgical excision. Animals with proven metastases have rarely been reported.[30] Adjunctive radiation therapy can be considered when adequate surgical margins cannot be achieved.

Trichoepithelioma

Trichoepitheliomas are benign neoplasms derived from the hair follicle sheath. They are relatively common in the dog and uncommon in the cat. Surgical excision is the treatment of choice. Malignant trichoepithelioma with metastases to lymph nodes and lungs has rarely been reported.

Pilomatricoma

Pilomatricomas are uncommon, benign tumors that arise from the hair follicle. They usually are solitary and well circumscribed. On cut section, the tumor consists of several layers of gray-white chalky tissue. Surgical excision is the treatment of choice. Rare cases of malignant pilomatricomas have been reported. Lymphatic invasion is seen histologically, and metastases to lymph nodes, the lungs, and the nervous system may occur.[31]

Trichoblastoma

Trichoblastomas are common benign tumors that predominately derive from primitive hair germ epithelium. This neoplasm was previously classified as basal cell tumor. Trichoblastomas are generally solitary and may be pigmented. Surgical excision is curative.

Other Follicular Tumors

Other uncommon follicular tumors include tricholemmoma, trichofolliculoma, dilated pore of Winer, and warty dyskeratoma. These are benign lesions, and adequate surgical excision should be curative.

Sebaceous Gland Tumors

Sebaceous gland tumors are derived from sebocytes and are among the most common skin tumors in dogs. They are uncommon in cats. Histologically, they are classified as sebaceous hyperplasia, epitheliomas, adenomas or, rarely, carcinomas. The lesions are wartlike or cauliflower-like in appearance and can occur throughout the body, including on the eyelids. They are usually solitary, but multiple sebaceous gland tumors can occur.

Surgical excision is the treatment of choice for all types of sebaceous gland tumors. Local recurrence is rare, but up to 10% of dogs may develop lesions at other sites.[32] Dogs with sebaceous hyperplasia may respond to therapy with oral retinoids.[12] Sebaceous carcinomas appear to have a low potential for metastasis.[32]

Hepatoid Gland Tumors (Perianal Gland Tumors)

Perianal gland tumors arise from canine circumanal glands, which are modified sebaceous glands. They are referred to as *hepatoid glands* because the cells morphologically resemble hepatocytes. Circumanal glands contain receptors for both testosterone and estrogen, and intact males are at increased risk for tumor development. The occurrence of these tumors in female dogs or in males that were castrated early in life suggests a need for evaluation for hyperadrenocorticism. The vast majority of perianal gland tumors are benign and histologically may include hyperplastic lesions, adenomas, or epitheliomas. Rarely, hepatoid gland carcinomas occur.

Most perianal gland tumors occur adjacent to the anus, but they can also occur on the ventral aspect of the tail and perineum. Fine needle aspiration cytology may help differentiate perianal gland tumors from other tumors of the perineum; however, it may be difficult to distinguish adenomas from carcinomas.

Castration is the treatment of choice for perianal gland hyperplasia and adenomas in intact males; 95% of lesions regress. Surgical excision is necessary in female dogs and castrated animals or when the tumors are ulcerated. Radiation therapy may cause nonresectable adenomas to regress, but limited information is available on this treatment.

Carcinomas do not regress after castration, therefore aggressive surgical excision must be done. In one study, 70% of dogs with tumors less than 5 cm in diameter survived for 2 years when treated by surgical excision alone.[33] Ten percent to 30% of tumors may metastasize to the iliac lymph nodes, liver, and lungs.[34] Radiation therapy can be considered for tumors that are incompletely excised or if metastasis to iliac lymph nodes is confirmed. Occasionally, lymphadenectomy may be an option. Doxorubicin and platinum compounds may be useful, but their efficacy is unproven.

Sweat Gland Tumors (Apocrine Gland Tumors)

Sweat gland tumors in dogs and cats commonly occur in the inguinal or axillary regions. These tumors have various clinical presentations, including solitary nodular masses or a diffuse, inflammatory and ulcerative, plaquelike growth. Cats with a histologic diagnosis of apocrine gland carcinoma of the digit may actually have digital metastases from a pulmonary carcinoma.

The majority of sweat gland tumors are histologically malignant (carcinomas), and more than 20% may have evidence of lymphatic or vascular invasion.[35,36] Wide surgical excision is the treatment of choice. In two retrospective studies, fewer than 2% of canine sweat gland carcinomas developed distant metastases.[35,36] Metastatic disease may have been correlated with intravascular invasion.[36]

Ceruminous Gland Tumors

Ceruminous gland tumors originate from modified apocrine sweat glands found in the external ear canal. Chronic otitis may be a predisposing factor.[37] Common clinical signs associated with ear canal tumors include the presence of a mass, aural discharge, odor, pruritus, and pain. Neurologic signs, including Horner's syndrome and vestibular disease, may also be present. Radiographs of the skull and/or computed tomography are important imaging modalities that should precede surgery. Careful evaluation of the mandibular and periauricular lymph nodes is essential.

Ceruminous gland adenomas can be managed by conservative surgical resection. For ceruminous gland carcinomas, however, aggressive surgical excision, including ear canal ablation and lateral bulla osteotomy, is the treatment of choice. Sixteen cats treated by ear canal ablation and bulla osteotomy had a 42-month median remission, a 25% recurrence rate, and a 75% 1-year survival rate. Six cats treated only with lateral ear resection had a 10-month median remission, four of the cats had recurrence, and the 1-year survival rate was only 33%.[38] In seven dogs, aggressive ear canal ablation with lateral bulla osteotomy resulted in no recurrences during follow-up for a median of 36 months, compared with a 75% recurrence

rate within 4 months for four dogs treated by a more conservative lateral ear canal resection.[39]

Radiation therapy can be used as an adjunct to incomplete resection. A median progression-free interval of 40 months and a 56% 1-year survival rate were achieved in one study of six cats and five dogs treated with radiation therapy after incomplete resection of ceruminous gland adenocarcinoma.[40]

Anal Sac Adenocarcinoma

Anal sac adenocarcinomas arise from the apocrine glands in the ventrolateral aspects of the anus. They occur almost equally in female and male dogs but are rare in cats. The tumors are usually unilateral, occasionally can be bilateral, and are either discrete or infiltrative when palpated rectally. Twenty-five percent to 50% of anal sac adenocarcinomas produce parathyroid hormone–related protein (PTHrP), leading to hypercalcemia of malignancy.[41,42] Metastases generally arise in the iliac lymph nodes, although distant metastases may also be seen in the liver, spleen, lungs, and other sites. Occasionally extension from the iliac lymph nodes into the lumbar vertebrae may occur.[42]

Aggressive surgical excision with or without chemotherapy and radiation therapy is recommended for treatment of anal sac adenocarcinoma. Hypercalcemia generally resolves quickly after resection of the primary tumor. The rate of local recurrence after surgical excision is approximately 50%. It is unclear whether this correlates with incomplete histologic margins.[41,42] In one study, dogs underwent surgical excision of the primary mass. Some also had surgical removal of metastatic lymph nodes. The median survival for dogs with metastases (n = 11) or hypercalcemia of malignancy (n = 5) was 6 months, compared to 15.5 months for dogs without metastases (n = 10) and 11.5 months for dogs with normocalcemia (n = 16).[41] In another study of 34 dogs, the overall median survival was approximately 8 months.[42]

Adjunctive treatment with radiation to the anal sac and iliac lymph node regions and chemotherapy with platinum agents or doxorubicin may improve outcome. However, this has not been substantiated.

ROUND CELL TUMORS

Round cell tumors may also be called *discrete cell tumors*. Cytologically, they appear as individually oriented, round cells that have no obvious attachments to each other. The round cell tumors include lymphoma, mast cell tumors, plasmacytomas, histiocytomas, and transmissible venereal tumors. Occasionally melanomas and basal cell tumors may mimic round cell patterns.

Lymphoma, Mast Cell Tumor, Histiocytoma, and Transmissible Venereal Tumor

For a discussion of these tumor types, the reader is referred to detailed information presented in other chapters of this text.

Plasmacytoma

Cutaneous plasma cell tumors (cutaneous extramedullary plasmacytomas) are usually solitary, and common locations of occurrence are the digits, lips, pinnae, oral cavity, and rectum.[43,44] The majority of cutaneous plasmacytomas in the dog are benign and are unrelated to multiple myeloma. The behavior of canine plasmacytomas does not seem to have any relationship to the degree of histologic atypia or pleomorphism.[43,44]

The treatment of choice for cutaneous plasmacytomas is surgical excision. Local recurrence may be associated with incomplete margins.[43] Radiation therapy can be considered for cases that are nonresectable, but information is limited.

MELANOCYTIC TUMORS

Melanoma

The etiology of cutaneous melanomas in dogs and cats is unknown, but breed predilection in dogs suggests a genetic basis. Breeds reported to be at risk include Scottish terriers, Airedales, Boston terriers, cocker and springer spaniels, boxers, golden retrievers, miniature schnauzers, and Doberman pinschers.[13] In dogs, lesions are usually solitary and are brown to black in appearance. Common sites include the eyelid, muzzle, trunk, interdigital skin, and subungual epithelium (nail bed). Digital melanomas are the second most common digital tumor in dogs, next to squamous cell carcinoma. In cats, the most common pigmented cutaneous tumor is a basal cell tumor. However, melanomas also are black. Common sites in cats include the pinna, nose, and neck.

Cutaneous melanomas can be behaviorally benign or malignant. Of critical importance is the location of the tumor. As a general rule, tumors arising from the haired skin are benign. Those arising from mucocutaneous junctions are malignant, the only exception being those arising on the eyelids. Melanomas of the digit may be highly malignant. Malignant melanomas commonly spread via lymphatics to draining lymph nodes and the lungs. Metastases to distant sites such as the liver, spleen, brain, heart, and bone marrow occasionally occur.

In dogs, the histologic mitotic index is highly predictive of biologic behavior.[45-47] A mitotic index of less than 3 per 10 high-power fields is generally associated with benign behavior.[45] It is difficult to predict the biologic behavior of cutaneous melanomas in cats based on the mitotic index, because 25% of malignant tumors may show no mitotic figures.[48]

The treatment of choice for cutaneous melanomas in both the dog and the cat is surgical excision. In one study, 59 dogs had a median survival of 26 months and a 2-year tumor-related death rate of 10% if the mitotic index of the tumor was less than 3. In contrast, 26 dogs had a median survival of 7.5 months and a 2-year tumor-related death rate of 73% if the mitotic index of the tumor was 3 or higher.[45] With digital melanomas in dogs, more than 50% may develop metastases. A median survival time of 12 months has been reported for dogs treated by amputation of the affected digit.[22] Other studies have reported median survival times of 18 to 24 months.[45,46]

The prognosis for cats with cutaneous melanomas is guarded. In one study of 57 cats with the tumors, metastases were documented at initial diagnosis in 11 (19%). Forty-five cats were treated by surgical excision, and 22 of these animals developed local recurrence or metastases.[49]

Coarsely fractionated radiation therapy is useful for treating dogs with oral melanoma and may be beneficial for local control of nonresectable cutaneous melanomas in dogs and cats.[50] Also, a clinical response to treatment with carboplatin can be seen in dogs with oral melanomas, therefore this may be considered as an adjunct therapy in dogs with digital melanomas or in dogs and cats with malignant or nonresectable tumors or metastatic disease.[51]

CHAPTER • 183

Soft Tissue Sarcomas

Rodney L. Page
Margaret C. McEntee

Soft tissue sarcomas represent a significant group of cancers in companion animals. Collectively, sarcomas include numerous histologic subcategories that are derived from neoplasms of mesenchymal origin. Box 183-1 lists the individual histologic categories of canine soft tissue sarcomas included in most discussions. In some instances, distinct biologic behaviors have been described for specific subcategories. However, the collective experience of pathologists and specialists managing sarcomas in dogs has permitted development of a histologic grading scheme that more uniformly describes clinical behavior by the degree of differentiation rather than specific histologic type (Table 183-1). The histologic grade of a tumor can dictate radical versus functional surgery or may determine the addition of radiation therapy or chemotherapy. In addition, the size of the tumor and its location will obviously affect the surgical options available for local control. Despite the general consensus that grade may influence the ultimate control of a tumor, debate continues about the universal applicability of histologic grade of sarcomas as a clinically meaningful predictor of response in dogs. To date, no convincing evidence exists for comparison of grade with outcome for feline sarcomas. Specific histopathologic types of sarcomas include fibrosarcoma, undifferentiated sarcoma, osteosarcoma, rhabdomyosarcoma, liposarcoma, malignant fibrous histiocytoma (or myofibrosarcoma) and leiomyosarcoma. Hemangiosarcomas (HSAs), synovial cell sarcomas, and mast cell tumors (MCTs) are discussed separately in this text due to the common occurrence of these cancers and their unique biologic and clinical features. Other, less common sarcomas are not included, because they cannot be considered as part of the collective terminology due to insufficient information (e.g., rhabdomyosarcoma).

Soft tissue sarcomas are typically focal, solitary, palpable, soft to firm lumps found in the dermis, subcutaneous tissue, or deeper muscular and musculofascial compartments. The most common owner concern is the identification of a palpable or visible nonpainful mass (or both) that may be growing. Masses that have grown rapidly or have been present for a prolonged time with resultant substantial growth can have an ulcerated surface and may be painful. The majority of masses are 2 to 4 cm in diameter at the time of initial examination. Tumor size can vary depending on a number of factors including location on the body, particularly whether it is located superficially in the dermis or deep in a muscle, whether an owner frequently handles or grooms the pet and identifies a new lump early, the overall body condition with masses more easily observed on a trim pet, and the length and thickness of the hair coat. Soft tissue sarcomas can develop in any location on the body but are most commonly identified on the limbs or head. In cats, soft tissue sarcomas are frequently associated with sites of previous vaccination and therefore are more commonly located on the trunk either in the interscapular region, dorsal lumbar, or flank region.

An accurate diagnosis is critical for appropriate treatment planning. An incisional biopsy is recommended for all but the smallest of nodules to prevent disruption of the surrounding normal tissue prior to definitive surgical planning. Excisional biopsies should be avoided unless the mass is small (<1 to 2 cm proportional to the size of the dog or cat) and surrounded by abundant normal tissue. In addition, all biopsy procedures should be carefully planned for all subcutaneous nodules to avoid inadvertent contamination of surrounding tissues. Although local control is expected with complete surgical removal, local recurrence is often observed after suboptimal surgical procedures. Aggressive tumor management at the first opportunity is required for successful management of soft tissue sarcomas. The challenge of surgical planning, the need

Box • 183-1

Histologic Categories of Soft Tissue Sarcomas in Dogs and Cats

Fibrosarcoma	Rhabdomyosarcoma
Hemangiopericytoma	Leiomyosarcoma
Malignant fibrous histiocytoma	Liposarcoma
	Undifferentiated sarcoma
Synovial sarcoma	Schwannoma
Neurofibrosarcoma	

Table • 183-1

Proposed Grading Criteria for Canine Soft Tissue Sarcomas*

SCORE	DEGREE OF DIFFERENTIATION	MITOTIC INDEX†	NECROSIS
1	Normal appearance	<10	None
2	Histologic type	10-19	<50%
3	Undifferentiated	>19	>50%

Grade (Cumulative Score)	
1	<5
2	5 or 6
3	>6

*Adapted from Kuntz CA et al: Prognostic factors for surgical treatment of soft-tissue sarcomas in dogs: 75 cases (1986-1996), *J Am Vet Med Assoc* 211:1147, 1997.
†Number of mitotic figures/10 high-powered fields (40×).

for multimodality therapy in many instances, and the potential for metastases despite local control in high-grade sarcomas add complexity to the treatment decision-making process. These challenges are particularly important for successful management of injection-site sarcomas in cats.

CAUSE

The genetic or specific biochemical mechanisms responsible for development of sarcomas in both dogs and cats remain unknown. It is believed that most sarcomas that develop in dogs occur sporadically. Germ-line mutations or familial forms of sarcomas have been confirmed in humans, and provocative anecdotal epidemiologic evidence suggests similar processes may be present in dogs. However, detailed genetic or pedigree characterization of dogs that develop sarcomas at a young age (<2 years) or where a breed prevalence seems likely have not been conducted. In one recent study, chromosomal translocation was identified in 1 of 30 canine sarcomas, although its significance remains unknown.[1]

It is well established that exposure to irradiation, viral infection (feline sarcoma virus), trauma, or chronic inflammatory conditions are associated with development of sarcomas in dogs and cats. Conventional irradiation schedules for management of a primary cancer carries less than 5% risk of a radiation-induced tumor occurring 3 to 5 years later.[2] Clearly, the benefits of primary tumor control outweigh the risk of radiation-induced second tumors. High, single doses of radiation used for intraoperative therapy are more likely to produce sarcomas (20% to 25%) in dogs with a median latency of 4 years postirradiation.[3]

The molecular development of injection-associated sarcomas in cats is not yet defined. There have been several reports eliminating the most common feline viral infections (oncorna, papilloma, polyoma viruses) as causes.[4-6] Unique molecular features of injection-associated sarcomas have been identified. Epidermal growth factor/receptor (EGFR), platelet-derived growth factor/receptor (PDGF), and transforming growth factor–beta expression is abundant on tumor cells and infiltrating lymphocytes in injection-site sarcomas but are not expressed in cells from noninjection site sarcomas of cats.[7] C-Jun overexpression, a proto-oncogene, has also been identified in feline injection site sarcomas and may be the result of persistent growth factor stimulation.[7]

P53 abnormalities have been reported in vaccine-associated sarcomas. In one report, approximately 43% of samples from sarcomas strongly overexpressed the p53 protein.[8] In another report, five of eight tumor samples overexpressing this protein had a mutated gene. No cats from a control group of 13 injection sarcomas without p53 protein overexpression had gene mutations.[9] In this study, no surrounding tissue had p53 mutations, suggesting that abnormalities in p53 function did not exist prior to tumor development. These data taken collectively indicate that molecular and cellular abnormalities exist and suggest several hypotheses; however, no specific cause has been associated with the development of feline injection sarcomas.

Abnormalities in p53 and MDM2, a gene with a product that suppresses p53 expression, have recently been reported in canine sarcomas.[10] Twenty percent (6/30) of sarcomas had base substitutions resulting in single amino acid misreads in the p53 gene. Three of these six tumors with mutations were malignant nerve sheath tumors. Interestingly, canine MDM2 gene amplification (threefold or greater) was identified in five of the 30 sarcomas. In all but one of these combined samples there was coordination of these abnormalities, resulting in p53 disruption (mutations) or secondary p53 suppression due to MDM2 overexpression. Thus directly or indirectly, almost one third of canine sarcomas appear to have altered p53 function. Interestingly, five of seven malignant peripheral nerve sheath tumors had p53 functional abnormalities.

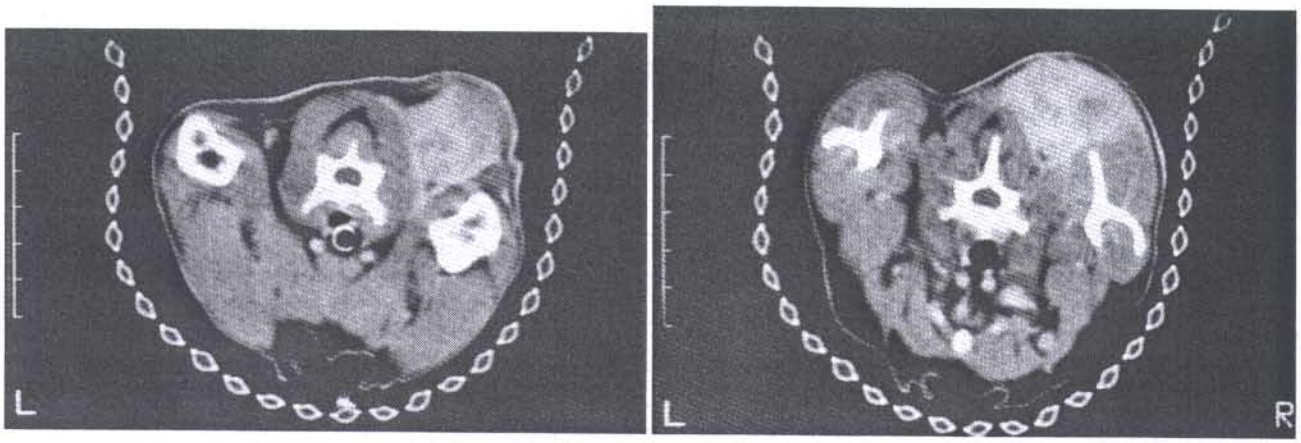
INITIAL CLINICAL EVALUATION

Routine evaluation of the patient should be conducted, including a thorough physical examination and laboratory evaluations. Tumor staging includes the assessment of the extent of local disease and detection of any evidence of regional or distant metastasis. A thorough description and measurement of the mass in three dimensions is essential and is important for documenting subsequent growth if initiation of therapy is delayed, or for documentation of therapeutic response. Soft tissue sarcomas, in general, have a relatively low metastatic rate, but the rate of metastasis increases with increasing tumor grade. The greatest concern of metastasis is with high-grade sarcomas. The regional lymph node should be evaluated by aspiration, biopsy, or both techniques, particularly if the lymph node is enlarged or if it is a high-grade tumor. Metastasis can occur to the regional lymph node, although this is not the most common site of metastasis. The incidence of metastasis for sarcomas at initial diagnosis is low, but without specific examination of regional lymph nodes or careful follow-up, the actual incidence of metastasis remains unknown. The most common route of metastasis is via the hematogenous route, and the most common sites of metastasis are the lung and liver. In cats with vaccine-associated fibrosarcomas, sites of metastasis that have been reported include lung, skin, or subcutaneous sites, regional lymph nodes, mediastinum, liver, and pelvis.

Appropriate imaging for evaluation of the primary tumor, as well as thoracic radiographs and abdominal ultrasound, should be conducted during the staging process if malignancy is confirmed. Imaging techniques may also aid in planning biopsy and treatment options. An ultrasound evaluation of the primary tumor may aid in determining the best site for biopsy; for deep-seated tumors, ultrasound guidance may be necessary for accurate tumor sampling. Imaging of soft tissue sarcomas increasingly involves more advanced cross-sectional imaging studies such as computed tomography (CT) or magnetic resonance imaging (MRI). CT with the administration of intravenous contrast can assist in delineating the extent of the local disease and extension into the surrounding tissues. It is highly recommended that imaging precede therapeutic intervention. The extent of invasion into surrounding tissues for vaccine-associated sarcomas in cats can be substantial, and an initial excisional biopsy can impair the ability to achieve local tumor control. It was recently determined that tumor volume measured from contrast-enhanced CT studies of feline sarcomas exceeded the physical measurements by two- to fivefold, and attachment of the tumor to surrounding muscle and tissue was much more extensive than predicted.[11] Figure 183-1 illustrates an infiltrative sarcoma in the prescapular and interscapular space of a cat. Obviously, a surgical procedure without accurate knowledge of tumor extent in feline injection sarcomas is not recommended. Furthermore, in dogs, soft tissue sarcomas frequently occur on the extremities where it is difficult to resect the tumor with the necessary margins. An initial biopsy and imaging can provide both a diagnosis and understanding of the extent of disease, with preplanning possible so that an owner can be appraised of whether or not combination therapy may be indicated, with the potential for increased duration and cost of therapy.

BIOPSY CONSIDERATIONS

As with any suspected tumor, the clinician needs a definitive diagnosis to determine the best treatment strategy. Aspiration cytology can provide initial information on a dermal or subcutaneous lump that may support the diagnosis of a



A B

Figure 183-1 Computerized tomography (CT) image with contrast agent of a feline vaccine-associated sarcoma in prescapular space. Extensive soft tissue infiltration is obvious with numerous muscles adjacent to tumor tissue.

non-neoplastic process. Additionally, aspiration cytology can be diagnostic for neoplasia and indicative of a round cell (e.g., MCT), epithelial or mesenchymal tumor. Mesenchymal tumors are less likely to exfoliate during aspiration, and for soft tissue sarcomas, aspiration cytology is performed primarily to rule out other disease processes. At times, cytology may be diagnostic for a sarcoma. An incisional biopsy is recommended to obtain a definitive diagnosis of a soft tissue sarcoma and to determine the specific histopathologic type. The biopsy procedure for sarcomas should be carefully planned to obtain a representative sample of the tumor and prevent any unnecessary complications or contamination of surrounding tissue with tumor. If a cutting needle is to be used, care should be taken not to penetrate beyond the known tumor perimeter. Sarcomas are often adhered to adjacent tissue, and extension along fascial planes can be difficult to appreciate on physical examination. Therefore biopsy samples such as those obtained from limited incisions, punch biopsy tools, or cutting needles are preferred to excisional biopsy to minimize any tissue disruption. The acquisition of a biopsy sample allows grading of the tumor based on assessment of a number of histopathologic features. The histologic features assessed in soft tissue sarcomas to arrive at a tumor grade include degree of differentiation, percentage of necrosis, and mitotic rate (see Table 183-1). Tumor grade for soft tissue sarcomas in dogs can have prognostic significance with a more progressive course and higher likelihood of metastasis with a high-grade tumor. One report on prognosis in cats after surgical excision of fibrosarcomas showed a correlation between mitotic index (sum of mitotic figures in ten high-power fields) and median survival. For cats with a mitotic index less than six the median survival was 32 months as compared with 4 months if the mitotic index was greater than or equal to six. More recent studies have not shown a correlation between tumor grade and survival in cats with vaccine-associated sarcomas. Such tumors may have a cell population that is generally more aggressive than many other sarcomas.

GENERAL TREATMENT CONSIDERATIONS

Surgical excision of any tumor without preplanning can result in incomplete removal and the need for a second, more extensive surgical procedure, radiation therapy, and potentially a higher complication rate. Soft tissue sarcomas in particular are likely to be incompletely removed with close marginal excision due to tumor extension beyond what is visible. Higher morbidity and cost associated with incomplete resection justify the referral of pets with large or high-grade soft tissue sarcomas for consideration of multidisciplinary evaluation and possibly multimodality therapy. Figure 183-2 represents a decision-making algorithm for soft tissue sarcomas, or any superficial nodule, based on the initial determination of surgical success. Pivotal decision points in this algorithm include the determination of whether curative surgery is possible, the success of the surgical procedure based on thorough evaluation of the surgical margins, and the need for any adjuvant chemotherapy determined by tumor grade and stage.

Decision regarding surgical resection of a soft tissue sarcoma is perhaps the most critical point in the algorithm. The decision to attempt resection should be made from accurate measurement of the mass and its deep tissue attachments, the location of the tumor and surrounding normal tissue limitations for deep resection, and the surgeons' skill. The surgical procedure should be well planned to accomplish the goal of complete resection and reduce or prevent the likelihood of inadvertent seeding of the tumor resection bed and surrounding tissue. Referral to a surgical specialist that has had extensive experience with cancer surgery should be considered for most sarcomas. New techniques are being evaluated and implemented that require advanced technology and training.[12]

After a surgical procedure it must be assumed that the entire operating field could be contaminated, including the scar. The use of appropriate technique is essential. This includes incision planning, avoidance of unnecessary manipulation of the tumor itself, or placement of drains with distant tissue dissection. During the procedure, hemoclips may be used to define the deep and lateral extent of the surgical plane. This will be of benefit to determine the area of resection if a second surgery is indicated or for radiation treatment planning if needed.

Examination of the deep margins for completeness of resection is of critical importance for determining local tumor control. The histopathologic analysis of tumor margins is aided by deep surface marking with permanent dye and a thorough description of the sites that might be suspect for closer examination by the pathologist.[13-15] Adequate margins around the tumor tissue can be difficult to estimate once the tissue has been processed for fixation and microscopic evaluation.

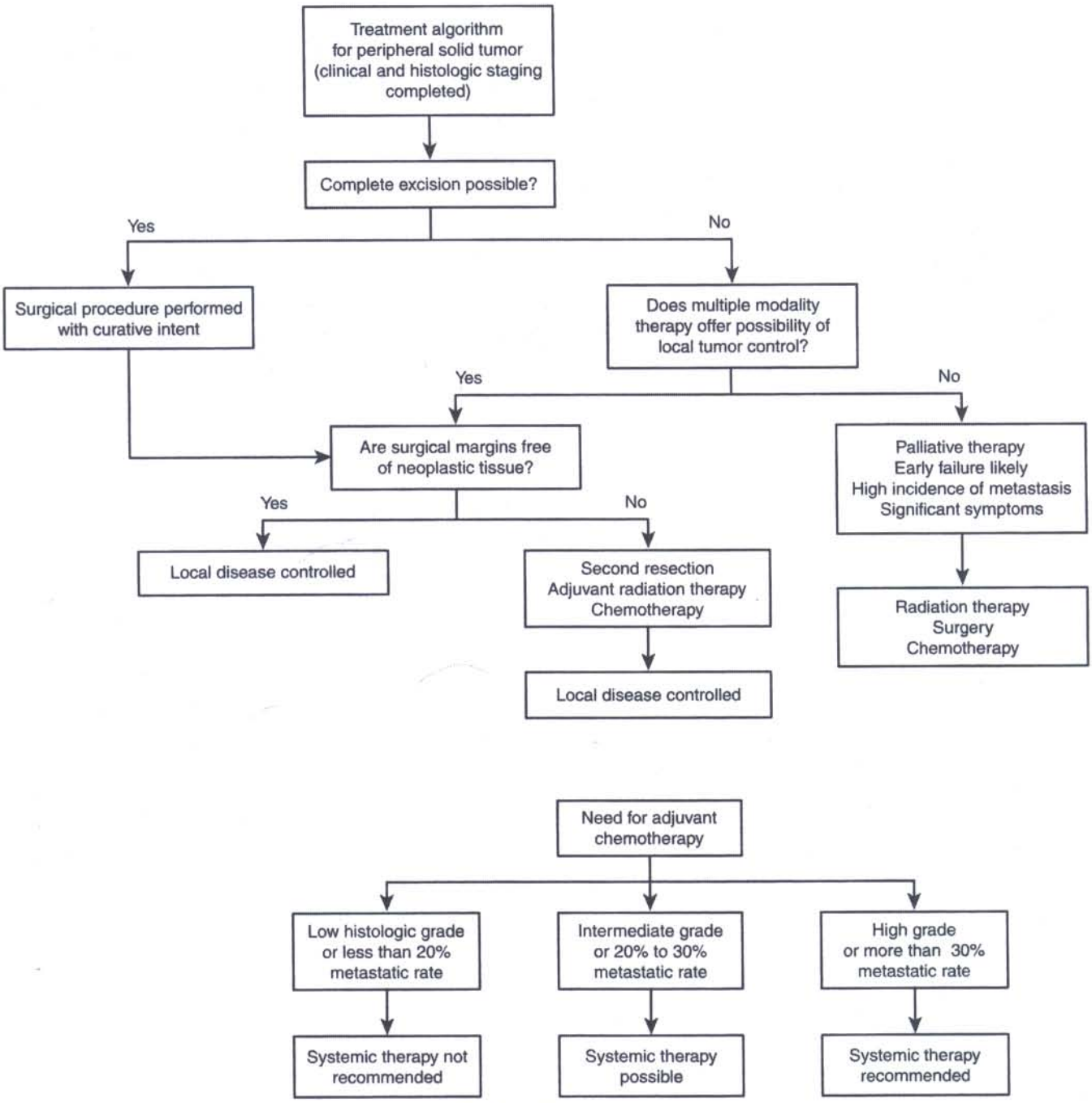


Figure 183-2 Soft tissue sarcomas.

For classification of complete resection, most pathologists recommend a minimum of ten cell diameters between tumor and deep surface. This arbitrary designation should be carefully examined with more defined measurements of distance that could be correlated to the required margin necessary to prevent recurrence for different grades of sarcoma.

Palliative therapy may be necessary for tumors that are not amenable to aggressive surgery or multimodality therapy. Palliative therapy should be actively pursued, and numerous treatment options have been devised specifically for management of dogs and cats with noncurable tumors or those with significant signs associated with the presence of tumors.

MANAGEMENT OF CANINE SOFT TISSUE SARCOMAS

To date, no known risk factors exist for the development of canine sarcomas. Therefore general recommendations for cancer screening and detection such as frequent physical examinations, radiographs, and other imaging studies should become more routine for earlier identification of sarcomas. Any mass that is apparent should be characterized early with measurements, appropriate imaging, and biopsy. If a sarcoma is identified, the procedures outlined previously for treatment planning should be implemented.

Figure 183-2 summarizes the treatment recommendations for management of the primary tumor and whether chemotherapy for adjuvant treatment should be instituted after local control. Surgical resection should be the first consideration for any sarcoma. The conclusion that a mass is potentially curable with surgery should be closely scrutinized because local recurrence represents a serious complication of inadequate surgery and will impact future treatment options.[16] Referral for more extensive tumor evaluation and aggressive management is warranted for tumors occurring in areas of complex musculofascial anatomy because adequate normal tissue removal around the sarcoma improves local control.[17] Multimodality therapy is an appropriate consideration for tumors that are not easily resectable.

Radiation therapy has been shown to be of significant benefit for local control in tumors that are not controllable with surgery alone. The use of preoperative or postoperative irradiation can be considered, although ideally, the schedule for application of radiation therapy should be made before the treatment is initiated rather than using radiation as a means to manage residual disease after an inadequate surgical procedure.[18] Several studies have demonstrated that irradiation results in long-term control of soft tissue sarcomas in dogs.[19,20] Local relapse-free survival has been estimated at 75% to 85% for 3 or more years, and this combination should be recommended for all incompletely excised sarcomas in dogs. Current treatment schedules and technology make irradiation of tumor sites less likely to result in limiting side effects than previous techniques. However, soft tissue sarcomas can arise in any tissue, and adjacent normal structures can be difficult to avoid in some instances without compromising tumor control.

Chemotherapy also has a role in management of canine soft tissue sarcomas. A recent review thoroughly describes the indications, options, and strategies for chemotherapy in sarcoma management.[21] Chemotherapy is indicated when animals have inoperable sarcomas because of size or location because a measurable reduction might allow function-preserving resection; pets with recurrent sarcomas that are not amenable to second surgical procedures; dogs with high-grade sarcomas to reduce or delay metastatic nodules; and those with sarcomas that have inherently greater likelihood of metastasis such as oral sarcomas, liposarcomas, and dogs with soft tissue sarcomas of the spleen. Adriamycin is the most active single agent for canine sarcomas.[21] Other options include platinum-containing agents and ifosfamide. Although no definitive evidence exists to make adjuvant chemotherapy a general recommendation for dogs with high-grade sarcomas, many specialists feel the chance for distant spread of the tumor even with local control (~40%) warrants a recommendation of treatment with chemotherapy.[17]

Palliative therapy is also available for dogs with tumors that have significant functional abnormalities directly related to the tumor. Irradiation schedules for palliative management are designed to deliver a significant dose to the tumor without debilitating side effects and with minimal hospitalization. Tumors associated with dysphagia, dyspnea, dyschezia, or dysuria, and that are assumed to be incurable with surgery should be considered for palliative irradiation. Palliative chemotherapy may also be offered in hopes of reducing the mass associated with debilitating clinical symptoms. Any response to treatment should be observed after the initial treatment course and is unlikely to occur after the second course of treatment. Therefore continuation of the chemotherapy is unnecessary if no response is observed. Surgical procedures designed specifically for improved quality of life in dogs with extensive disease include resolution of ulceration and management of secondary infection.

Management of Canine Soft Tissue Sarcomas with Unique Clinical Features

The majority of tumors listed in Table 183-1 can be managed with the principles described after considering the histologic grade and the likelihood of local control. Special consideration should be given to several sarcomas due to unique presentations or tumor biology. Discussion of synovial cell sarcoma, malignant fibrous histiocytoma, and HSAs are discussed in chapters 181, 184, and 187.

Leiomyosarcoma Sarcomas of smooth muscle occur most often in the intestinal tract and are singled out here due to special considerations of management related to their site of origin. Because second approaches are unlikely, it is recommended that intestinal tumors be resected widely and any lymph nodes or other sites of concern in the abdomen be resected to aid in staging during the laparotomy. Several retrospective reviews have reported clinical outcome of approximately 100 dogs with leiomyosarcoma of the intestine.[22-24] In addition, data is available describing the site or origin and metastases of 158 dogs and 22 cats with leiomyosarcomas.[25] Leiomyosarcomas are most often located in the small intestine, cecum, spleen, or urogenital tract. Feline leiomyosarcomas are uncommon but occur in the intestinal tract more often than other sites. If complete surgical resection can be accomplished, median survival times (MSTs) are approximately 18 to 21 months, and many dogs succumb to diseases other than recurrence or metastasis. Metastatic lesions are reported in 15% to 30% of dogs with leiomyosarcomas and are most likely to be found in the mesentery, spleen, or liver. Metastases may be slow to develop (1 to 2 years) and relatively slow to progress to clinical signs. No reports on postoperative chemotherapy are available.

Management of Feline Sarcomas

Surgical excision of soft tissue sarcomas in cats represents the best chance of affecting local tumor control.[26,27] If an initial biopsy is suggestive of soft tissue sarcoma in a cat, imaging (CT or MRI) will provide the most accurate assessment of the extent of disease and assist in developing an appropriate treatment plan. An excisional biopsy of a vaccine-associated sarcoma will rarely result in a complete resection and is likely to result in local recurrence and a second, more difficult surgery will be necessary. Tumor recurrence has been documented to

occur as early as 2 weeks after surgery and will typically occur by 6 months after incomplete surgical resection.[28] An aggressive surgical resection is necessary to effect local control, and this can entail resection of the tumor with 3 to 5 cm margins, removal of associated bone (e.g., dorsal spinous processes, partial scapulectomy), and at least one fascial plane deep to the involved tissues. Vaccine-associated sarcomas have commonly occurred in the interscapular space. This is a difficult location for surgery because it may require removal of dorsal spinous processes and the surrounding musculature. For this reason the Vaccine-Associated Feline Sarcoma Task Force has made the recommendation to vaccinate with rabies and feline leukemia virus (FeLV) in the distal hind limb. Therefore amputation would be possible to effect local tumor control. Even with amputation or hemipelvectomy, it may not be possible to completely excise a vaccine-associated sarcoma. It is often necessary to use a multimodality approach, combining radiation therapy and surgery. For instance, preoperative irradiation of a proximal limb sarcoma may be necessary prior to amputation. The use of radiation therapy in the preoperative setting will often result in reduction in tumor size, and theoretically sterilization of the peripheral components of the tumor that would otherwise be problematic and result in an incomplete resection and resultant rapid tumor regrowth.

Chemotherapy may be used in the management of vaccine-associated sarcomas as adjuvant therapy to address potential metastatic disease, as neoadjuvant therapy to reduce the tumor in size prior to surgical resection, or as palliative therapy for nonresectable tumors. The use of combination doxorubicin and cyclophosphamide has been reported in 12 cats with nonresectable tumors.[29] There was a 50% overall response rate. The MST was significantly longer in those cats that responded (242 days) than in those that did not respond (83 days).

A combination of surgery, radiation therapy, and chemotherapy may result in the greatest potential for long-term tumor control. The largest report to date details the results of preoperative radiotherapy in 92 cats with vaccine-associated sarcomas.[30] The median time to first event (time from the start of treatment to local recurrence, metastasis, or date of death or euthanasia) was significantly longer at 986 days (n = 59 cats) if a complete resection was accomplished compared with 292 days (n = 28 cats) with an incomplete resection. There was a trend toward improved survival with the addition of chemotherapy (carboplatin, other) with a median time to first event of 1059 days (n = 33 cats) in cats that received chemotherapy versus 584 days (n = 59 cats) in those cats that were treated with radiation and surgery alone. The overall rate of metastasis was 21.7% (20/92), although complete follow-up was not available for all cats. Ongoing investigations are being carried out to determine the optimal treatment approach for vaccine-associated sarcomas, but it is likely that the best chance for success will lie in early detection and aggressive management or prevention of the development of vaccine-associated sarcomas.

PREVENTION

The cause of the majority of canine soft tissue sarcomas is unknown and therefore it is not feasible to develop strategies for prevention. However, for cats where there has been an association between vaccination and the development of soft tissue sarcomas, it is possible to decrease the risk of development of a soft tissue sarcoma. It is important to limit the number of vaccinations that are administered to cats and to only give those vaccines that are necessary to maintain health. For instance, it is not necessary to vaccinate cats for FeLV when they are indoor cats that are not exposed to other FeLV-positive cats. It is also important to follow the recommendations that have been provided by the Vaccine-Associated Feline Sarcoma Task Force: limiting one vaccine per site and documenting the location of each of the vaccines (right hind limb for rabies, left hind limb for FeLV, and right lateral scapular region for feline viral rhinotracheitis calcivirus panleukopenia [FVRCP]). In this way even if a tumor is to develop, an owner can be informed as to what to watch for and where to check for a possible tumor. Additionally, vaccines have been developed that do not appear to result in a local inflammatory response and may therefore translate into a decreased risk of tumor development at that site, although no long-term studies have confirmed this. There have been isolated reports of tumor development in cats at sites not associated with vaccination but rather due to some other inciting event that has resulted in a local inflammatory response. For instance, a report exists of a cat that developed a condition similar to a vaccine-associated fibrosarcoma at the site of a deep nonabsorbable suture.[31]

SUMMARY

Soft tissue sarcomas include a diverse group of histologic types classified based on the cell of origin but, as a group, exhibit similar biologic behavior. Tumor grade has proven to be important and predictive for outcome in dogs with soft tissue sarcomas but has not been shown to be of prognostic significance in cats. Wide surgical resection is required for local control in dogs and cats with soft tissue sarcomas. Radiation therapy will control the majority of tumors after incomplete resection in dogs; however, complete surgical removal, with or without irradiation, is necessary for control of vaccine-associated sarcomas in cats. Currently, a multimodality approach including surgery, radiation therapy, and chemotherapy seems reasonable to optimize the chance of tumor control in dogs with high-grade soft tissue sarcomas and cats with vaccine-associated sarcomas.

CHAPTER • 184

Hemangiosarcoma

Philip J. Bergman

GENERAL FEATURES, PATHOLOGY, AND BIOLOGIC BEHAVIOR

Hemangiosarcoma (HSA) (angiosarcoma, malignant hemangioendothelioma) is an extremely malignant cancer of vascular endothelial origin. With this cellular origin, virtually any anatomic site can have HSA as a primary or secondary tumor diagnosis. HSA occurs most frequently in dogs (approximately 2% of all tumors), and the most common site of origin is the spleen; however, additional sites include right atrium, pericardium, liver, muscle, lung, skin and subcutis, bone, kidney, central nervous system (CNS), peritoneum and oral cavity.[1-3]

In three large canine splenic disease studies encompassing approximately 2000 dogs, a "rule of two thirds" was found, suggesting that approximately two thirds of dogs with a splenic mass have a malignancy (therefore one third are not malignant) and two thirds of the malignant tumors of the spleen are HSA.[2,4,5] It cannot be overemphasized that only histology can confirm the diagnosis of HSA. The differential diagnosis for a splenic mass should include lymphoma, leiomyosarcoma, fibrosarcoma, osteosarcoma, malignant fibrous histiocytoma, and other sarcomas (e.g., undifferentiated, liposarcoma, mesenchymoma), as well as non-neoplastic entities such as nodular hyperplasia, splenic hematoma, and hemangioma.[4,6,7] HSA can be single or multiple, and in those dogs with multiple tumors it can be extremely difficult to identify which is the primary tumor. HSAs are typically grossly soft, nodular, and dark red due to hemorrhagic and necrotic regions; however, extremely undifferentiated HSAs can lose this grossly vascular appearance and be more firm and pale gray, like other sarcomas. Immunohistochemistry (IHC) using antibodies against factor VIII, PECAM, and other antigens can be helpful to distinguish HSA from other undifferentiated neoplasms.[8,9]

Importantly, the right atrium and auricle is the third most common site for HSA in the dog, and HSA is the most common heart tumor.[10-15] Pericardial effusion, cardiac tamponade, or both are common sequelae to cardiac HSA.[16,17] Twenty-five percent of dogs with splenic HSA also have right atrial HSA.[18] It is not known whether the splenic or atrial lesion is primary or secondary. It seems most likely that right atrial lesions in dogs with splenic HSA are metastatic, because many dogs with right atrial HSA do not have splenic HSA. In addition to the aforementioned metastatic sites, HSA metastasizes to the brain in approximately 15% of cases.[19] HSA generally metastasizes via hematogenous routes (e.g., lungs, liver, brain) or by direct extension via transabdominal implantation via tumor rupture (e.g., omentum, mesentery).[13,18]

HSA tends to be a disease of older dogs and cats with a median age of 9 to 10 years. However, reports exist of extremely young dogs and cats with this disease (5 to 6 months to a few years of age).[20-23] German shepherd dogs are the most common breed of dog diagnosed with HSA.[10] Other large breed dogs, such as golden retrievers and Labrador retrievers, may also be over-represented. In cats, the most common breed is the domestic shorthair (DSH).[24-26] HSA appears to be less common in cats (< 0.5% of all tumors) than dogs, with the most common primary tumor sites including spleen, liver, or mesentery.[27-29] Intra-abdominal HSA in the cat appears to be a highly malignant neoplasm, similar to that in dogs; metastatic sites commonly include lungs, liver, omentum, diaphragm, and occasionally pancreas.[21-26] There does not appear to be an overt gender predisposition for HSA in dogs or cats; however, some reports suggest that male dogs are predisposed.[10,12,20,23]

The cause of HSA in dogs and cats is unknown. Exposure to toxins such as vinyl chloride, dioxides, radiation, and arsenicals have been reported in humans to be associated with HSA.[30-32] Radiation exposure in dogs has been implicated as a potential cause of HSA[33]; however, the implanted doses of radiation were high and lengths of time of implantation and subsequent exposure were long in these studies. Interestingly, the ingestion of methylnitrosamines from fish meal by mink has been implicated in the carcinogenesis of HSA.[20] Ultraviolet (UV) light exposure may be a potential cause of HSA in dogs because cutaneous HSAs are commonly seen in dogs with light hair and poor pigmentation (e.g., salukis, whippets, white bulldogs).[34]

HISTORY AND CLINICAL SIGNS

Due to its cell of origin, HSA can be found in dogs or cats in almost any anatomic locale; therefore the history and clinical signs can vary. At the most extreme, HSA can cause sudden death due to tumor rupture, acute blood loss, or both. At the other end of the spectrum, nonspecific signs such as anorexia, vomiting, and lethargy can be seen in dogs and cats with HSA. It is quite common for HSA patients with intra-abdominal or intrathoracic disease to have a history of weakness, pale mucous membranes, or collapse (or a combination of these signs). Other potential historical abnormalities that may be noted by owners are abdominal distension, dyspnea, and weight loss. Episodes with weakness and collapse can last for minutes to hours with recovery from the episode being a common feature. It is surmised that the weakness, pale mucous membranes and collapse are due to acute blood loss, whereas the dramatic recovery is likely due to discontinuation of the acute blood loss, autotransfusion of the blood lost into a body cavity, or both.

In those situations where the heart is involved, the acute blood loss from the HSA can result in pericardial or thoracic effusion (or both), which can result in cardiac tamponade. On physical examination, these dogs may have clinical signs of right heart failure, muffled heart sounds, and arrhythmias.[16,35] The neurologic form of HSA can cause a variety of neurologic signs that include seizures.[19] The cutaneous form of HSA generally causes discrete nonulcerative dermal to subcutaneous masses that are firm, raised, and dark purple to red. When involving the

deeper tissues such as muscle, deep fascia, or both, dogs may have a large mass, firmness in the muscle, lameness, or a combination of these signs. Swelling distal to the lesion can be seen with extremely large intra- or intermuscular HSA.

DIAGNOSIS AND STAGING

Presumptive diagnosis of HSA can be based on the history, signalment, and physical examination findings. In addition, other diagnostics such as radiography, ultrasound, and fine needle aspiration or paracentesis (or both) are valuable. Serosanguineous effusions associated with HSA generally do not clot and upon cytologic examination only reveal a confirmatory diagnosis in 25% of dogs.[35]

It cannot be overemphasized that the definitive diagnosis of HSA can only be made via biopsy and histopathologic examination (or in the rare instance of the aforementioned cytologic-based diagnosis). After surgical removal, large lesions should be "bread-loaf" sectioned to allow for full fixation by formalin, and then the entire sample submitted whenever possible. In those situations in which the sample and concomitant formalin represent too large a volume for transport to the pathology laboratory, one can either (1) fully fix the bread-loafed specimen overnight, remove the specimen, and submit in formalin-wetted towels to prevent sample drying or (2) submit representative smaller samples from a variety of regions of the lesion. Whenever possible the entire resection should be submitted no matter what type of neoplasia is suspected, because this best allows the pathologist to discern a final diagnosis with delineation of resection margins. If the diagnosis of HSA is suspected and histopathologic review does not document the presence of HSA, then further consultation with the histopathologist and additional review of submitted tissues may be helpful.

Nondermal HSA is commonly a metastatic neoplasm based on necropsy studies. Because the prognosis (discussed later in this chapter) and potential need for additional therapy is highly dependent on clinical stage, a thorough evaluation for evidence of metastatic disease is highly recommended. Thoracic radiographs with right and left lateral views and ventrodorsal views should be performed for delineation of possible lung metastasis, cardiac involvement, or both with the presence of pericardial effusion. Although many sarcomas with pulmonary metastasis will have a classic nodular or "cannonball appearance," HSA pulmonary metastases can have a miliary to coalescing miliary pattern as seen in Figure 184-1.[36,37] Radiography was able to detect pulmonary HSA metastasis and cardiac involvement (because of an abnormal silhouette) in 78% and 47% of dogs, respectively.[37] The most accurate diagnostic for cardiac involvement from HSA is echocardiography.[38,39] The value of echocardiography for staging HSA is continuing to be evaluated. Echocardiography is recommended for HSA staging whenever available and financially feasible.

Use of abdominal ultrasound is strongly recommended for additional staging of HSA. It can be a valuable tool for evaluation of a primary intra-abdominal tumor and delineation of the presence of metastatic spread. The echo pattern most commonly seen in dogs with splenic HSA is mixed or nonhomogenous (or both), whereas hepatic metastases generally appear anechoic or hypoechoic.[40] If metastatic spread is felt to be highly likely on ultrasound examination, it must be emphasized that a tissue-based histopathologic or cytopathologic diagnosis (or both) is necessary to prove that metastatic disease is indeed present. Importantly, abnormalities seen on abdominal exploratory for a splenic HSA, such as masses on the liver, omentum, diaphragm, should all be biopsied and evaluated histopathologically. The clinical staging system for HSA is shown in Box 184-1.

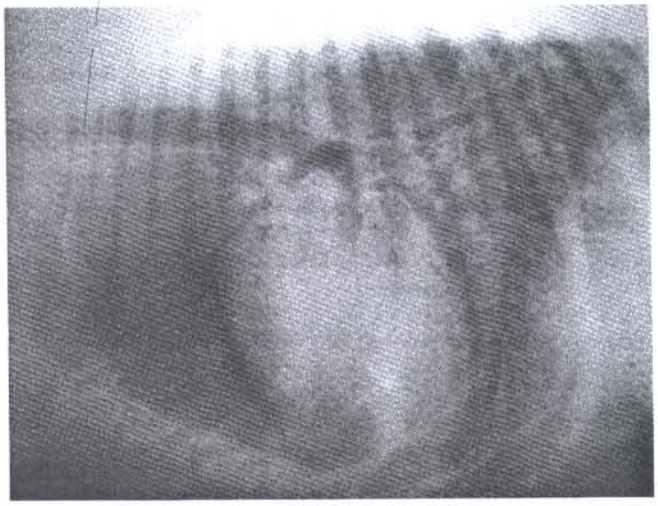


Figure 184-1 Lateral chest radiograph of a 6-year-old castrated male golden retriever 52 days after splenectomy for a splenic hemangiosarcoma. The reader should note the non-nodular miliary metastatic pattern.

The most common hematologic finding in dogs with HSA is anemia.[13,20,41] The anemia is generally a regenerative normocytic-normochromic anemia with polychromasia, reticulocytosis, nucleated red blood cells (RBCs), and anisocytosis.[13,20,41] The anemia associated with HSA is generally felt to be due to microangiopathic hemolysis and possibly intracavitary hemorrhage (with subsequent autotransfusion), which results in RBC fragmentation and schistocytosis in canine and human HSA but not feline HSA.[42] Other common hematologic abnormalities in dogs and cats with HSA also include

Box • 184-1

Canine Hemangiosarcoma TNM Clinical Staging System

T = Tumor (Primary Tumor)
T0 = No evidence of tumor
T1 = Tumor confined to primary site and/or dermis and <5 cm in diameter
T2 = Tumor invading SQ tissues and/or ≥ 5 cm in diameter
T3 = Any T1 or T2 with tumor invading adjacent structures and/or muscle

N = Node (Regional Lymph Nodes)
N0 = No evidence of regional lymph node involvement
N1 = Regional lymph node involvement
N2 = Distant lymph node involvement

M = Metastasis (Distant Metastasis)
M0 = No evidence of distant metastasis
M1 = Distant metastasis

TNM-Based Stages
I = T0 or T1, N0, M0
II = T1 or T2, N0 or N1
III = T2 or T3, N0 or N1 or N2, M1

neutrophilic leukocytosis, band neutrophilia, and thrombocytopenia. Significant thrombocytopenia can be seen in approximately one half of dogs with HSA.[43,44] In addition, spontaneous hemorrhage and disseminated intravascular coagulation (DIC) may occur in dogs and cats with HSA, and therefore a coagulogram is strongly recommended prior to the use of invasive diagnostics, surgery, or both.

TREATMENT AND PROGNOSIS

Surgery

Surgery continues to be the gold standard treatment for dogs and cats with HSA. Due to the metastatic propensity of nondermal HSA, this disease should be one that is routinely thought of as having two problems: (1) local tumor control and (2) systemic tumor control. Therefore even though surgery remains the gold standard, it is almost always used in concert with some systemic therapy modality in nondermal HSA because the prognosis for dogs with splenic HSA treated with surgery alone remains poor to grave with a median survival time (MST) of only 19 to 86 days.* The prognosis for cats is also poor. Cats have a MST after splenectomy for splenic HSA of only 20 weeks.[26] Surgery should be used as aggressively as possible for HSA to remove all diseased tissue whenever possible. For example, for dogs with intramuscular HSA, a radical myectomy or amputation would be recommended, whereas with splenic HSA a splenectomy would be the surgical methodology of choice. Due to aforementioned staging concerns, any suspicious lesions (e.g., omentum, diaphragm, liver, lymph nodes) noted at the time of surgery should also be biopsied and histopathologically examined. For dogs undergoing splenectomy for splenic HSA, development of ventricular arrhythmias, thought to be due to hypovolemia, anoxia, and anemia, occurred in approximately one quarter of dogs postoperatively.[47]

Local tumor control is especially problematic for dogs with HSA of the pericardium, right atrium, or both due to anatomic constraints. Exploratory thoracotomy may be performed with removal of the tumor by pericardiectomy for pericardial HSA, as well as the use of staples and hand suturing for right auricular and atrial tumors.[14,16,48] Unfortunately the prognosis for HSA at this anatomic location is also poor to grave, with death being reported within 3 to 5 months (median survival only weeks) after surgery.[14,16] Thoracoscopy appears to be a promising less-invasive diagnostic modality and has also been reported as a methodology for pericardiectomy.[48,49]

Cutaneous HSA without hypodermal invasion is less metastatic than nondermal HSA. The median survival of dogs with dermal only HSA (treated by surgical resection) was 780 days, whereas in dogs with hypodermal or deeper involvement of their cutaneous HSA (or both) have MSTs of 172 and 307 days, respectively.[50] Therefore it appears that hypodermal involvement in canine cutaneous HSA warrants a poorer prognosis and probable need for adjuvant therapy when compared with dermal HSA. Cats with cutaneous HSA treated by surgical excision had a MST of 44 weeks.[26]

Chemotherapy

Hypodermal or deeper canine and feline HSA appears to be routinely metastatic, and therefore adjuvant therapy is considered necessary after surgery. As shown in Box 184-2, doxorubicin-based protocols are most commonly reported. Similar MSTs are noted whether doxorubicin is used adjuvantly as a single agent or in combination with cyclophosphamide (i.e., adriamycin and cyclophosphamide) and vincristine (i.e., vincristine, adriamycin, and cyclophosphamide [VAC]) as shown in Table 184-1.[45,51-53] Because single-agent doxorubicin appears to have similar activity to VAC and AC with less toxicity, doxorubicin may be the therapy of choice for HSA.[45] However, doxorubicin appears to have limited therapeutic benefit. For those dogs with nondermal HSA receiving five doses of doxorubicin after surgery, negative prognostic factors included (1) younger age, (2) higher grade and degree of

*References 1, 4, 5, 13, 45, 46.

Box • 184-2

Canine Hemangiosarcoma Adjuvant Chemotherapy Protocols

1. A (Adriamycin)
Doxorubicin IV every 3 weeks for 5 treatments
30 mg/m2 for dogs >10 kg
1 mg/kg for dogs ≤10 kg OR cats
Note: Pretreatment CBC/platelet counts required.
Need >3000 neutrophils and >75,000 platelets to treat
Nadir CBC/Plt at 7-10 days

2. AC (Adriamycin and Cyclophosphamide)
Day 1—Doxorubicin (see "A" protocol) and 100-150 mg/m2 cyclophosphamide IV
Can substitute IV Cytoxan with Oral at 50 mg/m2 on days 3, 4, 5, 6
Day 22—Repeat cycle for 4-6 total cycles
Note: Antibiotics may be required due to significant myelosuppression.

3. VAC (Vincristine, Adriamycin, and Cyclophosphamide)
Day 1—Doxorubicin (see "A" protocol) and cyclophosphamide 100-200 mg/m2 IV
Day 8—Vincristine at 0.75 mg/m2
Day 15—Vincristine at 0.75 mg/m2
Day 22—Repeat cycle for 4-6 total cycles
Note: Clinician should stop chemotherapy for 1 week if any pretreatment CBC has <3000 neutrophils. Antibiotics may be required prophylactically and/or therapeutically because this protocol is extremely myelosuppressive.

Table • 184-1

Survival Times for Canine Hemangiosarcoma

TREATMENT	MEDIAN SURVIVAL IN DAYS	REFERENCES
Splenectomy	19-86	1, 5, 13, 45
Splenectomy and MBVacc +/– VMC	91-117	13
Splenectomy and VAC	145	51
Splenectomy and AC	141-179	53, 62
Splenectomy and AC and L-MTP-PE	273	55
Complete Surgery and A	172	45
Incomplete Surgery and A	60	45

anaplasticity and undifferentiation, and (3) incomplete gross tumor removal.[45] Other chemotherapy regimens such as single-agent vincristine and VCM (vincristine, cyclophosphamide, and methotrexate) have been reported in dogs with HSA[13,54]; however, their use is not recommended due to limited therapeutic activity.

Dogs with earlier-stage hypodermal or deeper HSA treated with surgery and chemotherapy appear to have a better prognosis compared with dogs with more advanced stage disease based on multiple studies.[13,55,56] When taken in concert with the aforementioned negative prognostic factor of incomplete tumor resection,[45] it appears that the use of adjuvant chemotherapy is most beneficial in dogs with earlier-stage, nonruptured, and completely resected HSA. It therefore cannot be overstated that preoperative staging is imperative for preoperative prognosis in dogs suspected of having HSA.

Immunotherapy and Biologic Therapy

Relatively few studies have been published investigating the therapeutic efficacy of biologic response modifiers in canine HSA. Modest improvement in survival was noted for dogs receiving a killed bacterial vaccine after splenectomy compared with splenectomy alone.[13] Macrophage-activating agents such as L-MTP-PE (liposome-encapsulated muramyl tripeptide phosphatidylethanolamine) appear to have tumoricidal activity against a variety of neoplasms.[57-59] In a surgical adjuvant-chemotherapy canine HSA study, L-MTP-PE significantly prolonged disease-free survival and overall survival[55]; unfortunately, this compound is presently not commercially available.

Based on the cell of origin, antiangiogenic approaches are thereby logical anticancer approaches to HSA. Minocycline is an antibiotic with antiangiogenic activity.[60,61] Dogs with HSA were treated with surgery, AC (i.e., doxorubicin and cyclophosphamide), and minocycline; however, no statistically significant change in survival was noted in comparison to historical controls.[53,56] Although these results are discouraging, additional investigations using novel rationally targeted therapies for HSA are desperately needed and encouraged.

Radiation

Due to HSA's predilection for visceral anatomic sites in concert with its metastatic nature, radiation is rarely used. It has been noted anecdotally that significant decreases in bulky disease has followed externally located HSA treated with palliative radiation, but the impact on prolongation of survival has not yet been published.

CHAPTER 185

Bone and Joint Tumors

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PRIMARY APPENDICULAR TUMORS

Canine Osteosarcoma

The four primary bone tumors are osteosarcoma (OSA), chondrosarcoma (CSA), fibrosarcoma (FSA), and hemangiosarcoma (HSA).[1] Liposarcoma, rhabdomyosarcoma, plasma cell tumors (solitary plasmacytoma and multiple myeloma), and lymphoma are also reported to involve bone; however, these tumors more typically involve bone as a secondary process.[1] OSA is the most common primary bone tumor accounting for greater than 85% of all appendicular bone tumors.[1] OSA occurs in the axial skeleton and may occur in extraskeletal tissues, including visceral organs, skin, and mammary glands.

OSA is a tumor of unknown cause. Repetitive injury to the physis has been proposed due to the high incidence of OSA in the metaphyseal region of large breed dogs with late-closing physes, however, recent evidence fails to support this theory.[1,2] Other potential causes include viral transmission and a genetic predisposition.[1,3] OSA has been reported in association with previous fractures, particularly in the femoral diaphysis, and other bone diseases, such as infarcts and bone cysts.[3] Radiation-induced OSA has also been documented and may be associated with protocols involving radiation doses greater than 3.5 Gy per fraction.[1]

Signalment Appendicular OSA is usually a disease of large to giant breeds of dogs.[1] OSA also affects smaller breeds but they are 20 times less likely to develop OSA.[4] Breed predispositions have been reported; however, size, and particularly height, are more important risk factors than breed.[1,5] Neutered dogs, regardless of sex, have a two-fold risk of developing OSA compared with sexually intact dogs.[5] The age distribution at diagnosis is bimodal, with most dogs between 7 and 9 years of age and a smaller population between 1 and 2 years of age.[1,5]

Diagnosis Lameness and localized limb swelling are the most common signs.[1] Pain and lameness are caused by microfractures, disruption of the periosteum with tumor extension, and pathologic fracture.[1] Appendicular OSA occurs in the metaphyseal region of long bones. The thoracic limb is involved 1.7 times more frequently than pelvic limb.[1,6] The distal radius (23.1% of OSA cases) and proximal humerus (18.5%) are the two most common sites for OSA.[1,6] In the hind limb, OSA occurs in the tibia and femur with equal frequency. The femur is the most common site in dogs weighing less than 15 kg.[4]

An orthopedic examination is necessary to localize the source of lameness and differentiate metaphyseal pain from other common orthopedic diseases in large breed dogs, such as osteoarthritis, cranial cruciate ligament rupture, and hip dysplasia. Physical examination and a minimum data base, consisting of hematology, serum biochemistry, and urinalysis, is important to evaluate general health status and ability to tolerate surgery and chemotherapy. Three basic types of OSA exist: (1) endosteal, (2) periosteal, and (3) parosteal.[1,7]

Periosteal and parosteal OSA are uncommon and originate from the periosteal surface or, less commonly, the endosteum and medullary canal.[1,7] Endosteal OSA is far more common.[1] Regional radiographs are recommended to establish a tentative diagnosis and differentiate primary bone tumors from other orthopedic diseases. The radiographic appearance of endosteal OSA can range from lytic to blastic and is usually a mixture of both patterns.[1,7] Other characteristic radiographic signs of primary bone tumors include cortical lysis, periosteal proliferation, palisading new bone formation perpendicular to the axis of cortical bone (sunburst effect), periosteal lifting due to subperiosteal hemorrhage (Codman's triangle), loss of the fine trabecular pattern in metaphyseal bone, and pathologic fracture with metaphyseal collapse.[1,7] Appendicular FSA and CSA have a similar radiographic appearance to OSA and cannot be differentiated radiographically. However, classic signalment and radiographic findings are often sufficient for the diagnosis of a primary bone tumor.[1,7]

Differential diagnoses for primary bone tumors include fungal osteomyelitis, especially *Coccidioides immitis* and *Blastomyces dermatitidis*.[1,7] A thorough history is necessary to determine whether the dog lives or has traveled through an area endemic for fungal disease. Dogs with fungal osteomyelitis often have systemic illness and polyostotic bone disease.[1,7] Conversely, dogs with primary bone tumors rarely have systemic illness and bone involvement is usually confined to a single site.[1,7] Bacterial osteomyelitis, atypical bone cysts, and metastatic neoplasia are other potential differential diagnoses.

Bone biopsy can be performed to confirm the diagnosis using closed or open techniques.[8-11] Fine needle aspiration, with or without ultrasound guidance, is a useful, minimally invasive technique to diagnose sarcoma and differentiate primary bone tumors from metastatic disease and fungal osteomyelitis.[8,9] Closed needle-core biopsy, using either a Jamshidi needle or Michele trephine, is invasive and requires general anesthesia.[1] Biopsies should be planned and performed meticulously, preferably by the primary surgeon, so the biopsy does not compromise surgical options.[1] The biopsy should be performed to ensure that the biopsy tract can be excised en bloc with the tumor and unaffected tissues are not contaminated during the biopsy procedure or by postbiopsy hematoma formation.[1] Large core samples can be obtained with a Michele trephine, resulting in a diagnostic accuracy rate of 94%, but the larger bone defect also increases the risk of pathologic fracture.[1,10] Bone biopsies procured with a Jamshidi needle have an accuracy rate of 82%, and the smaller gauge needle decreases the risk of complications and creates a significantly smaller biopsy tract.[11] Two to four biopsies should be collected from the center and periphery of the lesion through a single stab incision in the skin. The risk of pathologic fracture increases if the biopsy needle penetrates both the near and far cortices.[1] Multiple biopsies are preferred to increase diagnostic accuracy because small biopsy samples can be misdiagnosed due to the heterogeneous nature of OSA.[1] Central bone biopsies are recommended because the peripheral aspects of bone tumors often contain reactive bone.[1] After definitive surgery the entire tumor should be submitted for histology to confirm the diagnosis.

Appendicular OSA is a highly aggressive tumor. More than 90% of dogs have micrometastatic disease; however, less than 15% of dogs have clinically detectable metastasis at the time of initial diagnosis.[1] Metastasis occurs primarily through hematogenous routes, particularly to the lungs and other bone, although metastasis to the regional lymph node is reported in up to 37% of dogs with OSA.[1,6,9,12] Palpation of regional lymph nodes, thoracic radiographs, and nuclear scintigraphy are essential tools for thorough staging of dogs with a suspected primary bone tumor. The presence of detectable metastatic disease significantly influences the management options for dogs with OSA.[1,13-15] High-detail three-view inspiratory thoracic radiographs, including right and left lateral and ventrodorsal or dorsoventral projections, are required for the diagnosis of pulmonary metastases.[1,7] Lesions of 6 mm diameter or greater can be detected with good-quality radiographs.[1] Computed tomography (CT) provides greater sensitivity to detect lesions less than 6 mm in diameter, but advanced imaging may be cost prohibitive for some clients and has been associated with false-positive diagnoses of metastatic lesions.[1,13] Whole-body bone scintigraphy, using radiolabeled technetium pertechnetate, is highly sensitive for the detection of concurrent skeletal abnormalities, including both primary and metastatic tumors, but is not specific for the diagnosis of neoplasia.[1,14,15] In a recent study a second asymptomatic bone lesion, consistent with metastatic disease, was identified in 7.8% of 399 dogs with OSA.[15] If a suspicious lesion is identified, fine-detail radiographs should be performed of that region. Bone biopsy may be performed for confirmation if radiographic results are equivocal. Alternatively, survey radiographs of the skeleton, consisting of lateral radiographs of long bones and ventrodorsal radiographs of the pelvis, can be used to screen for bone metastases if nuclear scintigraphy is unavailable.[16] When present, metastatic skeletal disease is a negative prognostic indicator. This becomes extremely important for dogs in which limb amputation is planned, because occult skeletal metastases may become clinically symptomatic after surgery, rendering the dog nonambulatory.

Palliative Management Management options for dogs with appendicular OSA are broadly classified into two distinct pathways: (1) palliative-intent or (2) curative-intent. Palliation is indicated for dogs with metastatic disease or when owners do not want to pursue more aggressive treatment options. Palliative therapy is geared toward management of pain and lameness associated with the primary bone tumor but does not improve survival time. Analgesia is the cornerstone for the palliative management of dogs with primary bone tumors (Table 185-1).[17] Nonsteroidal anti-inflammatory drugs (NSAIDS) may initially be sufficient to manage pain and improve quality of life. Cyclooxygenase-1-sparing NSAIDS are preferred as adverse effects are reduced.[17] More potent analgesic drugs, or combinations of drugs, are often required for effective pain relief.[17] These include codeine acetaminophen, partial mu agonists or agonist-antagonists, sustained-release oral morphine, fentanyl patches, and adjunctive drugs, such as N-methyl-D-aspartate (NMDA) antagonists and tricyclic antidepressants.[17] Multiple drug combinations are most efficacious for refractory pain because different aspects of the pain pathway are targeted and result in an additive or synergistic analgesic effect. The median survival time (MST) for dogs with appendicular OSA treated with analgesic drugs alone has not been reported, although anecdotal evidence suggests that 1 to 3 months is a reasonable expectation.

Radiation therapy is effective for palliation of dogs with primary bone tumors. A number of different protocols have been described, most commonly 4 to 10 Gy administered on a 0-7-21 day or monthly protocol.[18-22] These protocols are relatively inexpensive and do not require prolonged hospitalization. Radiation reduces local inflammation, minimizes pain, slows progression of metastatic lesions, and improves quality of life in dogs with primary and metastatic lesions.[18-23] A 50% to 92% response rate has been reported with the median onset of response 11 to 14 days after initiation of radiation therapy and median duration of response lasting 73 to 130 days.[18-22] The duration of response is significantly improved when less than 50% of bone length is affected by tumor. Proximal humeral OSA has been reported to have the best response.[21,22] Higher cumulative doses, higher intensity of treatment, and the addition of chemotherapy to palliative

Table • **185-1**

Oral and Transdermal Analgesic Drugs Used for the Palliation of Dogs with Appendicular Osteosarcoma

ANALGESIC DRUG	DOSE	INTERVAL	COMMENTS
NSAIDS			
Carprofen	2.2 mg/kg	12 hr	Idiosyncratic hepatic failure, gastric ulceration, renal failure, lethargy
Deroxicab	1-2 mg/kg	24 hr	Gastric ulceration, renal failure
Etodolac	10-15 mg/kg	24 hr	Gastric ulceration, renal failure
Meloxicam	0.05-0.1 mg/kg	24 hr	Gastric ulceration, renal failure
Ketoprofen	0.5-1.0 mg/kg	24 hr	Gastric ulceration, renal failure, platelet aggregation inhibition
Piroxicam	0.3 mg/kg	48 hr	Gastric ulceration, renal failure
Partial Agonists			
Butorphanol	0.55 mg/kg	1-2 hr	Controlled substance, short duration of activity, ceiling effect of analgesia, sedation, respiratory depression
Opioids			
Morphine	0.5-1.0 mg/kg	8-12 hr	Controlled substance, sedation, euphoria, bradycardia, vomiting, urine retention, constipation
Fentanyl patch	50 µg/hr (10-20 kg) 75 µg/hr (20-30 kg) 100 µg/hr (>30 kg)	72 hr 72 hr 72 hr	Controlled substance; variable serum concentration due to application site, skin blood flow and temperature, and hydration; correct disposal required because residual dose lethal to humans
Miscellaneous			
Codeine-acetaminophen	0.5-2.0 mg/kg	6-8 hr	Controlled substance, anemia
Amantadine	3 mg/kg	24 hr	NMDA antagonist
Prednisone	0.5-1.0 mg/kg	12-24 hr	Anti-inflammatory, synergistic activity with opiates, contraindicated with NSAIDs
Amitriptyline	1-2 mg/kg	12-24 hr	Tricyclic antidepressant, alters serotonin and norepinephrine activity

radiation protocols have been reported to improve response rate and duration of response.[20-22] Palliative radiation therapy is not associated with acute effects and does not negatively influence quality of life.[18-22] The MST for dogs with appendicular OSA treated with palliative radiation is 122 to 313 days.[18-22] Radiopharmaceuticals, such as samarium, have been used for the palliation of primary and metastatic bone lesions but are expensive and, at this time, are not widely available in veterinary medicine.[24,25]

Limb Amputation Limb amputation can be used as palliative therapy and as part of the curative-intent treatment in dogs with primary bone tumors.[1,26,27] Amputation is an effective means of pain control, particularly in dogs with pathologic fracture and lameness unresponsive to analgesic drugs or radiation therapy. Osteoarthritis, neurologic disease, obesity, and large body size have been cited as relative contraindications.[1,26,27] Experience has shown that osteoarthritis, weight, and body size are rarely problematic. The majority of dogs with OSA are middle- to older-aged, large breed dogs with moderate preexisting osteoarthritis. They rarely have difficulties after amputation.[27] Dogs with neurologic disease or *severe* clinical osteoarthritis are exceptions, and palliative management or limb-sparing techniques should be considered in these dogs. When thoracic limb amputation is performed, the scapula should be removed. Tumor control, particularly for dogs with proximal humeral OSA, and cosmetic appearance is improved.[1] In the pelvic limb, coxofemoral disarticulation should be performed for dogs with OSA distal to the proximal femur, whereas dogs with proximal femoral OSA should be treated with either en bloc acetabulectomy or subtotal hemipelvectomy to achieve adequate tumor control and minimize the risk of local recurrence. Most dogs are able to ambulate unassisted within 12 to 24 hours after limb amputation. Amputees should be encouraged to ambulate at home by the owners after discharge to speed recovery. Studies have shown that most dogs fully adapt to amputation by 4 weeks after surgery. If the dog was significantly lame from the tumor prior to surgery, full recovery often occurs more quickly than 4 weeks once the painful limb is removed. In addition, a positive attitude by the owners shortens the time to adaptation after amputation.[27] Body weight and thoracic or pelvic limb amputation do not have a significant influence on the time to adaptation after amputation; however, early in the postoperative period, dogs with thoracic limb amputation have greater difficulty in balancing.[27] Behavioral changes, such as increased anxiety and loss of dominance, have also been observed but are relatively uncommon.[27] Complications associated with limb amputation are rare. Intraoperative complications may include hemorrhage, air embolism, and inadvertent thoracotomy (front-limb amputations). Possible postoperative complications include infection and stump recurrence. The survival time of dogs treated with amputation alone is significantly better than with the use of analgesic drugs or palliative radiation therapy.[9] The MST for dogs with OSA treated with limb amputation alone is 103 to 175 days with a 6-month survival rate of 47% to

52%, 12-month survival rate of 11% to 21%, and 24-month survival rate of 0% to 4%.[12,28-31]

Limb-Sparing Surgery Limb-sparing techniques are becoming more common, despite the success of limb amputation in dogs with primary bone tumors.[1,26,32-42] In fact, the most common reason for performing limb sparing in dogs with OSA is owner reluctance to proceed with amputation. Medical indications for limb sparing include previous amputation of another limb, severe concurrent osteoarthritis, or neurologic disease.[1,26]

Limb-sparing surgery is most successful for dogs with primary bone tumors in the distal radius and ulna.[26,32-34] Limb-sparing surgery for other anatomic locations is often associated with a high complication rate and poor postoperative limb function.[35,36] Candidates for limb-sparing surgery include dogs with tumors confined to the bone, minimal extension into adjacent soft tissue, and involvement of less than 50% of the bone length.[1,26] The extent of bone involvement is most accurately determined using CT scans.[43] Bone involvement is overestimated by radiographs, nuclear scintigraphy, and magnetic resonance imaging (MRI).[43-45] The use of imaging techniques that overestimate the degree of bone involvement may be acceptable because adequate surgical margins and complete resection of the bone tumor may be more readily achieved.[44] Pathologic fractures are a relative contraindication due to soft tissue contamination via hemorrhage and hematoma, although the risk of local tumor recurrence can be reduced by preoperative chemotherapy or radiation therapy.[26]

A number of surgical techniques have been reported to preserve limb function.[1,26,32-42] Marginal resection of the soft tissue component of the bone tumor is common to all techniques. After resection, the osseous defect is traditionally filled with a massive cortical allograft (Figure 185-1), although other options include vascularized ulna grafts, endoprostheses, and segmental bone transport osteogenesis.[1,26,32-42] Arthrodesis of the adjacent joint is often required due to the metaphyseal and periarticular location of appendicular OSA.[1,26] Pancarpal arthrodesis is well tolerated in dogs, but arthrodesis of the shoulder, stifle, and tarsal joints results in poor limb function. Rarely, joint preservation is possible with ulnar or diaphyseal OSA. The limb is placed in a lightly padded bandage postoperatively with dressing changes every 3 to 5 days for 2 to 3 weeks.[1,26] Weight-bearing and range-of-motion exercises can be started immediately postoperatively but should be restricted to leashed walks for the first 4 weeks.[1,26] Exercise is important in preventing flexure contracture of the digits and minimizing swelling of the foot and digits, both of which can occur as a result of resection of the digital extensor muscles and tendons and vascular structures during surgery. Good to excellent limb use is achieved in over 80% of dogs.[1,26,32,33]

The most commonly reported complications with limb-sparing surgery are implant failure, local tumor recurrence, and infection.[1,26,32,33,37-39] Implant failure occurs in approximately 10% of cases.[1,26,32,33,37] The injection of methylmethacrylate into the medullary canal of the allograft increases screw pullout strength and reduces the incidence of screw loosening, implant failure, and allograft fracture.[37]

Local tumor recurrence is caused by incomplete resection or, more commonly, residual neoplastic cells in the soft tissue adjacent to the tumor capsule after marginal resection of the primary bone tumor.[1,26] Local recurrence has been reported in up to 28% of cases[33]; however, this rate can be reduced to less than 10% with locally released chemotherapy agents, such as cisplatin from open-cell polylactic acid biodegradable implants, appropriate case selection, and experience.[1,26,38] Local recurrence either has no effect[2] or a negative influence on survival time depending upon the study cited.[35] Local recurrence can be managed with a second limb-sparing surgery, amputation, or palliative radiation therapy.[26]

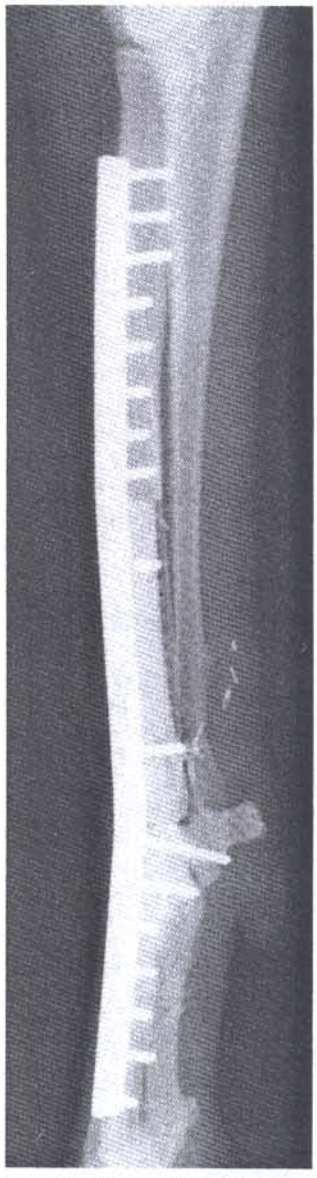

Figure 185-1 Lateral radiographic projection of limb-sparing surgery of the distal radius using a cortical allograft.

Infection is the most significant postoperative complication encountered with limb-sparing surgery.* The cause of infection is unknown, although the extensive soft tissue resection with vascular compromise to a poorly perfused site, poor soft tissue coverage, implantation of orthopedic implants and nonvascularized and possibly immunogenic cortical bone, and administration of local and systemic chemotherapy are thought to contribute.[26]

Infection occurs in over 40% of limb spare cases where reconstruction is performed with an allograft.[32,33,37,39] Several different bacterial organisms have been cultured with mono- and polymicrobial infections occurring in approximately 50% of cases each.[39] Initially, infections are treated with appropriate antibiotics based on culture and sensitivity results, isotonic saline lavages, and wet-to-dry bandages.[1,39] If the infection is unresponsive or recurrent, antibiotic-impregnated methylmethacrylate beads can be surgically implanted adjacent to the

*References 1, 26, 32, 33, 37, 39.

infected bone.[39] Limb amputation may be used as a salvage procedure in dogs with uncontrollable infection.[1,37,39]

Radiation Therapy Radiation therapy is most commonly used for palliation but can be used for control of the primary bone tumor in dogs where surgical options are either not indicated or refused.[46,47] Full-course external beam radiation therapy has been investigated.[46,47] The fractionation and radiosensitization protocols have varied, with total doses ranging between 24 to 54 Gy.[46,47] Complications include moist desquamation, alopecia, depigmentation, bone marrow suppression, and pathologic fracture.[46,47] The MST for dogs with OSA treated with curative-intent radiation therapy and adjuvant chemotherapy (AC) is 7 months.[46,47]

Chemotherapy Definitive management of dogs with appendicular OSA requires treatment of both the local bone tumor and micrometastatic disease. The efficacy of chemotherapy in other types of primary bone tumors is less clear. Surgery, unless combined with chemotherapy, is considered a palliative measure.[28-31,48-54] Conversely, chemotherapy without surgery does not provide a survival benefit over other palliative techniques.[55,56] In most institutions and oncology practices, chemotherapy is initiated at the time of suture removal. Current chemotherapy protocols include the use of cisplatin, carboplatin, and doxorubicin, either as a single agent or in combination (Table 185-2).[1,28-31,48-54] Studies have not shown large differences in survival times between the different protocols using single or multiple agents. Practically speaking, protocol selection is often dependent on drug cost, adverse effects, and intensity of treatment. If cisplatin is used, saline diuresis is necessary to minimize the risk of nephrotoxicity (Table 185-3).[1] Nephrotoxicity can also be reduced by using carboplatin instead of cisplatin or concurrently administering amifostine, which is used to prevent cisplatin-induced nephrotoxicity in humans.[1,42,53,54] Doxorubicin has been associated with myocardial toxicity, particularly with cumulative doses greater than 180 mg/m^2. Hence, an echocardiogram is recommended prior to starting chemotherapy, especially in high-risk breeds.[1]

After administration of chemotherapy, especially after the first chemotherapy dose, dogs should be discharged with antibiotics and antiemetics for palliation of gastrointestinal (GI) disease and nausea if needed at home. Hematology should be performed at the time of nadir, generally 7 to 10 days postchemotherapy, and again immediately prior to subsequent doses of chemotherapy to assess the presence and degree of myelosuppression. Chemotherapy administration should be delayed or the dose decreased if the neutrophil count is less than 2000/μL or platelet count is less than 100,000/μL.[1] The MST for dogs treated with surgery and chemotherapy is 235 to 366 days, with a 33% to 65% 12-month survival rate and 16% to 28% 24-month survival rate.[28-31,48-54]

The role of immunotherapy in the treatment of dogs with OSA is undefined. A significant improvement in disease-free interval (DFI) and survival time has been reported in dogs treated with a nonspecific immunostimulant, muramyl tripeptide phosphatidylethanolamine.[57,58] Increased immune stimulation is also suspected in the prolonged survival times in dogs with infected limb-sparing surgery and four dogs with spontaneous regression of OSA lesions.[53,59]

Digit Osteosarcoma OSA arising in bones distal to the carpus or tarsus are rare.[1,6] Treatment recommendations include limb salvage (i.e., amputation of the affected digit and metacarpal or metatarsal bones) followed by chemotherapy.[1,60] Similar to humans, the prognosis for dogs with OSA distal to the carpus or tarsus is better than other appendicular sites, with a MST of 466 days.[60] However, the biologic behavior is still aggressive with most dogs euthanatized due to metastatic disease.[60]

Metastasis Metastatic disease is the most common cause of death or euthanasia in dogs with appendicular OSA after definitive treatment.[1] Pulmonary and skeletal sites are most frequently involved, although other metastatic sites include subcutaneous tissue, mediastinum, myocardium, diaphragm, kidneys, spleen, small intestine, spinal cord and brain, and lymph nodes.[1,9,12]

Interestingly, metastatic disease rarely occurs in dogs undergoing palliative, nonsurgical treatment but is the major cause of death in dogs treated with surgery alone, despite the minimal difference in survival time. A recent study, using

Table • 185-2

Chemotherapy Protocols Used in the Management of Dogs with Appendicular Osteosarcoma*†

AGENT OR AGENTS	DOSE	INTERVAL	NUMBER	COMMENTS
Cisplatin	70 mg/m^2	3 weeks	5	Vomiting during administration, nephrotoxicity, gastrointestinal (GI) toxicity, mild myelosuppression; nadir at 10 days; MST 262-413 days
Carboplatin	300 mg/m^2	3 weeks	4	Myelosuppression, GI toxicity; nadir at 11-14 days; MST 321-366 days
Doxorubicin	30 mg/m^2	2-3 weeks	5	Anaphylaxis during administration, GI toxicity, myocardial toxicity, myelosuppression, nadir at 10 days; MST 366 days
Cisplatin Doxorubicin	50 mg/m^2 15 mg/m^2	3 weeks	4	Cisplatin administered on day 1 and doxorubicin on day 2; MST 300-540 days
Carboplatin Doxorubicin	300 mg/m^2 30 mg/m^2	3 weeks	6	Carboplatin and doxorubicin administered alternately every 3 weeks for 3 doses each, for a total of 6 doses; MST 388 days

*Adapted from Dernell WS et al: Tumors of the skeletal system. In Withrow SJ, MacEwen EG, editors: *Small animal clinical oncology*, ed 3, Philadelphia, 2001, WB Saunders.

†Liptak JM et al: Survival analysis of dogs with appendicular osteosarcoma treated with limb-sparing surgery and adjuvant carboplatin or carboplatin and doxorubicin, *Pers Comm, Proc Vet Cancer Soc Conf* 21:39, 2001.

Table • 185-3

*Saline Diuresis Protocols Used to Minimize Cisplatin-Associated Nephrotoxicity**

PROTOCOL	PHASE I	PHASE II	PHASE III
6 hr	Saline, 18.3 mL/kg/hr, 4 hr	Cisplatin for 20 min	Saline, 18.3 mL/kg/hr, 2 hr
24 hr	Saline, 3.75 mL/kg/hr, 16 hr	Cisplatin for 16 hr	Saline, 3.75 mL/kg/hr, 6 hr

*Adapted from Dernell WS et al: Tumors of the skeletal system. *In* Withrow SJ, MacEwen EG, editors: *Small animal clinical oncology*, ed 3, Philadelphia, 2001, WB Saunders.

a mouse OSA model, showed that primary tumor resection enhanced systemic angiogenesis resulting in progression of distant metastatic lesions.[61] The distribution of metastatic lesions depends on the type of treatment. Pulmonary metastases are more common when only the local tumor is ablated, whereas skeletal metastases are more prevalent when chemotherapy is added to the treatment regimen. Pulmonary metastasis accounts for 61% of all metastatic lesions in dogs treated with amputation alone and 26% when treated with amputation and cisplatin.[12,50] In comparison, skeletal metastases develop in 47% of dogs after surgery and postoperative cisplatin.[50]

Generalized malaise is the most common sign in dogs with pulmonary metastasis. Respiratory signs are usually a late development (Figure 185-2). Occasionally, hypertrophic osteopathy may be the first indication of pulmonary metastasis. Chemotherapy, using platinum and antibiotic agents, is ineffective in prolonging survival time in dogs with measurable pulmonary metastasis.[62] Surgical resection of metastatic lesions, by either subpleural resection or partial lung lobectomy, can significantly improve survival time in select cases (Figure 185-3).[63] Candidates for pulmonary metastasectomy include dogs that develop pulmonary metastasis greater than 300 days after initial diagnosis of appendicular OSA, have no more than three radiographically evident metastatic lesions, and have lesions that do not double in size or no new lesions that develop in a 4-week period.[63] The MST for dogs with metastasis to the lungs is 61 days when treated with chemotherapy and 176 days after metastasectomy.[62,63]

Management options for dogs with skeletal metastasis include pain control with analgesic drugs, bisphosphonates, and palliative radiation therapy. Bisphosphonates block osteoclast activity, thereby minimizing the risk of pathologic fracture.[64,65] Limb-sparing surgery and curative-intent radiation therapy have been used to treat metastatic skeletal lesions for select cases but are not routinely recommended.

Prognostic Factors In dogs with appendicular OSA, a number of factors have been identified as being prognostic. OSA can be histologically subclassified into osteoblastic, chondroblastic, fibroblastic, telangiectatic, and undifferentiated OSA; however, histologic subtype has not been shown to be prognostic in dogs or humans.[1] Poor prognostic factors in dogs

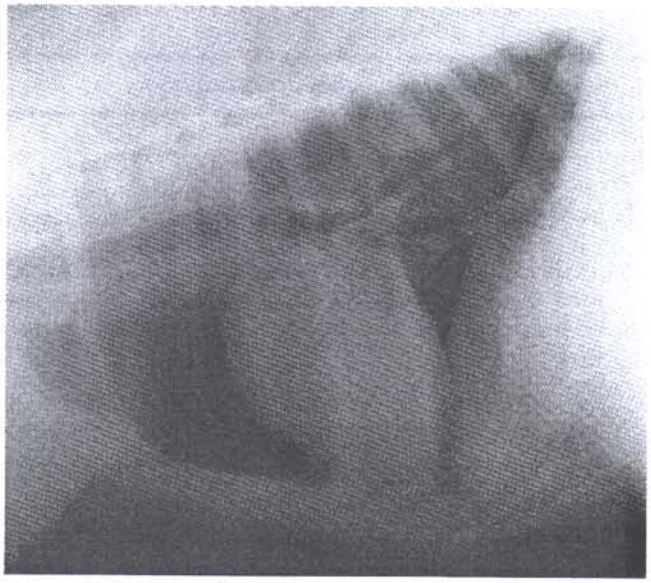

Figure 185-2 Lateral radiographic projection of a dog 8 months after limb-sparing surgery for a distal radial osteosarcoma (OSA). Two metastatic lesions are seen in the dorsal lung fields.

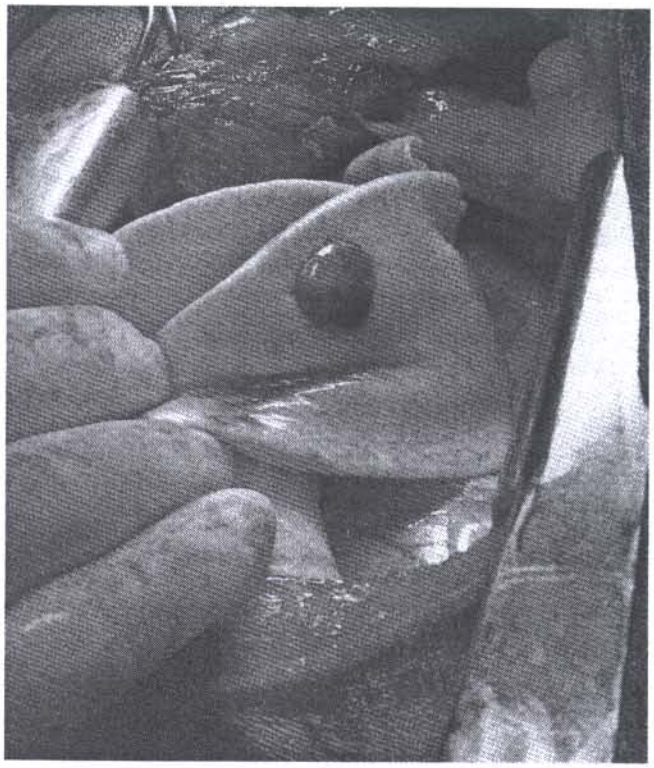

Figure 185-3 Intraoperative image of a metastatic lesion from an appendicular osteosarcoma (OSA). Partial lung lobectomy was performed and the dog is still alive 256 days after metastasectomy.

with OSA include age less than 7 years and older than 10 years, body weight greater than 40 kg, large tumor volume, proximal humeral location, increased preoperative total and bone-specific serum alkaline phosphatase (ALP) activities and failure to normalize within 40 days of surgical removal of the tumor, high tumor grade, and presence of metastatic disease.* Dogs with proximal humeral OSA have a significantly shorter DFI and MST than other appendicular OSA sites; however, this may be a function of tumor volume rather than site.[48] The MST for dogs with normal and elevated total serum ALP is 12.5 and 5.5 months, respectively.[66] The MST for dogs with normal and elevated bone-specific serum ALP is 16.6 and 9.5 months.[66] For both bone-specific and total serum ALP, each increase of 100 IU/L increases the risk of death due to OSA by 25%.[66,67]

Other Canine Appendicular Tumors

Chondrosarcoma CSA is the second most common primary bone tumor in dogs.[1] Appendicular CSA accounts for 9% to 17% of all canine CSA cases.[68-71] The cause is unknown, although CSA has been reported to arise from osteochondroma or sites of previous trauma.

Golden retrievers, German shepherds, and boxers are over-represented, and the median age at presentation is 6 to 8.7 years.[68-71] Clinical findings are similar to dogs with appendicular OSA, and biopsy is required to differentiate tumor types. The femur is most commonly involved, and CSA may have a more lytic radiographic appearance than OSA.[70,71] Limb amputation and limb salvage procedures can be used to manage the local tumor. Metastatic disease is reported in up to 21% of dogs with CSA but usually occurs late in the course of disease.[68-71] Chemotherapy does not provide a survival benefit in humans with CSA, and a similar situation probably exists in dogs.[72]

Fluoroquinolones may have a role in the management of dogs with CSA because these antibiotics are toxic to chondrocytes and, in in vitro studies, inhibit chondrocytic proliferation and induce chondrocyte apoptosis.[73] The MST for dogs with untreated CSA is 46 days compared with 540 days for dogs treated with limb amputation alone.[71] Prognostic criteria in dogs include tumor location and histologic grade, although these are not well defined.[70,74]

Fibrosarcoma FSA is the third most common skeletal neoplasm in dogs and occurs more commonly in axial than appendicular sites.[69] Two distinct appendicular FSAs exist: (1) central and (2) parosteal.[75] A palpable mass is often present in dogs with parosteal but not central FSA. Parosteal FSA may represent a tumor of soft tissue origin with secondary invasion into bone.[69,75] The radiographic features of appendicular FSA are similar to OSA, although lytic lesions and pathologic fracture are reported in up to 50% of dogs with FSA.[75] Amputation and limb salvage are the main surgical treatment options. The role of AC is unknown. Appendicular FSA metastasizes late in the course of disease, often to sites other than the lungs, such as myocardium, pericardium, skin, and other bones.[75] Survival times are difficult to interpret because more than 50% of fibroblastic OSAs are misdiagnosed as FSA.[1,75] The 12-month survival rate for dogs with appendicular FSA treated with limb amputation alone is 66%.[75]

Hemangiosarcoma HSA is rare and accounts for 3.6% of all primary bone tumors. German shepherd, Great Dane, and boxer dogs are over-represented, with a mean age at presentation of 6.2 to 8.2 years. This is a younger age at presentation than what is reported with most other primary bone tumors.[69] A relatively equal distribution exists between appendicular and axial sites, with 43% of cases occurring in the appendicular skeleton.[69,76] The proximal humerus is the most common appendicular site.[76] Skeletal HSA has a different biologic behavior than other primary bone tumors. The majority of appendicular HSAs have a lytic radiographic appearance. Cortical and periosteal changes may be minimal.[69,76] Polyostotic disease, soft tissue extension, and pathologic fractures are common.[69,76] In dogs with appendicular HSA, abdominal ultrasonography and echocardiography are recommended (in addition to the other standard staging tests), because 82% of dogs are reported with extraosseous disease or metastasis.[76] The value of local and systemic treatment is uncertain because the majority of dogs develop metastatic disease before 6 months and the 12-month survival rate is less than 10%.[69,76] However, limb amputation and doxorubicin-based chemotherapy protocols may be indicated for dogs with nonmetastatic monostotic appendicular HSA.[77] Palliative radiation therapy may be used in dogs with polyostotic disease.

Multiple Cartilaginous Exostoses Multiple cartilaginous exostosis (MCE) is a developmental disease of immature dogs.[78-86] A hereditary predisposition is suspected. The true pathogenesis of MCE in dogs is unknown. Bony lesions in metaphyseal areas near endochondral ossification sites characterize MCE. The lesions can be single (osteochondroma) or multiple.[78-80] They originate at the metaphysis but move away from the physis with progressive longitudinal bone growth.[1] MCEs usually stop growing when dogs reach skeletal maturity. Continued growth beyond skeletal maturity is suggestive of malignant transformation, although continued non-neoplastic growth has been reported.[78-80] Malignant transformation to OSA or CSA of single osteochondromas has been reported.[80-85] A persistent cartilage cap on the apical margins of the MCE has been present in the majority of dogs with malignant transformation and, in humans, where up to 25% of MCE become neoplastic, the potential for malignant transformation can be predicted from the thickness of the apical cap on MRI.[85,86]

The incidence of MCE is difficult to determine because many dogs are clinically asymptomatic. When they occur, clinical signs are caused by interference or compression of adjacent structures, such as the spinal cord, peripheral nerves, or high motion tendons.[78-80] Regional radiographs will reveal a bony mass on the surface of the affected bone.[78-80] The radiographic appearance is consistent with a benign, nonaggressive proliferative process and minimal cortical disruption. Bilaterally symmetrical lesions may be present. The medullary cancellous bone is radiographically and histologically contiguous with the parent bone.[78-80] Epiphyseal bone is nearly never involved.[1,78-80] Vertebral and rib MCE lesions are typically spherical, with a sessile or pedunculated base. Long bone MCE lesions have a more irregular surface.[78-80] The radiographic features of malignantly transformed MCE include an indistinct, poorly mineralized mass with a thickened cartilage cap.[78-85]

Treatment options for MCE vary with age, location, and severity of symptoms. For appendicular lesions, conservative management with analgesic drugs is appropriate until skeletal maturity. Local excision is indicated if the dog is unresponsive to medical management.[1] The entire lesion, including the cartilage cap, should be submitted to ensure accurate histologic interpretation. Neutering is recommended in dogs with MCE due to its possible heritable nature.[1]

The prognosis for dogs with monosteal or bilaterally symmetrical appendicular MCE is good. However, the prognosis for MCE may be guarded when multiple lesions are present. In one review, 38% of dogs were euthanized before 12 months of age due to progressive clinical signs. Malignant transformation of MCE, particularly solitary lesions, was reported in 83% of 6 dogs older than 6 years.[79,80]

*References 1, 9, 12, 48, 66, 67.

Cats

Osteosarcoma Primary bone tumors are uncommon in cats.[87-90] Unlike dogs, 10% to 33% of primary bone tumors in cats are benign.[88] OSA is the most common tumor, accounting for 70% to 80% of all feline bone tumors, whereas FSA, CSA, HSA, and rhabdomyosarcoma have also been reported.[87-89,92] The mean age at diagnosis of appendicular OSA is 10.2 years, and males are over-represented with a male-to-female ratio of 1.7:1.[88] A number of differences are seen in the presentation and biologic behavior of OSA in cats versus dogs. In feline OSA, bones of the pelvic limb are involved 1.6 times more frequently than the thoracic limb.[88] The proximal humerus is the most common site, closely followed by the distal femur and proximal tibia.[87-91] The radiographic features of primary bone tumors in cats are similar to dogs, although lytic and juxtacortical lesions are more common.[87,88,90,91] Metastasis is uncommon and is diagnosed in less than 10% of cats with OSA.[87-91] Metastatic sites include lungs, brain, liver, kidneys, and spleen. Due to the infrequency of metastatic disease, limb amputation without chemotherapy is recommended for the treatment of cats with appendicular OSA. The MST after limb amputation alone is reported to be 11.8 to 49.2 months.[87,88,90,91]

Other Feline Appendicular Tumors FSA and CSA have a similar biologic behavior to OSA (Figure 185-4). Limb amputation may be curative although metastatic disease has been reported for both tumor types.[87,88]

PRIMARY AXIAL TUMORS

Canine Osteosarcoma

OSA of the axial skeleton accounts for 25% of all OSA and 59% of OSA in dogs weighing less than 15 kg.[4,93] However, medium to large breed dogs are commonly affected.[93,95] Boxers may be over-represented, and a female predisposition is reported for all axial sites except the ribs and vertebrae.[93,94] The most common sites of axial OSA, in order of frequency, are mandible (27% of axial OSA), maxilla (16% to 22%), vertebrae (7% to 15%), scapula (13%), skull (11% to 12%), ribs (10% to 11%), nasal and paranasal sinuses (9%), and pelvis (4% to 5%).[93,94] OSA of the hard palate and patella have also been reported.[96,97]

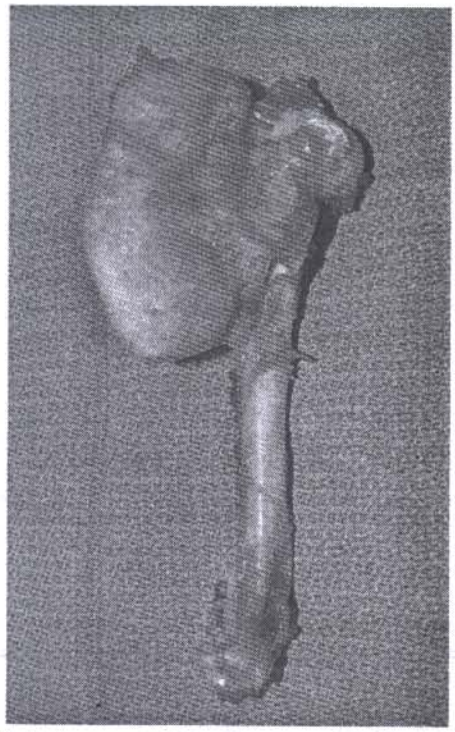

Figure 185-4 Juxtacortical chondrosarcoma (CSA) of the proximal humerus of a cat.

Advanced imaging, particularly CT scans, are useful for staging and surgical planning of tumors of the axial skeleton. Surgical resection is recommended although radiation therapy can also be used for control of the local tumor.[93-95] Local recurrence is reported in up to 80% of dogs, and the metastatic rate varies between 11% to 46%.[93-95] Local recurrence, rather than metastasis, is the most common cause of death and chemotherapy has not been shown to improve metastatic rate or survival time.[93-95,98-103]

Overall, the MST for dogs with axial OSA is 120 to 154 days, with a 12- and 24-month survival rates of 26.3% and 18.4%, respectively.[93-95] Prognostic factors include anatomic site, body size, breed, and surgical margins.[94,95,98-103] Smaller breed dogs have a significantly better survival than large breed dogs.[94] The MST of golden retrievers with axial OSA is 100 days, compared with 182 days in pure bred dogs and 264 days in mixed-breed dogs.[95] Mandibular OSA has a better prognosis than OSA of the ribs, scapulae, and skull.[94] The MST after palliative and curative-intent radiation therapy of axial OSA in large breed dogs is 79 and 265 days, respectively.[95] Incomplete surgical resection significantly increases the risk of local recurrence and metastasis.[98-103]

Skull Tumors

OSA of the skull can involve the calvarium, nasal and paranasal sinuses, maxilla, and mandible. Calvarial OSA accounts for 11% to 12% of axial OSA.[93,94] Signs include a visible external mass and neurologic signs due to extradural compression of the brain. Direct invasion of the brain is rare.[1] Surgical resection is recommended after CT imaging. Intra- and postoperative complications include cerebral edema, brain herniation, pneumomeningocoele, aspiration pneumonia, and death.

Axial OSA may also involve the maxilla and mandible; however, it is less common than the other tumors affecting these bones. The most common canine oral tumors are malignant melanoma, squamous cell carcinoma, FSA, OSA, and the benign epulides.[98-102] In the majority of these tumors, except for OSA, mandibular and maxillary bone is secondarily involved by tumor invasion.[98-102] Signs include a visible mass, halitosis, ptyalism, exophthalmos, and jaw pain; eating difficulties and dyspnea are also reported.[98-102] Regional radiographs are sufficient for local staging of most mandibular tumors, although CT imaging is recommended for tumors of the vertical mandibular ramus (Figure 185-5) and maxilla. Surgical resection (i.e., mandibulectomy, maxillectomy) provides the best opportunity for local tumor control. Postoperative cosmesis is usually excellent.[98-102]

The most common cause of death in dogs with axial OSA is local tumor recurrence rather than metastasis. Metastasis is reported in up to 30% of skull OSA. The MST for mandibular OSA treated with mandibulectomy is 7 to 18 months with a 12-month survival rate of up to 71%.[98-100] Histologic grade and score are predictive of survival in dogs with mandibular OSA.[100] In contrast, the MST for maxillary OSA treated with maxillectomy is 4.5 to 10 months, with a 12-month survival rate of 17% to 27%.[101,102] Aggressive surgical excision, with complete histologic resection, results in a significant improvement in local recurrence and survival rates, with a reported MST greater than 1503 days.[103] Postoperative radiation therapy and chemotherapy have not been shown to provide a survival benefit, even in dogs with incomplete tumor resection.[95,103]

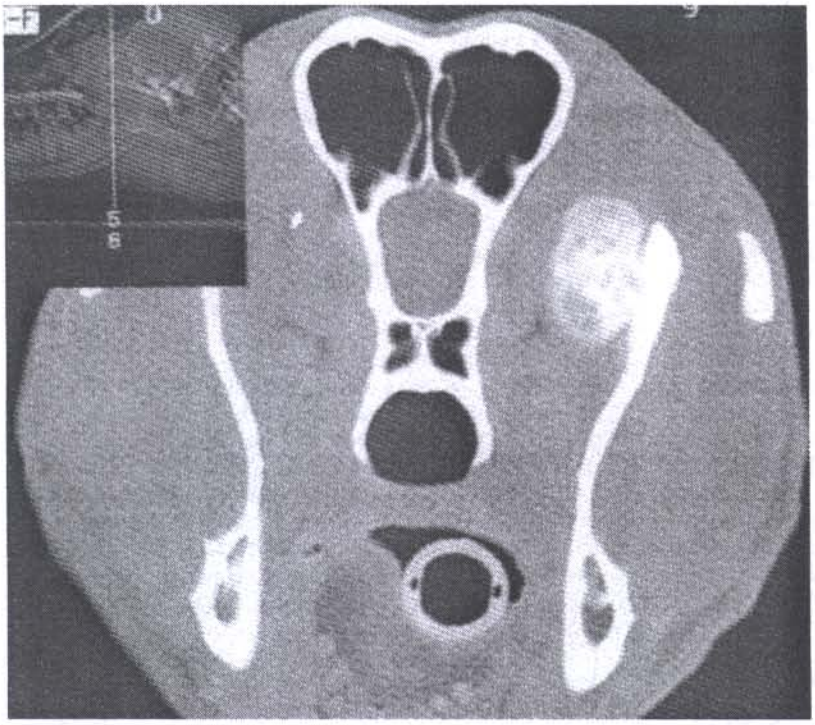

Figure 185-5 Sagittal computerized tomographic (CT) image of a grade III multilobular osteochondrosarcoma (MLO) of the vertical ramus of the mandible. Complete resection was performed with a caudal mandibulectomy and the dog is alive and disease free 308 days postoperatively.

Scapular Tumors

Scapular OSA is relatively uncommon and accounts for up to 13% of all axial OSA.[69,93-95] CSA, FSA, and HSA have also been reported to involve the scapula.[70,104-106] Lameness is the most common clinical sign. Radiographic changes are consistent with appendicular OSA, with a mixed pattern of lytic and productive changes most common.[104] However, due to positioning difficulties and superimposition of the body wall, the extent of disease may be difficult to determine. CT imaging is helpful to determine the location and extent of scapular involvement. Surgical resection (partial scapulectomy) is recommended with good to excellent limb function after subtotal scapulectomy of up to 90% of the scapula.[104,105] Because a high metastatic rate has been reported in dogs with scapular OSA, postoperative chemotherapy is recommended.[93,94]

Pelvic Tumors

OSA of the pelvic bones accounts for 4% to 6% of axial OSA.[69,93,94] Pelvic FSA, CSA, and OSA occur at relatively equal frequencies.[68,70,71,107] Boxer dogs may be predisposed to pelvic CSA.[68] Lameness is common, although tenesmus, due to compression of the rectum, and neurologic deficits, as a result of peripheral nerve compression, have also been observed. Radiographic abnormalities are similar to appendicular OSA (Figure 185-6). CT imaging is helpful for local staging and surgical planning. Surgical resection, with either subtotal or total hemipelvectomy, is the recommended treatment for dogs with pelvic tumors.[107] If necessary, the lateral third of the sacrum, lateral to the dorsal sacral foramina, can be resected en bloc with the affected pelvis. Limb salvage is possible if the weight-bearing axis can be preserved by internal hemipelvectomy. Chemotherapy is recommended for dogs with pelvic OSA because their biologic behavior is similar to appendicular OSA with a high metastatic rate.[107] However, the metastatic rate of pelvic FSA and CSA is low and chemotherapy is probably not required.[107]

Rib Tumors

Rib tumors are uncommon and reported tumor types include OSA, CSA, FSA, HSA, multilobular osteochondrosarcoma (MLO), and mast cell tumor.[1,93-95,108,109] OSA is the most common rib tumor accounting for 73% of rib tumors and 11% of axial OSA.[93,94,108,109] No breed or sex predispositions have been reported, but rib tumors tend to occur in younger, large breed dogs with a mean age of 4.5 to 6 years.[93-95,108,109]

Rib tumors usually occur in the distal third of the rib adjacent to the costochondral junction.[108,109] A palpable firm and fixed mass is the most common clinical sign, although pain and dyspnea are also reported. Radiographic changes include lysis, sclerosis, or a mixture of lytic and blastic patterns, with displacement of adjacent ribs and intrathoracic structures, such as the heart and lungs, and medial displacement of the parietal pleura resulting in an extrapleural sign (Figure 185-7).[108,109] Intrathoracic extension and invasion of adjacent pericardium and lung lobes are relatively common. Pulmonary metastasis is common, particularly with telangiectatic OSA, and up to 45% of dogs with rib OSA have metastatic disease at diagnosis.[108,109] Metastasis was detected in 100% of dogs with rib OSA, 53% to 57% with CSA, 67% with HSA, and 100% of dogs with rib FSA at the time of death.[108,109] Due to the similar biologic behavior of rib and appendicular OSA, rib OSA should be treated with rib resection and postoperative chemotherapy. The role of chemotherapy in other tumor types is undefined but warrants consideration due to the high metastatic rate.

Tumor type and surgical margins are prognostic. The MST after rib resection alone for OSA and CSA is 90 and 1080 days, respectively.[108,109] Completeness of surgical margins is an important prognostic indicator. Dogs with incomplete excision are 5.6 times more likely to develop local recurrence and possibly metastatic disease.[109] In dogs with rib OSA, postoperative treatment with chemotherapy extends the MST to 240 days.[109]

Vertebral Tumors

OSA is the most common extradural tumor of the nervous system and accounts for up to 16% of axial OSA.[93,94,110,111] Other vertebral tumors include CSA, FSA, HSA, MCE, lymphoma, liposarcoma, giant cell tumor, plasma cell tumors, either as solitary plasmacytoma or multiple myeloma, and metastatic carcinomas and sarcomas.[110,111] A breed predisposition has not been reported, although German shepherd

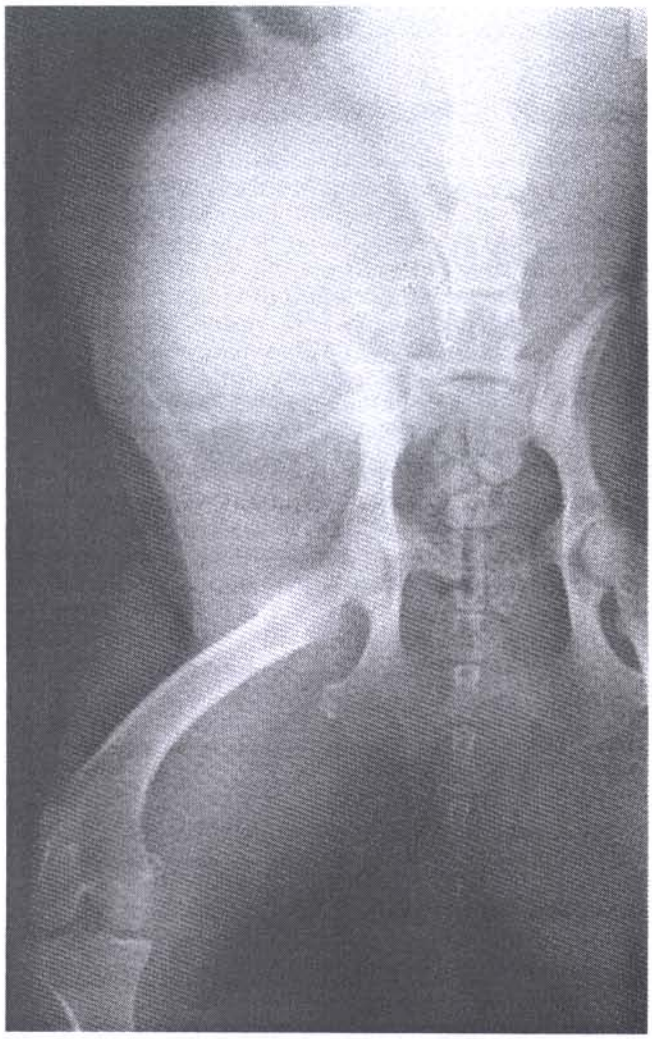

Figure 185-6 Ventrodorsal radiograph of a grade I chondrosarcoma (CSA) of the right ilium. The reader should note the large tumor volume and compression rather than invasion of the transverse processes of the sixth and seventh lumbar vertebra. Hemipelvectomy was performed, and the dog is alive and disease free 516 days postoperatively.

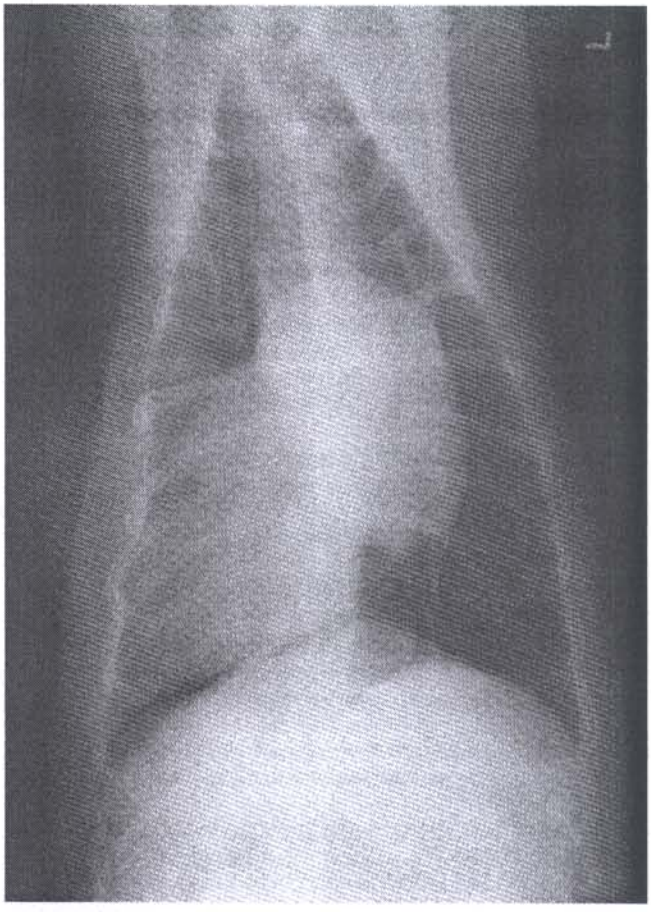

Figure 185-7 Ventrodorsal radiograph of an osteosarcoma (OSA) of the seventh rib is displacing the heart and caudal lung lobes to the left side.

dogs, Labrador retrievers, and standard poodles were overrepresented in one study.[110] Large breeds are commonly affected. Only 5% of dogs with vertebral tumors weighed less than 20 kg.[110,111] Primary vertebral tumors tend to occur in a younger subset of dogs than metastatic tumors of the vertebrae. The median age for dogs with primary vertebral tumors is 6 to 8 years and 8 to 9 years for secondary tumors.[111] A thorough physical examination should be performed to identify possible occult primary tumors. Carcinomas of the mammary and thyroid glands, bladder, and prostate, and visceral HSA are known to metastasize to the vertebrae. Thoracic and lumbar vertebrae are most commonly involved.[110]

Pain and neurologic deficits are the two most common signs in dogs with vertebral tumors.[110,111] Neurologic deficits are caused by compression of nerve roots or the spinal cord.[110,111] Neurologic signs are typically slowly progressive, but pathologic fracture will cause an acute deterioration in neurologic function. A neurologic scoring system has been devised and is prognostic for outcome and survival.[111]

A spectrum of radiographic changes is observed in dogs with vertebral tumors. These changes can be difficult to detect due to inconsistent vertebral shape and superimposition of overlying ribs and soft tissue.[110] Cortical lysis with vertebral body collapse is a characteristic finding in primary vertebral tumors but a late event in metastatic tumors.[110,111] Skip and multiple tumors are reported in up to 25% of dogs with vertebral OSA and can be difficult to differentiate from metastatic tumors.[110] Osteochondromas and MCE are well-circumscribed benign lesions that frequently involve the dorsal spinal elements, such as the dorsal lamina and spinous process, rather than the vertebral body.[78,79] Other imaging techniques include myelography, CT and MRI, and nuclear scintigraphy.

Nuclear scintigraphy can be beneficial in identifying the location of single and multiple lesions but cannot differentiate multifocal OSA from multiple metastatic lesions. Furthermore, most plasma cell tumors are photophenic due to marked osteolysis and minimal new bone production. Myelographic changes include collapse of the subarachnoid space and unilateral or asymmetric displacement of the spinal cord.[110] Advanced imaging provides the most accurate information for evaluating the degree of vertebral involvement but differentiating intra- and extradural involvement can be difficult.[112]

Surgical resection, with vertebrectomy, is rarely feasible, although dorsal decompression can provide meaningful palliation in dogs with localized dorsal tumors.[111,113] Radiation therapy, either with palliative- or curative-intent, can be beneficial in dogs with vertebral tumors.[111] The role of chemotherapy is unknown, even in dogs with vertebral OSA, because most

dogs are euthanatized due to the local tumor rather than metastatic disease.[111]

Overall, the MST for dogs with malignant vertebral tumors is 135 days.[111] Survival time is not significantly influenced by preoperative neurologic score, tumor type (OSA or FSA), primary or metastatic disease, anatomic location (cervical, thoracic, or lumbar), chemotherapy, or radiation therapy.[111] Although not significant, neurologic score can provide useful information as dogs with a preoperative score of 1 had a survival time of 330 days compared with 120 days if the neurologic score was greater than 1.[111] Furthermore, dogs with a posttreatment neurologic score of 1 or 2 were 12 times more likely to survive than dogs with posttreatment score of 3 or 4.[111] Curative-intent radiation therapy provides a significant improvement in survival time when compared with palliative radiation, with survival times of 150 and 15 days, respectively.[111]

Nasal and Paranasal Tumors

Adenocarcinoma is the most common tumor of the nasal and paranasal sinuses.[114-116] Sarcomas, such as CSA and OSA, are uncommon.[68-71,93-95,114-116] Dolichocephalic breeds are predisposed, particularly if living in an urban environment with exposure to smoke. Nasal and paranasal tumors, regardless of tumor type, are characterized by local invasiveness and a low metastatic rate, although up to 50% of dogs have metastasis to the regional lymph nodes and lungs at necropsy.[114-116] Unilateral epistaxis is the most common sign. Other less frequent signs include sneezing, dyspnea, stertorous respiration, facial deformity, and seizures.[114-116] Advanced imaging is recommended for local staging and determination of the caudal extent of the tumor in relation to the cribriform plate. Unlike tumors of other axial and appendicular sites, nasal and paranasal tumors are usually not amenable to surgical resection. Full-course fractionated radiation therapy is the recommended treatment resulting in a MST of 424 to 580 days.[114-116] An improved survival time is seen when radiation is combined with radiation sensitizers, such as local or systemic cisplatin.[114]

Other Canine Axial Tumors

Multilobular Osteochondrosarcoma MLO is an uncommon tumor arising from the periosteum of bones formed by intramembranous ossification.[117,118] The skull is most commonly involved, including the calvarium, orbit, zygomatic arch, mandible, and maxilla.[117,118] Other sites include the pelvis, ribs, and hard palate. Cats have also been reported with MLO.

MLO is usually a disease of middle-aged, large breed dogs.[117,118] No known sex or breed predisposition exists. Clinical signs are dependent on tumor location and include a palpable firm and fixed mass, neurologic signs with calvarial MLO, pain on opening of the jaw with mandibular and zygomatic arch MLO, exophthalmos with orbit MLO, and dyspnea with MLO of the tympanic bulla.[117,118] The imaging changes associated with MLO are characteristic with the tumor described as having a popcorn appearance with well-defined borders and a lobulated pattern on both radiographs and CT scans.[117-120] Advanced imaging is indicated for surgical planning of calvarial MLO because the extent of intracranial involvement can be extensive (Figure 185-8).[119,120]

Treatment options include surgical resection and radiation therapy.[117,118] Cranioplasty, using either allografts or bone cement, has been described after calvarial resection but is probably unnecessary. Neurologic recovery, particularly with marked intracranial involvement, can be prolonged, although the majority of dogs will return to normal function within 2 weeks. MLOs have a slow growth rate, and this would usually result in a relative resistance and poor response to radiation therapy. Although not well investigated, good responses have been reported using external beam radiation therapy and radiopharmaceuticals.[118]

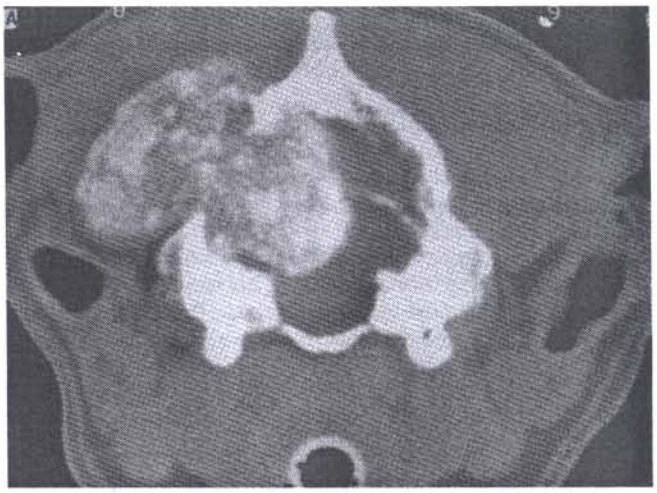

Figure 185-8 A sagittal computerized tomographic (CT) image of a grade I multilobular osteochondrosarcoma (MLO). The reader should note the characteristic popcorn appearance of the mass and significant intracranial involvement.

A histologic grading scheme for MLO is prognostic for local recurrence and metastasis.[117] Other prognostic factors include site and completeness of surgical resection.[117,118] The overall rate of local recurrence is 47% to 58%, with a median DFI of 426 to 797 days, although this rate varies with histologic grade.[117,118] The local recurrence rate for grade I MLO is 30%, grade II is 47%, and grade III is 78%.[117,118] Furthermore, an aggressive surgical approach is recommended because incomplete resection significantly increases the risk of local recurrence. The median DFI after incomplete resection is 330 days, but median DFI was not reached and greater than 1332 days with completely resected MLO.[117,118]

Metastasis is reported in up to 58% of dogs with MLO. The lungs are the most common metastatic site, accounting for 90% of cases, although other sites include brain, pancreas, kidneys, mediastinum, and ribs.[117,118] Surgical margins and histologic grade are prognostic for the development of metastatic disease.[118] Metastasis is diagnosed in 25% of dogs after complete resection and 75% of dogs with incompletely resected MLO.[118] The metastatic rate for grade I MLO is 30%, grade II MLO is 60%, and grade III MLO is 78%.[118] The MST after diagnosis of recurrent or metastatic disease is 239 days, and many dogs with pulmonary metastasis from MLO are good candidates for pulmonary metastasectomy.[117,118]

The MST for untreated MLO is 24 days compared with 669 to 797 days for surgically resected MLO.[117,118] Tumor site is prognostic with mandibular MLO having a significantly better MST than other sites, with 1487 days for mandibular MLO and 528 days for nonmandibular MLO.[118] The MST for grade I MLO is greater than 897 days, whereas the MST for grade II and III MLO is 520 and 405 days, respectively.[118]

Osteoma Osteomas account for 6% of all primary bone tumors in cats and dogs.[1,69,87] Osteomas are formed by intramembranous bone and occur in the axial skeleton, particularly the skull. A palpable, nonpainful mass is usually present and appears as well-circumscribed dense bony projections on regional radiographs. Osteomas have similar histologic features to reactive bone. Surgical resection is recommended for problematic or uncosmetic lesions.[1]

Cats

Osteosarcoma OSA is the most common tumor of the feline axial skeleton.[87,91] FSA and CSA are also reported to

involve the axial skeleton.[87,88] The mean age at presentation for cats with axial OSA is 10.4 years, which is significantly older than cats with appendicular OSA.[91] The skull and pelvis are frequently affected, although other sites include ribs, vertebrae, and scapulae.[87-91] The presenting signs, radiographic features, and treatment recommendations are similar to malignant canine axial tumors. Periosteal new bone formation and juxtacortical tumors are more common in cats with axial OSA.[87,90] Complete surgical resection is complicated by tumor location, resulting in incomplete resection and poor tumor control. The MST for cats with axial OSA is 5.5 to 6.1 months, with most euthanatized due to local recurrence rather than metastatic disease.[90,91]

Feline Multiple Cartilaginous Exostosis In contrast to dogs, feline MCE develop after skeletal maturity, appendicular skeletal involvement is rare, and the majority have a viral or familial cause.[88] The mean age at diagnosis is 3.2 years.[88] A sex or breed predisposition is unlikely, although Siamese were over-represented in early reports.[1] The vast majority of cats with MCE are positive for feline leukemia virus (FeLV).[1,88] In these cats the disease is rapidly progressive with firm, painful swelling of axial sites such as the scapula, vertebrae, and ribs. Radiographically, feline MCEs appear as sessile or pedunculated masses arising from the surface of affected bones with bony lysis and loss of smooth bony contour.[1,88] Surgical resection is indicated for painful lesions, although complete resection is difficult, because the cartilage caps tends to infiltrate adjacent tissue and local recurrence is common.[1,88] Malignant transformation and metastasis are also possible.[88]

METASTATIC BONE TUMORS

Metastatic bone tumors are infrequently diagnosed in cats and dogs. Metastasis usually occurs via the hematogenous route. In dogs, urogenital carcinomas, particularly bladder and prostate, are the most common primary tumors to metastasize to bone.[4,121] Skeletal metastasis is also reported in dogs with OSA, mammary carcinoma, thyroid carcinoma, pulmonary carcinoma, nasal carcinoma, apocrine gland anal sac adenocarcinoma, and renal tumors.[1,4,121-124] Metastatic lesions represent 24% of all bone tumors in dogs weighing less than 15 kg and only 5% in large breed dogs.[1,4,123] The most common metastatic sites are the axial and proximal appendicular skeleton with less than 11% of dogs having metastatic lesions distal to the elbow or stifle.[121] In contrast, acrometastasis involving one or more digits is the most common presentation for cats with metastatic pulmonary carcinoma.[122-125]

Nuclear scintigraphy is recommended for the identification of multiple bone lesions (Figure 185-9). Treatment options for skeletal metastasis include surgery, radiation therapy, and pharmaceutical agents.[64] Surgical curettage and stabilization of metastatic lesions is uncommonly performed in veterinary medicine but may provide a meaningful response in select cases. Radiation therapy is indicated for management of pain and inflammation.[22]

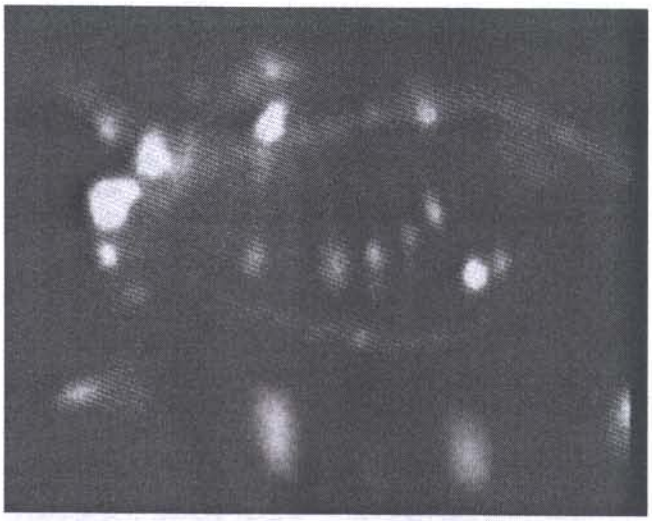

Figure 185-9 Nuclear scintigraphy of a dog with prostatic transitional cell carcinoma. The reader should note the numerous metastatic lesions in the proximal radius, proximal humerus, cervical and thoracic vertebrae, ribs, and sternum.

PRIMARY JOINT TUMORS

Dogs

Joint tumors are usually primary and malignant.[126-130] Previously, synovial cell sarcoma was considered the most common tumor of the canine joint.[126,127] However, recent evidence suggests that other soft tissue sarcomas of periarticular tissue are more prevalent and immunohistochemistry (IHC) is required to differentiate these tumor types.[128,129] Other reported joint tumors include histiocytic sarcoma and malignant fibrous histiocytoma, synovial myxoma and myxosarcoma, OSA, FSA, CSA, HSA, liposarcoma, rhabdomyosarcoma, and undifferentiated sarcoma.[1,128,129]

Synovial cell sarcomas are malignant tumors arising from mesenchymal cells within tenosynovial tissue of joints, bursa, and tendon sheaths.[126] The stifle, elbow, shoulder, carpal, tarsal, and hip joints are most commonly involved, in decreasing order.[1,126] The mean age at presentation is 6 to 8 years, and a sex and breed predisposition has been reported.[126-130] Males are over-represented and flat-coated retrievers are predisposed.[26-130] Metastasis to the regional lymph nodes and lungs is reported in up to 32% of dogs at diagnosis and in 41% to 54% of dogs during the course of disease.[126-130]

Diagnosis Typically, dogs have lameness, joint pain, and synovial effusion. Dogs with suspected joint tumors should be staged with palpation of regional lymph nodes and regional and three-view thoracic radiographs. Regional radiographs will often reveal a soft tissue opacity adjacent to the affected joint. Mineralization of the soft tissue mass is occasionally seen in humans but rarely in dogs. Bone involvement is observed in 11% to 100% of cases and can either be smooth and well delineated, due to pressure necrosis from the expansile mass, or permeative to punctate lysis as a result of bony invasion.[126-130]

Biopsy is required for a definitive diagnosis. Analysis of synovial fluid is usually consistent with chronic, low-grade inflammation, and neoplastic cells are rarely identified. Large core biopsies, using either a Jamshidi needle or open wedge, are sufficient to establish a diagnosis and histologic grade.

Synovial cell sarcomas have two distinct populations of cells: (1) epithelioid and (2) spindle.[1,126] Based on these cells, synovial cell sarcomas are subclassified as either monophasic, with one cell type, or biphasic, with both cell types.[126] However, this histologic appearance is not adequate to differentiate synovial cell sarcoma from other types of soft tissue sarcoma. Recently, IHC stains have been used to differentiate joint tumors with synovial cell sarcomas staining positive with cytokeratin antibody AE1/AE3, histiocytic sarcomas staining positive with CD18 antibody, and malignant fibrous histiocytomas staining positive with smooth muscle actin.[129]

Treatment Limb amputation is the recommended treatment for dogs with a histologically confirmed joint tumor.[126-130] Local recurrence is common after conservative excision and has also been reported with relative frequency in the stump of the amputation site.[126] The role of radiation therapy and chemotherapy is unknown. Chemotherapy does not improve survival time in humans with synovial cell sarcoma.[131] However, doxorubicin-based chemotherapy protocols are recommended for high-grade synovial cell sarcoma due to their high metastatic potential.

Prognosis Several prognostic factors have been identified in dogs with synovial cell sarcoma, including clinical stage, treatment, histologic grade, and IHC staining.[126-130] Synovial cell sarcoma is locally staged as well-defined with no evidence of invasion into regional structures (T_1), invading soft tissue (T_2), and invading bone and joints (T_3).[126] Local staging is not prognostic; however, dogs with metastatic disease, to either regional lymph nodes (N) or lungs (M), have a MST less than 6 months. Aggressive surgical treatment is important in prolonging both DFI and survival time. Local tumor control is poor after conservative local excision with a median DFI of 4.5 months compared with 30 months after limb amputation.[126,130] Furthermore, survival time is significantly improved with more aggressive local treatment regimens: 93 days with no treatment, 455 days with conservative resection, and 840 days with limb amputation.[130] Histologic grade is also prognostic because the MST for dogs with grade I synovial cell sarcoma is greater than 48 months, grade II is 36 months, and grade III only 7 months.[126]

Cats

Synovial cell sarcoma is rarely diagnosed in cats. As a result, the disease has not been investigated in detail, and management and prognostic criteria have not been established. Seven cases have been reported in the veterinary literature, three with benign and four with malignant disease.[132,133] Based on these reports, synovial cell tumors in cats may have a more benign behavior than dogs. However, two cats have recently been diagnosed with metastatic synovial cell sarcoma at Colorado State University. Regional lymph node metastases were present at diagnosis in both cases, and one cat was diagnosed with pulmonary metastasis 12 months postoperatively. Limb amputation is recommended for the local management of synovial cell sarcomas because, similar to dogs, local recurrence has been reported after conservative excision.[132,133] The role of chemotherapy in malignant or metastatic synovial cell sarcomas is unknown.

CHAPTER • 186

Mast Cell Disease

Kenita S. Rogers

OVERVIEW OF CANINE AND FELINE MAST CELL DISEASE

Differences in the incidence, clinical forms, and biologic behavior associated with canine and feline mast cell disease are remarkable enough that separate discussions are required. Briefly, the incidence of cutaneous mast cell disease is higher in the dog and constitutes the most important form in this species; primary noncutaneous forms are uncommon. The biologic behavior of mast cell disease in the dog is also more variable and unpredictable, with a greater risk of systemic spread. Like dogs, cats can develop cutaneous mast cell disease, but primary visceral mastocytosis appears to be an equally important disease process. A primary gastrointestinal (GI) form is infrequently reported in the cat.

INCIDENCE OF CANINE MAST CELL DISEASE

Mast cell tumors (MCTs) remain one of the most important and frequent neoplasms affecting the canine dermis and subcutis, having been reported to account for 7% to 21% of all canine skin tumors and 11% to 27% of all cutaneous malignancies.[1,2] Mast cell disease can occur in any breed, but those that appear to be at increased risk are most of the brachycephalic breeds and Golden retrievers. Although boxers are at increased risk for developing MCTs, they often develop a well-differentiated form of the disease, which has a more favorable prognosis. Other breeds with an apparent predisposition in some reports include Bassett hounds, Labrador retrievers, Bernese mountain dogs, Chinese Shar Peis, Scottish terriers, pointers, beagles, and German shorthaired pointers. The average age of dogs that develop MCTs is 8.5 to 9.5 years, but they can develop at any age, with no apparent gender predisposition. Development of multiple tumors is a common clinical observation, occurring in approximately 10% to 15% of cases.

BIOLOGY OF MAST CELLS

Mast cells are a heterogenous cell population that originate in the bone marrow from a CD34+ pluripotential hematopoietic stem cell that is promoted to mast cell differentiation by a hemopoietin called stem cell factor or c-*kit* ligand.[3] Undoubtedly, the development of MCTs involves many factors including genetic propensity, but alteration of c-*kit* receptor expression for stem cell factor in a proportion of canine MCTs suggests that loss of normal regulation may be an important factor in tumor development.[4] Cytoplasmic receptors for estrogen and progesterone have been identified in canine MCTs, but their importance in the pathogenesis of disease is unclear. Committed mast cell precursors move from marrow to blood to tissues where maturation occurs. Besides the skin, the

GI tract and lungs are rich in normal mast cells, but development of tumors at these sites is rare.

Normal mast cells play an important role in mediating inflammatory responses. Mast cell activation stimulates release of a variety of substances from the variably sized intracytoplasmic granules, including vasoactive amines (histamine, seratonin), enzymes (acid hydrolases, cathepsin G, phospholipase A, chymase, tryptase, carboxypeptidase) and proteoglycans (heparin, chondroitin sulfate).[3] Mast cells can also synthesize and release lipid mediators and cytokines. The ability to release these active substances and mediators explains many of the clinical manifestations of these tumors. Mast cell functions include promoting hypersensitivity reactions, modulating immune responses by stimulating T cells, defending the host against tissue parasites, and promoting acute and chronic inflammatory responses by stimulating leukocyte migration, endothelial-leukocyte adhesion, angiogenesis, fibrin deposition, and fibroblast proliferation.[3]

Local release of biologically active substances from the granules can lead to recruitment of other cytokines and inflammatory cells. Unique local clinical signs that are related to these cellular products can range from nonpainful swelling to pruritus, ulceration, erythema, bruising, or prolonged hemorrhage. Poor wound healing may be attributed to proteolytic enzymes and vasoactive amines, but mouse studies suggest that histamine binds to H_1 and H_2 receptors on macrophages, resulting in release of a fibroblastic suppressor factor that decreases normal fibroplasia and results in delayed wound healing.[2] MCTs may cyclically wax and wane in size; manipulation on examination may also lead to degranulation and subsequent swelling or wheal formation. Systemic effects can also occur as part of a paraneoplastic syndrome because plasma histamine concentrations in dogs with MCTs are significantly greater than normal.[5] Increased concentrations of circulating histamine can be associated with gastric hyperacidity and GI ulceration, because binding of histamine to H_2 receptors of gastric mucosal parietal cells stimulates gastric acid secretion and hyperacidity. Histamine also increases GI motility and capillary permeability, promoting intravascular thrombosis and subsequent mucosal ulceration. With marked systemic histamine release, potential also exists for arrhythmias, systemic hypotension, and shock due to H_1 and H_2 receptor binding on blood vessels, cardiac muscle, and smooth muscle.[1]

Biologic Behavior of Canine Mast Cell Tumors

Cutaneous MCTs are likely to arise from tissue mast cells in the dermis. The clinical course of mast cell disease is somewhat unpredictable, but all tumors are considered potentially malignant due to their ability to metastasize. The typical metastatic pattern for MCTs is to the reticuloendothelial system. The first and most common site of metastasis is the regional lymph node, followed by the spleen, liver, and bone marrow.

One of the unique features of MCT behavior is the concurrent development of multiple dermal or subcutaneous tumors. When it occurs, the tumors may seem to erupt simultaneously or develop over months to years. It is unknown if each of the masses is a new individual tumor or whether each tumor represents metastatic spread. The best way to describe the typical biologic course of MCTs is "predictably unpredictable." MCTs may have a very slow nonprogressive clinical course, they may be present for long periods prior to disseminating, or they may be locally invasive with systemic spread early in the disease course.

Histologically, canine MCTs have been graded 1 through 3, with the grade of the tumor having substantial impact on overall prognosis. Some confusion has existed because of two distinct grading systems. The Patnaik scale is more popular because it uses the more conventional nomenclature of Grade 1 representing the most well-differentiated tumors that are confined to the dermis, Grade 2 representing more pleomorphic tumors that extend into lower dermis and subcutaneous tissues, and Grade 3 representing pleomorphic tumors that replace subcutaneous and deep tissues.[6,7]

Clinical Presentation Tremendous variation exists in the clinical appearance of MCTs. They may be soft and fluctuant or firm, discrete or diffuse, small or large, solitary or multiple, haired or hairless, and dermal or subcutaneous. A good rule of thumb is that MCTs can look like anything! They remain one of the most important reasons that any dermal or subcutaneous mass should be evaluated cytologically, because they can mimic lipomas and other nonneoplastic lesions. At least one half of these tumors have been reported on the trunk and perineum, but the extremities, head, and neck remain common sites. Although most commonly located within the dermis, some tumors, particularly those that are rapidly growing, extend into the underlying subcutaneous tissues and muscle. Disseminated mastocytosis without an associated cutaneous MCT is reported infrequently in dogs.[8,9] Equally uncommon are reports of MCTs of GI origin.[10] Rare reports exist of MCTs arising from a variety of sites, including the oral cavity, nasal cavity, larynx, and conjunctiva.

Dogs with MCTs often have a solitary nonpainful mass, but more profound local clinical signs that should raise clinical suspicion of a MCT include swelling that may wax and wane (particularly after manipulation of the mass), pruritus, erythema, ulceration, or bruising. Systemic signs of GI ulceration, abdominal discomfort, vomiting, melena, hypotension, or coagulation abnormalities are less common but remain clinically important. If GI ulceration and hemorrhage is persistent, anemia will develop that is progressively less regenerative as external iron loss occurs.

Diagnosis and Staging Early diagnosis of mast cell disease is important because a number of precautions may be taken if the diagnosis is known preoperatively, most notably premedication with H_1 and H_2 receptor blockers and more extensive planning for wide surgical margins. Most MCTs are easily diagnosed with fine needle aspiration due to distinctive cytologic characteristics. It has been suggested that manual quick stains, such as Diff Quick, may stain mast cell granules poorly.[3] Because the lack of adequate staining may be associated with dissolution of the mast cell granules by these largely aqueous stains if fixation is inadequate, particular care should be taken to adequately fix the slides when using these in-hospital stains. MCTs are categorized as round cell tumors because they typically have round cytoplasmic borders, do not cluster, and exfoliate well. Specific cytologic characteristics include a round to ovoid nucleus, a moderate amount of cytoplasm, and the presence of red-purple variably sized intracytoplasmic granules. In heavily granulated cells, the nucleus may stain pale blue due to the high affinity of the mast cell granules for the stain, with subsequent understaining of nuclear DNA. Well-differentiated tumors are typically homogenous in appearance with few malignant characteristics, even though the tumor remains potentially malignant. As tumors become more poorly differentiated, the number and size of granules within the cell may diminish and the degree of cellular pleomorphism will increase. The most poorly differentiated or anaplastic MCTs may have no visible granules on light microscopy and require special stains such as toluidine blue for definitive diagnosis. A subset of tumors remains that is cytologically and histologically defined only as *anaplastic round cell tumors*, with MCT being only one possible diagnosis within a list of differentials that may include lymphoma, transmissible venereal tumor, histiocytic disorder, plasma cell tumor, amelanotic melanoma, and anaplastic carcinoma. Immunohistochemical techniques may be helpful for differentiating these tumors (MCTs are vimentin + and most are

alpha-1 antitrypsin +), but electron microscopy of ultrastructural features may be required in some cases for definitive confirmation.[3] Another useful cytologic characteristic supporting the diagnosis of MCT is the presence of a concurrent eosinophilic infiltrate due to chemotactic attraction of these inflammatory cells to histamine.

Histologic examination of MCTs is important, not only to confirm the diagnosis but also to accurately grade the tumor and evaluate for completeness of surgical resection. Histologic tumor grade plays a substantial role in prognosis by correlating with both recurrence and survival. Four-year survival rates after surgical excision are 83% for Grade 1 tumors, 44% for Grade 2 tumors, and 6% for Grade 3 tumors.[6] Many studies have confirmed the trend that well-differentiated tumors are least likely to metastasize and have longer postoperative survival times. Although it is recognized that even with wide resection, well-differentiated MCTs can locally recur and metastasize, it is usually considered that the metastatic potential of well-differentiated tumors is low (<10%) and that of intermediate-grade tumors is low to moderate.[2] Poorly differentiated MCTs are associated with the greatest risk of metastasis and shortest survival times.

Clinical staging also provides important information regarding prognosis (Box 186-1). Because metastasis is typically to the reticuloendothelial system, the regional lymph nodes, liver, spleen, and bone marrow are usually targeted for evaluation. The first site of mast cell metastasis is the regional lymph node. If an apparent regional node exists, it should always be aspirated, even if palpably normal in size. Early in the course of disease, MCTs may metastasize without causing a concomitant lymphadenopathy. It is important to remember that a palpably normal node does not rule out metastasis. Conversely, an enlarged regional lymph node may represent only reactive changes associated with lymphoid hyperplasia or secondary inflammatory changes. It is quite common for a peripheral lymph node to contain a small population of normal mast cells, particularly if the animal has allergic or parasitic skin disease, making definitive diagnosis of nodal metastasis problematic. In a population of 56 healthy nontumor-bearing beagles, approximately 24% of lymph node aspirates contained mast cells, with a range of one to 16 mast cells per slide.[11]

Differentiating inflammatory from neoplastic mast cells within a node can be difficult at best. Typically, inflammatory mast cells are spread somewhat evenly throughout a node and on the cytologic preparation. Tumor mast cells have a greater tendency to arrange themselves in groups within a node, and this may be apparent on the smear. Another helpful finding may be noting the degree of differentiation of the mast cells within the node. Inflammatory mast cells are usually well differentiated and heavily granulated. Tumor mast cells may also have this appearance, but if the cells in the node are more poorly differentiated with few granules, the cells are more likely to represent metastatic tumor.

As is true with lymph nodes, buffy coat smears and aspirates of spleen and bone marrow must also be interpreted carefully because small numbers of mast cells can normally be seen in these preparations, particularly if concurrent inflammatory disease exists. When few mast cells are present in potential metastatic sites, it is difficult or impossible to determine if the mast cell infiltrate represents metastatic neoplasia, mast cell hyperplasia, or a nonpathologic condition.[3] Mastocytemia is uncommon in dogs, but unless extensive blood involvement occurs, the number of mast cells seen in blood samples cannot be used to accurately distinguish nonmalignant from malignant disease. Indeed, more than 1000 mast cells per buffy coat preparation were described in nonneoplastic disorders in dogs.[12] A few mast cells may be present normally in a bone marrow smear, and mast cell hyperplasia associated with marrow hypocellularity has been reported.

Because the lymph node is the first site of metastasis, nodal assessment with cytology or histology is the single most important diagnostic step in staging. In the dog with no evident lymph node involvement, evaluation of the spleen, liver, and bone marrow is unlikely to yield useful information. Unfortunately, several areas of the body (particularly on the trunk) do not drain to a single, easily accessible peripheral lymph node. In these cases the regional node may be within the thoracic or abdominal cavities, and access for aspiration or biopsy is more difficult.

Diagnostic evaluation of splenic or hepatic involvement may include radiographs, ultrasound, and aspiration. The bone marrow is most commonly assessed with aspiration cytology; the presence of more than 10 mast cells/1000 nucleated cells can indicate systemic spread of mast cell disease. In a study of 16 dogs with systemic mastocytosis, bone marrow aspiration was deemed superior to blood smear and buffy coat examination.[8] In dogs with low and intermediate-grade cutaneous MCTs, the value of bone marrow examination is questionable due to the low incidence of finding metastasis in this location, particularly if the regional node can be evaluated. Because pulmonary metastasis is rare, thoracic radiographs are only indicated for assessing intrathoracic lymphadenopathy for MCTs located on the cranial portion of the body. A complete blood count (CBC) may show nonspecific eosinophilia, basophilia, and anemia if GI hemorrhage has occurred.

Treatment As is true with most types of neoplasia, the conventional choices for therapy are surgery, radiation, and chemotherapy. Each of these treatment modalities has a role in mast cell disease. The location of the mass, the number of masses, the grade of the tumor, and the presence or absence of metastasis are all important factors in choosing the most appropriate course of therapy for dogs with mast cell disease. However, the unpredictable biologic behavior of MCTs must always be kept in mind when making therapeutic decisions.

Surgery Complete surgical excision has been the mainstay of therapy for canine MCTs, and remains the treatment of choice. Curative intent can be expected with surgery of Grade 1 and 2 tumors that have no evidence of metastasis and are located in areas where surgery will allow adequate resection while maintaining cosmesis and function. The preoperative diagnosis of MCT allows the clinician to prepare the dog with prophylactic H_1 and perhaps H_2 receptor blockers, if appropriate. In addition, decisions regarding the size of surgical margins is

Box • 186-1

World Health Organization Clinical Staging of Canine Mast Cell Tumors

Stage 0: One tumor incompletely excised from the dermis, identified histologically, without regional lymph node involvement
Stage I: One tumor confined to the dermis, without regional lymph node involvement
Stage II: One tumor confined to the dermis, with regional lymph node involvement
Stage III: Multiple dermal tumors; large infiltrating tumors with or without regional lymph node involvement
Stage IV: Any tumor with distant metastasis (including blood or bone marrow involvement) or recurrence with metastasis
Substage a: without systemic clinical signs
Substage b: with systemic clinical signs

often altered when the clinician has made a preoperative diagnosis of mast cell disease. Classically, it has been recommended that 2-3 cm margins be obtained if possible when resecting a MCT due to often inapparent extension of the tumor into surrounding tissues. Equally important is the recommendation that excision include at least one fascial plane beyond the apparent extent of the tumor (i.e., if the tumor is dermal, underlying subcutaneous tissue should be removed; if the tumor is located in the subcutis, at least one layer of underlying muscle should be excised to routinely obtain adequate surgical margins free of tumor cells). All surgical margins should be clearly identified to allow the pathologist to examine for remaining tumor cells. Interestingly, many clinicians have noted that even when adequate surgical margins have not been obtained, a subset of patients exist in which the tumor does not occur.[13] Regardless, the current recommendation remains to widely excise tissue to obtain clean margins or follow with radiation therapy of the tumor bed and immediate surrounding tissues. For low to intermediate-grade MCTs on a distal extremity, limb amputation is also a surgical option for obtaining wide margins (albeit with less remaining function). Alternatives for limb salvage for tumors in this area include radiation alone, or more ideally, a combination of cytoreductive surgery followed by radiation therapy (Figure 186-1). The use of deionized water to treat surgical wounds after MCT removal has been reported, but this approach must not delay the use of more conventional therapy.

Radiation Radiation alone for gross mast cell disease has generally been considered poorly effective with variable control rates cited; 1-year control rates using doses of 40 to 45 Gy are approximately 50%.[2] Use of more aggressive doses or different fractionation schemes may improve these results. A palliative course of radiation (coarse weekly fractions of 800 to 1000 Gy) for 3 to 4 weeks may result in responses that improve quality of life and decrease local clinical signs for unresectable MCTs but may also result in GI upset and weakness, most likely associated with mast cell degranulation.[14]

Radiation therapy is best applied as adjunctive therapy for incompletely resected tumors where further surgery is not deemed possible (i.e., Stage 0 disease). The prognosis after radiation for Grade 1 and 2 MCTs is good, with 1- and 2-year disease-free intervals of 79% to 97% and 77% to 85%, respectively.[15-18] Common toxicities associated with the use of conventional radiation include alopecia, haircoat color changes within the treatment field, and temporary moist desquamation. Prophylactic irradiation of cytologically negative regional lymph nodes is controversial with little guidance in the literature to suggest improved survival times with use of this technique. However, after cytoreductive surgery of the primary mass, radiation of regional nodes with metastasis in 19 dogs (16 with Grade 2 tumors) resulted in a median disease-free survival of 1240 days.[19]

Whether surgery or radiation is chosen as local therapy, dogs should be evaluated regularly for local recurrence and metastasis. For dogs with high-grade, poorly differentiated MCTs, surgery, and radiation may be used as local therapies but will not address the high risk of systemic spread that will typically occur within weeks to months of the local therapy. It is extremely important that clients be fully educated regarding the high risk of metastasis in this subset of dogs, prior to initiating surgery or radiation therapy.

Chemotherapy With poorly differentiated MCTs or documented metastasis, local treatments such as surgery and radiation may provide only palliative therapy. Systemic adjuvant chemotherapy can be offered in an attempt to decrease the likelihood of systemic involvement or potentially to improve disease-free intervals.[2] MCTs appear to be quite resistant to the effects of chemotherapy, because many different agents have been used with little reported efficacy and most responses have been of short duration. P-glycoprotein and multidrug resistance–associated protein have been detected in canine cutaneous MCTs.[20]

Prednisone is commonly advocated for treatment of MCTs, but the reported response rates are low. One prospective clinical trial with daily oral prednisone at 1 mg/kg demonstrated disappointing results.[21] Only 4 of 25 dogs had a partial response (PR) and only one dog had a complete response (CR). Most responses lasted only a few weeks. However, it must be recognized that many dogs in this study had poorly differentiated tumors that may respond differently to prednisone than lower-grade tumors, potentially due to differences in numbers of steroid receptors. As an anti-inflammatory agent, prednisone may be helpful by decreasing swelling and edema associated with mast cell degranulation and concomitant inflammation, as well as stabilizing cytoplasmic membranes and helping to prevent further degranulation. Intralesional use of triamcinolone at 1 mg/1 cm of tumor diameter at 2-week intervals has been anecdotally reported to be effective at controlling local tumor volume. Corticosteroids may also be useful in combination with other chemotherapy agents.

Although the response rate to vincristine was low in a study of dogs with Grade 2 and 3 tumors (0 CR and 3 PR) and administration caused an unacceptable rate of GI toxicity, the use of vinblastine has met with more favorable results.[22,23] As adjuvant therapy to incomplete surgical resection, a combination of prednisone and vinblastine conferred a 57% 1- and 2-year disease-free rate. In dogs with evaluable gross disease, the overall response rate was 47% with 5 CR and 2 PR. Lomustine is an oral alkylating agent in the nitrosourea subclass. It was evaluated in 19 dogs with measurable MCT.[24] Eight of the 19 dogs (42%) had a measurable response; one dog had CR for 440 days and 7 dogs had PR for a median duration of 77 days. Six dogs (32%) had stable disease for a median duration of 78 days. The dose-limiting toxicity was neutropenia. Combination chemotherapy may improve response rates.[25,26] Supportive medical management of patients with MCTs may include H_1 and H_2 receptor antagonists, omeprazole, misoprostol, sucralfate, metoclopramide, and prednisone in an anti-inflammatory dose.

Prognosis Although the biologic behavior of each individual MCT is unpredictable, the prognosis roughly follows the Patnaik grade, with other recognized prognostic factors being the stage of disease, tumor location, tumor duration, and several proliferation markers. As the Patnaik grade increases, average survival times diminish. Dogs with Stage 0 or 1 disease have a better prognosis than those with higher stage disease. Visceral or bone marrow involvement represents advanced disease and a poor prognosis. In 16 dogs with visceral MCT, the median survival was 90 days, and all dogs with follow-up died of their disease.[8] Dogs with systemic signs such as GI ulceration and vomiting do more poorly than dogs with no evidence of illness on presentation, because these signs are associated with more advanced and aggressive forms of mast cell disease.

Dogs with tumors on the extremities may have longer survival than those with tumors on the trunk. Tumors located on the perineal, inguinal, preputial, and subungual areas and noncutaneous sites, such as the oral cavity and GI tract, have a poorer prognosis and are often more poorly differentiated. The growth rate of a tumor can be prognostic, because tumors that remain localized and are present for months without metastasizing are often cured with complete surgical excision. The length of time that a tumor has been present prior to surgical resection is inversely related to survival time.[7] Recent rapid growth is a poor prognostic sign.

Although not routinely performed, at least four laboratory tests can provide further prognostic data: argyrophilic nucleolar

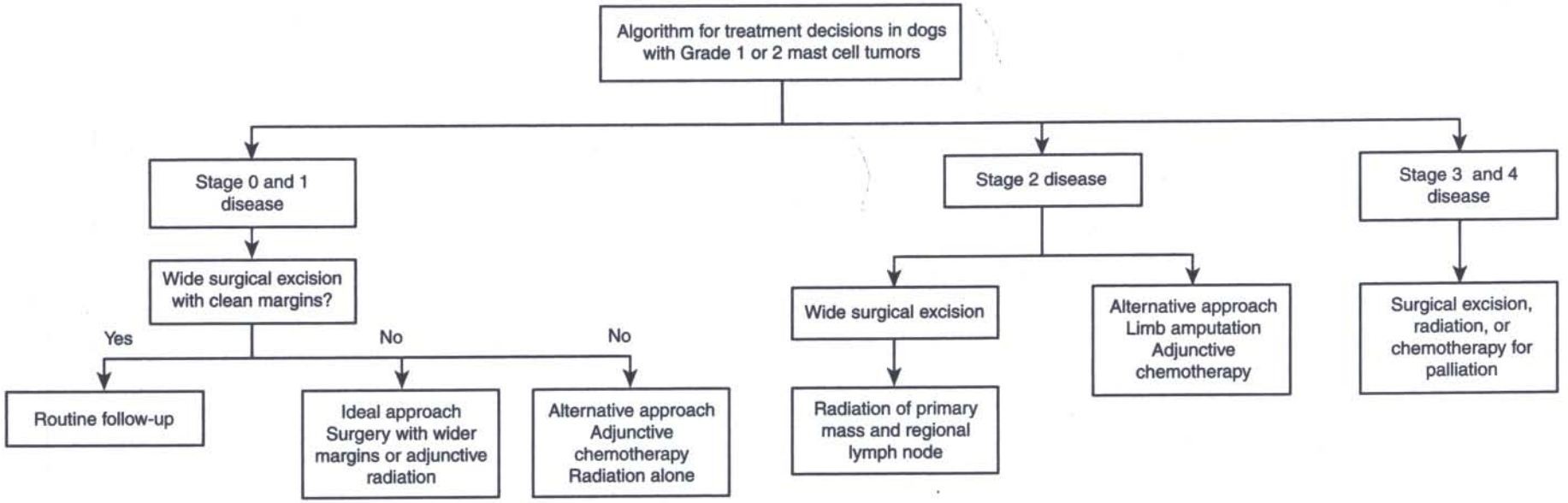

Figure 186-1 Algorithm for treatment decisions in dogs with Grade 1 or 2 mast cell tumors (MCTs).

organizer (AgNORs), proliferating-cell nuclear antigen (PCNA), Ki-67–positive nuclei, and ploidy. The relative frequency of AgNORs is predictive of postoperative success because higher AgNOR counts are associated with a poor prognosis.[27,28] In addition, a higher percentage of PCNA immunopositivity and a higher number of Ki-67–positive nuclei are associated with a more guarded prognosis.[27,29] These tests represent indirect measures of cellular proliferation. Dogs with aneuploid tumors have a trend toward shorter survivals and higher-stage disease.[30]

Feline Mast Cell Disease

The three forms of mast cell disease in the cat are (1) cutaneous, (2) visceral (systemic, splenic), and (3) GI . Although mast cell disease is diagnosed less frequently in the cat than the dog, it remains among the four most common skin tumors in the cat (with basal cell tumor, squamous cell carcinoma, and fibrosarcoma) and accounts for 12% to 20% of all skin neoplasms.[31] Visceral MCT and lymphoma are the two most common hematopoietic tumors of the spleen, and MCT is the third most common intestinal tumor in the cat after lymphoma and adenocarcinoma. MCTs are most commonly diagnosed in middle-aged to older cats with no gender predilection, but Siamese appear to be over-represented in many studies.

Cutaneous Form Cutaneous lesions in the cat appear as solitary or multiple dermal nodules that are discrete, nodular, papular, or plaquelike, and occasionally, diffusely swollen. Plaquelike lesions can be confused with eosinophilic granuloma complex, and indeed, some eosinophilic plaques contain mast cells as a part of the inflammatory component. Unlike the dog, feline cutaneous MCTs appear to occur more frequently on the head and neck, although some reports have not documented a site predilection. Occasionally, cutaneous lesions may represent metastasis from the visceral form of the disease, and it is recommended that any cat with multiple cutaneous lesions be evaluated for primary visceral disease. There has been no evidence of a relationship between the development of MCTs and feline leukemia virus (FeLV), but there has been a suggestion of a relationship between multiple cutaneous MCTs and feline immunodeficiency virus (FIV) infection.[1]

Diagnostic techniques used in the dog are similar for cats, with cytology and histology being the most useful for the mast cell variety of MCT. Some feline mast cells have fine granules that are difficult to visualize, even with additional stains such as toluidine blue or Wright-Giemsa. Unfortunately, the histologic grading systems used for canine MCTs do not provide prognostic information in the cat.[32] Metastasis is less common, but when it occurs it is primarily to a regional node. In several studies few cats demonstrated metastasis, but development of new cutaneous lesions occurred in one third to one half of the cats.[31,33,34] A histiocytic variety of MCT exists that has been reported primarily in young Siamese. These cats often have multiple lesions, typically developing in the same region of the body. The mast cells are poorly granulated, and the tumors are often infiltrated by numerous lymphoid aggregates. Many of these tumors are small and may spontaneously regress.

The treatment of choice for feline cutaneous mast cell disease is complete surgical excision. The overall survival of cats with cutaneous mast cell disease is long. If tumors are incompletely resected or evidence of systemic disease exists, radiation and chemotherapy may be considered. Because vinblastine and CCNU (Lomustine) are active agents in canine MCTs, they may have role in the cat. Although histamine may play a role in the clinical signs associated with feline mast cell disease, seratonin may be a more important inflammatory mediator in feline mast cells.[35] Therefore cyproheptadine may be a more effective agent than diphenhydramine for cats with clinical signs related to mast cell degranulation. The effectiveness of corticosteroids is also less clear in cats.

Visceral Form Visceral or systemic mastocytosis is a disease that is relatively unique to the cat. This form of disease has been reported to comprise up to 50% of all feline mast cell disease and typically involves the spleen, liver, and often abdominal lymph nodes; infrequently it has been diagnosed involving mediastinal or peripheral lymph nodes.[1,2] The disease affects older cats (average age of 10 years) with no breed or gender predilection and occurs most often in domestic shorthair and longhair breeds. Clinical signs include a palpable or visible intra-abdominal mass, vomiting with or without hemorrhage, weight loss, anorexia, abdominal discomfort, ascites, and lethargy. GI signs are due to either the space-occupying nature of the large mass or histamine release with resultant gastric ulceration. An acute abdominal crisis can occur with intestinal perforation secondary to ulceration or with splenic rupture. Laboratory abnormalities may include anemia and mastocytemia, with circulating mast cells noted in up to 50% of affected cats. In addition, there may be mast cells noted within body cavity effusions. Neoplastic cells frequently spread from the spleen to the liver, abdominal lymph nodes, and bone marrow. Cytology of these organs is typically consistent with a mast cell infiltrate, and occasionally neoplastic cells will demonstrate erythrophagocytosis. Manipulation of the enlarged spleen for aspiration poses modest risk, and pretreatment with antihistamines and vigilance for precipitation of shock must accompany fine needle aspiration. Use of a 25-gauge needle allows for adequate cellular collection while minimizing the risk of hemorrhage or degranulation. Abdominal radiographs or ultrasound can demonstrate enlargement of the spleen, liver, or mesenteric nodes and may aid in obtaining diagnostic aspirates. Thoracic radiographs may be helpful in identifying pleural effusion that may occur in up to one third of cats with visceral mastocytosis. Treatment of these cats can consist of supportive care (prednisone, H_1 and H_2 antagonists, cyproheptadine), splenectomy, or chemotherapy. In most cases supportive care measures alone fail to ameliorate the clinical signs of disease. The longest survival times have been associated with successful splenectomy, even without the benefit of other therapies and in the presence of overt metastatic disease. Median survival time after splenectomy is between 12 and 19 months, but some cats live 2 to 3 years postsplenectomy.[2] Intraoperative risks include excessive hemorrhage, as well as hypotension and shock when the splenic mass is manipulated. Prior to splenectomy, cats should be medicated with H_1 and H_2 receptor blockers and cyproheptadine to mitigate the adverse effects of intraoperative mast cell degranulation. Although not reported in the cat, use of chemotherapy may have a role in management of visceral mast cell disease.

Gastrointestinal Form This form of mast cell disease has been infrequently reported and arises primarily from the small intestines. Clinical signs are associated with GI upset, including vomiting, diarrhea, anorexia, and weight loss. Interestingly, ulceration has not been reported, so the vomiting noted in these cats is most likely due to mechanical obstruction.[1] Many cats have a palpable mass that can be localized with imaging to the intestinal wall. Most of these tumors are solitary, but multiple tumors have been reported. Intestinal MCT are often poorly differentiated and may be difficult to definitively diagnose, particularly with cytology. These tumors usually have systemic involvement, so surgical resection is often not curative. Reported sites of metastasis have been the regional lymph nodes, liver, spleen, bone marrow, and lung. Life span is typically less than 4 months, but occasionally cats will survive long-term.

CHAPTER 187

Canine and Feline Histiocytic Diseases

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OVERVIEW OF CANINE HISTIOCYTIC DISEASES

At least four well-defined histiocytic proliferative diseases have been recognized in dogs. They are a frustrating group of diseases because it may be difficult to differentiate them from granulomatous, reactive inflammatory diseases or from lymphoproliferative diseases by examination of regular paraffin sections. The clinical presentation and behavior and responsiveness to therapy vary tremendously between the syndromes observed. Clinical and pathologic images of canine histiocytic diseases and details of histiocytic lineages are available on a web site maintained by the authors (http://www.histiocytosis.ucdavis.edu). *Canine cutaneous histiocytoma* usually occurs as a single lesion in young dogs and spontaneously regresses. Multiple histiocytomas and metastatic histiocytomas are examples of less common but more aggressive subgroup of this tumor. *Langerhans' cell histiocytosis* (LCH) is a rare disease characterized by extensive regional cutaneous infiltration by histiocytes, which otherwise resemble those in histiocytoma, although rapid systemic metastasis is observed. *Cutaneous histiocytosis* (CH) typically occur as single or multiple lesions, which tend to wax and wane and may even spontaneously regress. Few cases respond to corticosteroids; the remainder persist and may require more aggressive immunosuppressive therapy. *Systemic histiocytosis* (SH) is a familial disease of Bernese mountain dogs and also occurs sporadically in other breeds. SH causes prominent skin manifestations identical to those seen in CH, but mucous membranes (ocular and nasal) and a variety of other organ systems, including lymphoid organs, lung, and bone marrow, may also be involved. Although the lesions may wax and wane, SH is a progressive disease that often requires continuous immunosuppressive therapy. *Histiocytic sarcoma* (HS) and *malignant histiocytosis* (MH) occur with high incidence in Bernese mountain dogs, Rottweilers, flat-coated retrievers, golden retrievers, and sporadically in many other breeds. HSs occur as localized lesions in spleen, lymph nodes, lung, bone marrow, skin and subcutis, brain, and periarticular tissue of large appendicular joints.

HS can also occur as multiple lesions in single organs (especially spleen) and rapidly disseminate to involve multiple organs. Hence, disseminated HS is difficult to distinguish from MH, which is a multisystem, rapidly progressive disease that includes simultaneous involvement of multiple organs such as spleen, lymph nodes, lung, bone marrow, skin, and subcutis. Response of HS and MH to chemotherapy is at best brief.

Histiocytic Differentiation and Canine Histiocytosis

The development of canine-specific monoclonal antibodies for many of the functionally important molecules of macrophages and dendritic antigen presenting cells (DCs) has enabled the identification of the cell lineages involved in canine histiocytic disorders.[1-4] Despite the large variation of clinical and pathologic features of canine histiocytic diseases, the majority represent proliferations of cells of various DC lineages.

Histiocytes differentiate from CD34+ committed stem cell precursors into *macrophages* and several DC lineages, which include *epithelial DCs* or *Langerhans' cells* (LC), *interstitial DCs* in many organs (e.g., dermal DCs in skin), and *interdigitating DCs* of T-cell domains in peripheral lymphoid organs. Cytokines influencing DC development include GM-CSF and TNF-alpha. Macrophage development from CD34+ precursors is influenced by GM-CSF and M-CSF. Blood monocytes can differentiate into either macrophages under influence of M-CSF or into DCs under influence of GM-CSF and interleukin (IL)-4.[5,6] Recently a new human dendritic lineage of myeloid origin was identified. These DCs differentiate under the influence of GM-CSF and IL-3 and are the major source of nonactivated resident DCs in T-cell domains of peripheral lymphoid organs.[7] They are supplemented by migration of activated DCs from skin and interstitial tissues, which arrive in lymph nodes as veiled cells in afferent lymph after contact with antigen.

Dendritic cells are the most potent antigen presenting cells (APCs) for induction of immune responses in naïve T cells. Canine DCs have been best defined in canine skin. They occur in two major locations: (1) within the epidermis (LC) and (2) within the dermis especially adjacent to postcapillary venules (interstitial DCs or dermal DCs). Canine DCs abundantly express CD1 molecules,[3,4] which together with MHC class I and MHC class II molecules are responsible for presentation of peptides, lipids, and glycolipids to T cells. Hence, DCs are best defined by their abundant expression of molecules essential to their function as APC. Of these, the family of CD1 proteins is largely restricted in expression to dendritic APC in skin; whereas MHC class I and II are more broadly expressed.

The beta-2 integrins (CD11/CD18) comprise the major family of adhesion molecules on leukocytes and as such are useful markers of leukocytic differentiation. CD11/CD18 expression is highly regulated in normal canine macrophages and DCs. CD11c is frequently expressed by DCs; whereas macrophages predominately express CD11b (or CD11d in the splenic red pulp and bone marrow).[8,9] In diseased tissues these beta-2 integrin expression patterns may be diversified.

Langerhans' cells (epidermal DCs) and interstitial DCs are distinguishable by their differential expression of E-cadherin (LC+) and Thy-1 (CD90) (interstitial DC+). Lineage distinctions among histiocytes are best made via immunohistochemistry (IHC) performed on frozen sections (CD1, CD11b, CD11c, CD11d, CD18, CD90, MHC II, and E-cadherin expression). Less definitive but useful distinctions can also be attained via IHC on formalin-fixed paraffin sections with panels of leukocytic markers developed for use in this format (CD3, CD11d, CD18, CD45, CD45RA, CD79a, and E-cadherin).

Regardless, dendritic APC arise in bone marrow and migrate through blood to a variety of epithelial sites (cutaneous and mucosal), where they take up residence either within epithelia or in dermis and lamina propria. In these sites they function as antigen processing cells and ultimately APCs, which interact

with T cells. Migration of DCs (as veiled cells) beyond the skin to the paracortex of lymph nodes occurs after contact with antigen. The interdigitating dendritic APCs of lymph node paracortex are partially derived from such migration. Aspects of this developmental and migratory program of cutaneous DCs are recapitulated in the DC proliferative disorders of canine skin.

Successful interaction of dendritic APC and T cells in response to antigenic challenge also involves the orderly appearance of costimulatory molecules (B7 family—CD80 and CD86) on dendritic APC, as well as their ligands (CD28 and CTLA-4) on T cells. Defective interaction of dendritic APC and T cells appears to contribute to the development of reactive cutaneous histiocytic proliferative diseases (CH and SH), which are related DC disorders arising out of disordered immune regulation (see following). Much research is currently directed at the molecular events associated with maturation and migration of dendritic APC and the costimulatory function of dendritic APC. To some extent this research should be of future benefit to understanding the pathogenesis of proliferative diseases of dendritic APC in both human and dog.

Cutaneous Histiocytoma Complex

Several discrete clinical entities exist, in which proliferation of histiocytes, which resemble those encountered in histiocytoma, are seen. *Histiocytoma* is a common, benign, cutaneous neoplasm of the dog. Histiocytomas usually occur as solitary lesions, which undergo spontaneous regression. The age-specific incidence rate for histiocytomas drops precipitously after 3 years, although histiocytomas do occur in dogs of all ages.[10] Recurrence of histiocytomas at the same or other sites is uncommon. The occurrence of multiple tumors is also uncommon. Epidermal invasion by cells of histiocytoma frequently occurs (incidence about 60%), and intraepidermal nests of histiocytes resemble Pautrier's aggregates, characteristically found in epidermotropic lymphoma (mycosis fungoides [MF]). Epidermal invasion in histiocytoma, or presence of simultaneous *multiple histiocytomas* especially in aged dogs, can present a diagnostic dilemma, and distinction from MF and nonepidermotropic cutaneous lymphoma (NECL) is difficult on purely morphologic grounds.[3,11,12] It is imperative to request IHC stains to resolve these issues particularly in older dogs or if equivocal comments appear in the pathology report.

Multiple histiocytomas can be confused with CH on clinical appearance. Morphologically, however, histiocytomas are consistently epidermotropic and commonly epidermally invasive; these are not features of CH. Multiple histiocytomas appear to be more common in Shar Pei dogs but can occur in any breed. Delayed regression of multiple histiocytomas can occur, and lesions can persist for up to 10 months before onset of regression.

Metastatic Histiocytoma Several dogs with histiocytomas have been observed in which histiocytes had migrated to and completely obliterated draining lymph nodes. Each dog had been diagnosed as having HS, and each was assigned a poor prognosis. However, three dogs had complete spontaneous regression of their lesions within 3 to 4 weeks of diagnosis.[3] In other instances the metastatic lesions of histiocytoma persisted without regression and the dogs were euthanized. The disease course in these dogs extended over several months. Spread from lymph nodes to lung has also been observed in some dogs but is rare. Veterinarians should remember that the primary lesion in most of these dogs looked no different from an uncomplicated histiocytoma.

Langerhans' Cell Histiocytosis The presence of multiple histiocytomas is now a well-recognized syndrome. However, another presentation exists in which widespread cutaneous lesions histologically identical to histiocytoma are observed. Clinically the lesions are almost confluent in affected regions. Rapid internal spread is observed, and affected dogs have all been euthanized. One published account of such a case exists,[13] and the authors have data on four dogs with similar signs. This disease is most like cutaneous LCH of humans.[14]

Immunophenotypic Studies IHC is best performed on frozen sections of tumor or cytologic preparations (not formalin fixed material). Histiocytoma is readily distinguished from other histiocytic disorders and cutaneous lymphoma with the aid of IHC. Histiocytomas have the phenotype of epidermal Langerhans' cells.[3] They express CD1a, CD1b, CD1c, MHC class II, CD11c, and E-cadherin. In leukocytes, E-cadherin expression is unique to Langerhans' cells. Langerhans' cells use E-cadherin to localize in the epidermis via homotypic interaction with E-cadherin expressed by keratinocytes. E-cadherin expression has only rarely been observed in HS in canine skin and subcutis. Histiocytomas lack expression of CD4 and Thy-1, which are consistently expressed by histiocytes in CH and SH. Therefore cutaneous histiocytoma is a localized epidermal Langerhans' cell tumor. The rare dogs with multiple histiocytoma and metastasis to local lymph nodes can be compared with dogs with confluent histiocytic lesions that occur in many cutaneous sites with rapid systemic spread. These two conditions may represent one disease with a spectrum of diverse clinical behavior and are perhaps best characterized as LCH. LCH is also recognized as a rare disease of humans in which marked variation in clinical behavior is recognized.[14,15]

Regression of Histiocytomas The factors that determine the onset of regression in canine histiocytomas are unknown. Evidence of regression is usually observed in lesions that have been present for only a few weeks, although regression can be delayed for many months. Regardless, CD8+ alpha beta T cells mediate regression; only scant numbers of CD4+ T cells are observed in histiocytoma lesions. Migration of tumor histiocytes, tumor infiltrating reactive DCs to draining lymph nodes, or both could activate CD4+ T cells, which would assist in CD8+ cytotoxic T-cell recruitment. Because massive CD8+ T-cell infiltration is observed in all instances of histiocytoma regression, therapeutic intervention with the aim of immunosuppression should be avoided once a definitive diagnosis of histiocytoma has been reached (to allow unfettered cytotoxic T-cell function).

Histiocytic Sarcoma Complex

The *HS complex* encompasses a number of distinctive clinical entities (see following). Some definitions are in order and reflect the preferred nomenclature of the Histiocyte Society. Histiocytic neoplasia that originates at a single site is called *HS*. This form of HS, which is often encountered on the extremities, has the best prognosis if treated early by surgical excision or by amputation of a limb. When spread to distant sites beyond the local lymph node occurs, the disease is then termed *disseminated HS*; this is more likely to occur unnoticed when primary lesions are located in cryptic sites (e.g., spleen, lung, bone marrow). This latter form of HS is most like MH. MH is an aggressive, histiocytic neoplasm that arises in multiple sites simultaneously. Most lesions previously defined as MH are probably more correctly termed *disseminated HS*. The occurrence of true MH is difficult to establish because the lesions often occur in cryptic sites, and the existence of histiocytic neoplasia is only recognized after clinical signs have appeared and disease progression is advanced. HS and MH are capable of widespread metastasis, hence in time the two syndromes merge clinically and it is not always possible to differentiate true multicentric origin (i.e., MH) from widespread metastasis

of disseminated HS. In addition, it is never possible to know exactly how long the disease process has been operative. Hence, the perception is that both disseminated HS and MH follow a rapid clinical progression despite therapeutic intervention. This is certainly true once clinical signs are apparent, but the subclinical period is of unknown duration.

The HS complex of diseases is best recognized in the Bernese mountain dog, in which a familial association is apparent. Other breeds predisposed to HS complex diseases include Rottweilers, Golden retrievers, and flat-coated retrievers. HS complex is not limited to these breeds and can occur in any. Primary lesions of HS occur in spleen, lymph node, lung, bone marrow, skin and subcutis (especially of extremities), and in periarticular tissues of the limbs. Secondary sites are widespread but consistently include liver and lung (with splenic primary) and hilar lymph node (with lung primary). Clinical signs include anorexia, weight loss, and lethargy. Other signs depend on the organs involved and are a consequence of destructive mass formation. Accordingly, pulmonary symptoms such as cough and dyspnea have been seen. Central nervous system (CNS) involvement (primary or secondary) can lead to seizures, incoordination, and paralysis. Regenerative and nonregenerative anemias have been consistently documented in hemophagocytic HS/MH. Lameness is often observed in periarticular HS.

Treatment of Histiocytic Sarcoma Complex Localized HS affecting skin and subcutis have been cured by early surgical excision. In others, surgery supplemented by local radiation therapy has been curative. In the case of periarticular HS, which occurs in the subsynovial tissues of the extremities, amputation of the affected limb is necessitated by the inoperable nature of the primary lesion, which usually ensnare structures vital to limb function. Prior to amputation it is important to support absence of metastasis with thoracic radiographs, abdominal ultrasound, and draining lymph node aspiration cytology. Disseminated HS (including MH) is not readily treated surgically, because even in the splenic form, early metastasis to the liver has been documented. Response to chemotherapy has been at best brief, and the disease progresses rapidly (weeks to months) to death or euthanasia.

Morphologic Features of Histiocytic Sarcoma Lesions of HS are typically destructive mass lesions with a uniform, smooth cut surface and a white or cream to tan color. Lesions have a soft consistency and may contain discolored areas (typically yellow and extensive), which indicate area of necrosis. Lesions can be solitary or multiple within an organ (especially spleen). Periarticular HS has a distinctive appearance: it occurs as multiple tan nodules located in the subsynovium. These lesions may encircle the affected joint. Hemophagocytic HS does not initially form mass lesions in the primary sites (spleen and bone marrow). Typically, diffuse splenomegaly and ill-defined mass lesions are observed; the cut surface is dark red and the consistency is firm. The liver is usually bile stained (jaundice), and disruption of the lobular pattern due to metastasis is observed—marked liver involvement can occur before destructive liver masses are noticeable.

The histological appearance of HS lesions is consistent regardless of location. Lesions are most frequently composed of sheets of large, pleomorphic, mononuclear cells and multinucleated giant cells, which show marked cytologic atypia and numerous bizarre mitotic figures. Some lesions may include spindle cell forms either alone or mixed with the mononuclear cells and multinucleated giant cells. Pure spindle cell lesions resemble spindle cell sarcomas of diverse cell lineage. Confirmation of histiocytic lineage can only be achieved with IHC in these instances. Phagocytosis of red cells, leukocytes, and tumor cells occurs but is not prevalent in most forms of HS. However, in *hemophagocytic HS* this behavior is amplified. Neoplastic histiocytes manifest marked erythrophagocytosis, and the infiltrates obliterate the splenic red pulp and invade red pulp sinuses. Foci of extramedullary hemopoiesis (EMH) occur within and adjacent to the tumor infiltrates in the splenic red pulp. Simultaneous involvement of bone marrow is frequent, and erythrophagia is observed here as well; these cases are probably equivalent to hemophagocytic MH in recognition of the simultaneous involvement of multiple sites. In some instances the neoplastic infiltrates can be deceptively cytologically bland. The cytologic appearance can be asynchronous between sites (e.g., spleen and bone marrow), which can contribute to diagnostic ambivalence if only one site is evaluated. Invasion of splenic red pulp sinuses portends invasion of the hepatic sinusoids. In the early stages, liver metastases can easily be overlooked grossly and histologically, because histiocytic infiltrates creep along sinusoids and do not form discrete masses until later. Neoplastic histiocytes in hemophagocytic HS express a distinctive surface antigen profile much like that expressed by macrophages in splenic red pulp and bone marrow (see following).

Immunophenotypic Studies MH and HS lesions express leukocyte surface molecules characteristic of DCs (CD1, CD11c, and MHC II). Diffuse expression of E-cadherin, Thy-1, and CD4 has not been observed in HS or MH in skin or other sites; this, together with cytomorphology, assists in the distinction of MH and HS from histiocytoma and reactive histiocytosis (SH and CH). In histiocytoma the phenotype is quite similar to that of HS, except for the expression of E-cadherin, which occurs in histiocytoma (especially in the cellular infiltrate immediately adjacent to the epidermis). E-cadherin expression is visibly weaker in tumor cells in the deep dermis. In reactive histiocytosis, infiltration and proliferation of activated interstitial (dermal) DCs (CD1+, CD11c+, MHC II+, E-cadherin-), which consistently express CD4 and Thy-1 is observed.

In hemophagocytic HS, histiocytes express CD11d (instead of CD11c) and MHC II. Expression of CD1 molecules is uniformly low or occasionally moderate but with a patchy distribution. This phenotype is consistent with macrophage differentiation rather than DC differentiation, in which abundant expression of CD1 and CD11c is expected.

The exact sublineages of DCs involved in HS have not been determined in most instances. The most likely candidates include interdigitating DCs in lymphoid tissues and perivascular interstitial DCs in other involved tissues. Immunophenotyping and careful morphologic assessment should also avoid confusion of HS and MH with the large cell form of T-cell lymphoma (CD3+) and with poorly differentiated mast cell tumors (CD18+ variable, CD45+, CD45RA+, Tryptase+, c-kit+).

Reactive Histiocytosis

Systemic Histiocytosis SH was originally recognized in related Bernese mountain dogs.[16] SH is a generalized histiocytic proliferative disease with a marked tendency to involve skin, ocular and nasal mucosae, and peripheral lymph nodes. The disease predominately affects young to middle-aged dogs (2 to 8 years). SH has been observed less commonly in other breeds (Irish wolfhounds, Basset hounds, and others). Clinical signs vary with the severity and extent of the disease and include anorexia, marked weight loss, stertorous respiration, and conjunctivitis with marked chemosis. Multiple cutaneous nodules may be distributed over the entire body but are especially prevalent in the scrotum, nasal apex, nasal planum, and eyelids. Ulceration of the skin overlying the nodules is common. Peripheral lymph nodes are often palpably enlarged. The disease course may be punctuated by remissions and relapses, which may occur spontaneously (especially early in the disease course). In severe disease, lesions become persistent and do not respond to immunosuppressive doses of corticosteroids.

Cutaneous Histiocytosis CH is a histiocytic proliferative disorder that primarily involves skin and subcutis and does not extend beyond the local draining lymph nodes.[17] CH occurs in a number of breeds. Evidence of spread beyond the skin would invoke the diagnosis of SH—a closely related disorder. Lymphadenopathy has not been emphasized in published reports and has only been documented in a small number of the authors' cases. The lesions occur as multiple cutaneous and subcutaneous nodules up to 4 cm diameter. Overlying skin ulceration is common. Lesions may disappear spontaneously or regress and appear at new sites simultaneously. Topographically, lesions may be found on the face, ears, nose, neck, trunk, extremities (including foot pads), perineum, and scrotum.

Treatment Options in Systemic Histiocytosis and Cutaneous Histiocytosis SH has proven to be a difficult and frustrating condition to treat. Consequently, many dogs were euthanized. Originally dogs were treated with thymosin (derived from bovine thymus) because of reports of its effectiveness in human LCH cases. Some dogs appeared to respond to this but not consistently. The original rationale for using thymosin was that SH was likely an immunoregulatory disorder and not cancer.[16] In the majority of instances, corticosteroid treatment is ineffective, although in about 10% of dogs with CH, steroid administration is effective. Hence, steroids are worth trying in this disease, given the expense of the alternatives.

Intractable cases are best treated with immunosuppressive doses of cyclosporine A (Neoral, Sandoz, East Hanover, NJ) or leflunomide (Arava, Aventis Pharmaceuticals, Bridgewater, NJ). These drugs are potent inhibitors of T-cell activation, and their ability to abrogate clinical disease supports the hypothesis that SH and CH are disorders of immune regulation. Treatment with these drugs is expensive and may be needed for life. It is preferable not to invoke such powerful immunosuppressive therapy until disease progression is evident or troublesome sites are involved, because in some cases of CH (and even SH) spontaneous regression of lesions or episodic disease activation can occur. Cost of treatment can be substantially reduced by coadministration of cyclosporine A and ketoconazole. It is imperative to measure 12-hour plasma trough levels of cyclosporine A (with twice-daily dosing); this is especially important if ketoconazole is coadministered! The 12-hour plasma trough target for cyclosporine A is 500 to 600 ng/mL. Neoral is the preferred cyclosporine A drug, because it is a microemulsion preconcentrate with superior gastrointestinal (GI) absorption compared with Sandimmune (Sandoz) (cyclosporine A in an olive oil base). Hence, Neoral can be used at a lower dose.[18]

Microscopic Features of Systemic Histiocytosis and Cutaneous Histiocytosis The lesions of SH in most tissues consist of perivascular infiltrates of large histiocytes and variable populations of lymphocytes, neutrophils, and eosinophils. The histiocytes frequently invade vessel walls, and this may lead to vascular compromise and infarction of surrounding tissues, which contributes to ulceration of the cutaneous lesions. The widespread distribution of lesions of SH is only fully appreciated at necropsy. Histiocytic lesions have been observed in skin, lung, liver, bone marrow, spleen, peripheral and visceral lymph nodes, kidneys, testes, orbital tissues, nasal mucosa, and other sites.

In skin, the lesions of SH and CH are virtually identical. The lesions usually involve the deep dermis and subcutis. Involvement of the superficial dermis is inconsistent, and epidermotropism of the histiocytes is not observed. In CH the lesions are limited to the skin but may involve the draining lymph nodes.

Immunophenotypic Studies Histiocytes in SH and CH express markers expected of DCs such as CD1, C11c, and MHC II. However, the lack of consistent epidermotropism in SH and CH lesions and the expression of Thy-1 (expressed by dermal DCs) and CD4 (a marker of DC activation) suggest that histiocytes in these diseases are activated interstitial-type DC[1]. In skin, dermal DCs are mostly of interstitial DC type. Expression of Thy-1 and CD4 in SH and CH clearly distinguishes these diseases from histiocytoma, in which an epidermal LC phenotype is observed. LCs are epithelial DCs; they express CD1, CD11c, MHC II, and E-cadherin. LCs lack expression of Thy-1 and do not express CD4 in the nonactivated state.

Pathogenesis The clinical behavior and consistent clinical response to immunosuppressive therapy with agents capable of profoundly inhibiting T-cell activation has reinforced the concept that SH and CH occur in the context of disordered immune regulation arising from defective interaction of DC and T cells. The end result of this dysregulated immune interaction is chronic proliferation of DC and T cells. The initiation of the process is probably antigen driven, although studies to identify the nature of the antigens involved have been unrewarding. Hence, it is important to perform tests to rule out infectious agents in the initial evaluation of a dog suspected of having reactive histiocytosis (i.e., culture, special stains for microorganisms in tissue). The lesions can wax and wane over a considerable period of time, and spontaneous regression without therapy has been observed. The lymphoid component of the lesion consists of predominately CD8+ alpha beta T cells, which have numbers that can vary markedly between lesions. These T cells can comprise up to 50% of the cells in some instances. The role played by T cells is unknown. T cells may be involved in a key way in the exaggerated proliferation and activation of DCs via T-cell-derived cytokines such as GM-CSF and TNF alpha, which are known to influence the proliferation and differentiation of DCs.

Concluding Remarks The continued distinction of SH and CH as separate entities is probably no longer justifiable. It would be preferable to consider them within the spectrum of reactive histiocytoses of interstitial DC origin, in which clinical outcome is predictable more by the distant migratory potential of the proliferating histiocytes beyond the skin. In this view, CH and SH would be regarded as skin-limited and systemic interstitial DC proliferations, respectively. A wide range of clinical behavior is to be expected within each grouping, with SH usually exhibiting more aggressive disease. CH and SH should not be confused with malignant DC disorders (HS and MH), which can occur in the same topographic locations. Cytologic and immunophenotypic differences can distinguish these diseases in most instances. Clear evidence of progression of reactive histiocystosis to HS or MH is not evident.

FELINE HISTIOCYTIC PROLIFERATIONS

True histiocytic proliferative diseases in cats have not been extensively documented. The lesion referred to as *malignant fibrous histiocytoma* is most likely a soft tissue sarcoma with giant cells; the neoplastic population does not express histiocytic markers. At least two different histiocytic proliferative diseases have been recognized in cats: (1) progressive histiocytosis and (2) HS/MH.

Feline Progressive Histiocytosis

Data on 19 cats with feline progressive histiocytosis have been accumulated since 1995. The incidence and recognition of cases seems to be increasing. Clinical presentation and progressive

behavior resemble LCH in humans and multiple persistent histiocytomas or LCH in dogs. Affected cats may have a solitary skin nodule, but usually multiple papules, nodules, or plaques develop, measuring up to 1.5 cm in diameter. The nodules are firm, nonpruritic, and nonpainful. The surface is often alopecic and may be ulcerated. The lesions are mostly located on the head, lower extremities, or trunk. Occasionally, the lesions are limited to one extremity. Feline progressive histiocytosis is a disease of middle-aged to older cats, the age ranging from 7 to 17 years. Sex or breed predilection has not been seen. The lesions may wax and wane, but spontaneous regression does not occur. In general, the nodules progress in size and may coalesce to large plaques. In addition, new lesions may develop. Some cats develop lesions in lymph nodes and internal organs including the lungs, kidneys, spleen, and liver. Additional clinical signs vary depending on the internal organ systems involved. Feline progressive histiocytosis has a guarded to poor long-term prognosis, because no successful treatment has been recognized to date.

Morphologic Features Lesions consist of diffuse dermal histiocytic infiltrates, which may extend into the subcutis. The overlying epidermis is either intact or ulcerated. Histiocytes have irregular, vesicular nuclei and finely dispersed chromatin. Cytologic atypia is present in a minority of lesions. Multinucleated tumor cells and occasional intralymphatic tumor cell aggregates may be present. The mitotic activity varies, and atypical mitoses are seen. Some cases are epitheliotropic (epitheliotropic progressive histiocytosis), characterized by intraepidermal single cells or cell aggregates, other cases lack epithelial involvement (nonepitheliotropic progressive histiocytosis). As the lesions progress the cells may exhibit numerous cytoplasmic vacuoles and hence have a foamy appearance. The extent of reactive infiltrates, composed of dispersed lymphocytes and fewer neutrophils, varies between cases.

Feline progressive histiocytosis has to be differentiated from xanthomas and from multicentric round cell tumors, such as lymphomas and mast cell proliferations. Xanthomas often have small areas of hemorrhages and deposition of cholesterol crystals, and they are composed of markedly vacuolated macrophages. Xanthomas are usually associated with underlying metabolic disorders such as diabetes mellitus or hypertriglyceridemia. Cutaneous papular mastocytosis (urticaria pigmentosa) is usually composed of well-granulated mast cells and Toluidine blue or Giemsa stains demonstrate their metachromatic granules. However, IHC may be required to rule out xanthomas, lymphomas, or poorly granulated mast cell tumors ("histiocytic" mast cell tumors).

Immunophenotypic Studies Histiocytes of feline progressive histiocytosis consistently express CD18, CD1a, CD1c, and MHC II. This immunophenotype is consistent with a DC origin.[4] However, both the epitheliotropic and nonepitheliotropic forms lack expression of E-cadherin, and Birbeck's granules could not be found in the only case evaluated by electron microscopy. These features indicate that feline progressive histiocytosis is not composed of Langerhans' cells, despite the existence of epitheliotropic infiltrates. The DCs are most likely of interstitial (dermal) type. The admixed reactive lymphocytes are CD8+ cytotoxic T cells.

Feline Histiocytic Sarcoma

Localized HS has been observed in cats. The poorly demarcated tumor masses were located in the subcutis of the ventral abdomen or the extremities. Metastasis to draining lymph nodes occurs. Alternatively, primary HS may occur in the spleen.[19] In essence, feline HS resembles the canine counterpart in terms of location of lesions and disease progression, but the incidence of feline HS is markedly lower. Feline HSs have a guarded to poor prognosis and most cats have been euthanized.

Morphologic Features Feline HS shares morphologic features with canine HS, including variable cytology encompassing mononuclear and multinucleated round cells and discrete to aggregated spindle cells. Anisocytosis and anisokaryosis exist in tumor cells of all types. A moderate to high mitotic rate with bizarre mitotic figures is common. IHC is required to differentiate between HSs and vaccine-induced sarcomas or anaplastic sarcomas with giant cells (incorrectly referred to as *malignant fibrous histiocytoma*).

Immunophenotypic Studies The round and spindle-shaped tumor cells express CD18, CD1, and MHC II. This immunophenotype is consistent with a DC origin, although the precise sublineage of DC has yet to be determined. The tumor cells lack expression of E-cadherin and hence are not of Langerhans' cell origin.

CHAPTER • 188

Urogenital and Mammary Gland Tumors

Ruthanne Chun
Laura Garrett

KIDNEY

Renal tumors are uncommon in cats and dogs, but they are almost always malignant. The most common renal tumor in cats is lymphoma; up to 50% of these cats are FeLV positive. Affected cats are usually middle aged (6 years) with no breed or sex predilection. In dogs the most common primary renal tumors are epithelial in origin (i.e., carcinoma or adenocarcinoma). Older dogs are affected, with an average age of 9 years, and males are overrepresented (1.5:1). Rare tumors include cystadenocarcinoma with concurrent nodular dermatofibrosis in German shepherd dogs and tumors of embryonal origin (e.g., Wilm's tumor) that are typically recognized in younger dogs. Animals with renal tumors usually have nonspecific signs of weight loss, anorexia, and lethargy. Less commonly, they have abdominal distention, lameness, and pain. Gross hematuria is a possible but uncommon finding. Physical examination may reveal unilaterally or bilaterally enlarged kidneys. A rare physical examination finding in dogs is palpable thickening and warmth in the distal long bones—a finding compatible with the paraneoplastic syndrome of hypertrophic osteopathy. Renal cystadenocarcinoma may be associated with firm, nodular dermal lesions and benign uterine growths. The genetic determinant of this unusual triad has yet to be identified.

Diagnosis may be obtained via cytology, especially in cats with lymphoma. However, biopsy is the gold standard for definitive diagnosis of most renal tumors. Ancillary tests such as a complete blood count (CBC), serum chemistry profile, and urinalysis provide important information regarding the overall health of the pet and the presence of paraneoplastic syndromes. Animals with renal tumors may have either anemia or polycythemia secondary to decreased or increased erythropoietin production, respectively. Another rare paraneoplastic syndrome of uncertain etiology in dogs with renal adenocarcinoma is neutrophilic leukocytosis. Animals with bilateral disease may have renal failure, as evidenced by increases in BUN and creatinine and a low urine specific gravity. Although tumor cells are only infrequently recognized on evaluation of urine sediment, finding RBCs and proteinuria on urinalysis is common. Up to one third of dogs and cats with epithelial renal tumors have radiographic evidence of pulmonary metastases. Abdominal radiographs show renomegaly but abdominal ultrasonography is both more sensitive and specific for identifying renal tumors. Ultrasound may also be helpful in obtaining preoperative biopsy specimens. Renal carcinomas are often bilateral and biologically aggressive, invading into the vena cava and metastasizing to regional lymph nodes, liver and bone.

Treatment with chemotherapy is indicated for cats with renal lymphoma. In addition to being bilateral, this is typically a systemic disease. With treatment, the average survival time is 6 months.[1] A doxorubicin-based combination chemotherapy protocol is recommended with the caveat that doxorubicin may be associated with nephrotoxicity in cats and thus renal parameters should be closely monitored before, during, and after use of doxorubicin.[2] As central nervous system (CNS) involvement has been documented in cats with renal lymphoma, the addition of a drug that reaches effective concentrations within the CNS (e.g., cytosine arabinoside) into a multidrug protocol is recommended. Nephrectomy is the most effective treatment for dogs with unilateral tumors, with average survival of 6 to 10 months. Renal cystadenocarcinomas in German shepherds, although malignant and metastatic, progress more slowly than other renal malignancies and survival times may be longer.[3] Ovariohysterectomy (OHE) is indicated for treatment of the uterine leiomyomas if the animal is symptomatic for those lesions.

URINARY BLADDER

Tumors of the urinary bladder are uncommon in dogs and rare in cats. Transitional cell carcinoma (TCC) is the most common primary tumor of the urinary bladder in both species. Other differentials include squamous cell carcinoma, leiomyosarcoma, leiomyoma, and rhabdomyosarcoma. The bladder may also be invaded by prostatic neoplasia or metastatic disease (e.g., hemangiosarcoma, lymphoma). Bacterial cystitis and urolithiasis are common differentials for the clinical signs seen, and a rare but important differential diagnosis for mass lesions is benign polyps of the urinary bladder.

Affected cats are usually middle aged and male. No underlying causes have been identified in cats. Older (10 years) female dogs of small breeds such as West Highland white and Scottish terriers, beagles, Dachshunds, and Shetland sheepdogs are reportedly at higher risk. Potential etiologies in dogs include obesity, cyclophosphamide therapy, and organophosphate, carbamate, pyrethrin, or pyrethroid-based flea dips.[4,5] Client complaints of recurrent stranguria, pollakiuria, hematuria, dysuria, urinary incontinence, or any combination of the above signs in an older dog should initiate a search for bladder cancer. In advanced cases, a mass is palpable in the caudal abdomen or abnormalities, such as a thickened urethra or enlarged sublumbar or intrapelvic lymph nodes, are identified on rectal examination. TCC can also metastasize to the inguinal lymph nodes and thus palpation of the inguinal fat pads may reveal firm nodes. Rarely, dogs have shifting leg lameness, or warm, swollen, and painful limbs. Palpation of the affected limbs reveals a firm, irregular, periosteal proliferation—a finding suggestive of hypertrophic osteopathy.

Diagnostic evaluation of any animal with the above clinical signs should begin with careful abdominal palpation and a rectal examination. CBC and biochemistry may be normal or may show azotemia. The urine sediment may reveal carcinoma; the presence of inflammation may cause "reactive" epithelial cells to exhibit criteria of malignancy. When a bladder

tumor is suspected, urinalysis should be obtained by free catch, catheterization, or ultrasound-guided cystocentesis, with caution to avoid penetrating the bladder through the tumor mass. Ideally, urine culture and sensitivity should be performed to rule out concurrent lower urinary tract infection. Unless the lesion is mineralized, abdominal radiographs will not reveal urinary bladder disease but may show sublumbar lymphadenomegaly or bony metastases. Although contrast cystography may be indicated for identification of urethral involvement, imaging of the urinary bladder via double contrast cystography has been widely replaced by ultrasonography. Ultrasound (Figure 188-1) is a highly sensitive tool in localizing and defining the extent of disease and for monitoring response to therapy.[6] Cytology may be diagnostic, with the finding of characteristic pink, intracytoplasmic transitional bodies (Figure 188-2). Failing a cytologic diagnosis, biopsy (traumatic catheter, surgical, or cystoscopic) and histologic examination may be necessary. Ultrasound-guided biopsy is not recommended as seeding of the biopsy tract with viable tumor cells is a possible complication.[7]

TCC often involves the apex of the bladder in cats. As this tumor is uncommon, the disease may go undiagnosed until it is diffusely invasive. However, even in cases of extreme local invasion, metastatic disease is not a common finding. In dogs, TCC typically involves the trigone. Obstruction of the ureters and urethra as well as invasion and disruption of the normal function of the urethral sphincter are common. TCC in dogs is metastatic; up to 40% of cases show spread by the time of diagnosis, 17% involve the lungs.[8]

Localized cases of TCC are treated with surgical resection if possible. TCC is highly exfoliative; caution is warranted to avoid "seeding" the tumor into the abdomen or along the surgery site.[9] The use of stay sutures to lift the bladder out of the abdominal cavity and moistened gauze sponges to pack off the rest of the abdomen can greatly decrease the risk of tumor seeding. Instruments and gloves that touch the tumor are contaminated. Once the tumor is exposed, use "clean" instruments to resect the tumor, switch gloves and use "clean" instruments to close the abdomen. Because the trigone region is most commonly involved in dogs, complete resection with acceptable postoperative function is rarely feasible. Most dogs with TCC should be managed medically or, less commonly, with radiation therapy.

Although no published studies discuss the medical management of TCC in cats, treatment of dogs is well described. Single agent therapy with piroxicam or cisplatin has a response rate of 20% with median survival times of 6 months.[10,11] Other studies report that single agent mitoxantrone or the combination of doxorubicin and cyclophosphamide have some activity.[12,13] Although cisplatin and piroxicam combination therapy has a response rate of 70%, 12 of 14 dogs treated with this protocol went into renal failure; most required early termination of their therapy and, in spite of the impressive response rate, median time to tumor progression or death was 4 months.[14] Mitoxantrone and piroxicam combination therapy has a response rate of 35% with a median survival time of 11½ months.[15] The current treatment recommendations are either single agent therapy with piroxicam (0.3 mg/kg orally once daily), or combination therapy of piroxicam and mitoxantrone (5 mg/m² IV every 21 days) with response to therapy used as a guideline for continued treatment.

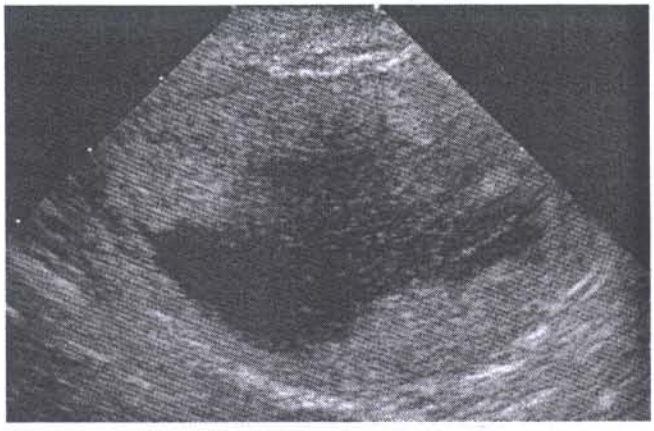


Figure 188-1 Transverse ultrasonographic image of a thickened, irregularly marginated circumferential urinary bladder wall mass in a spayed female collie with TCC. (Courtesy Todd Henrikson, Kansas State University.)

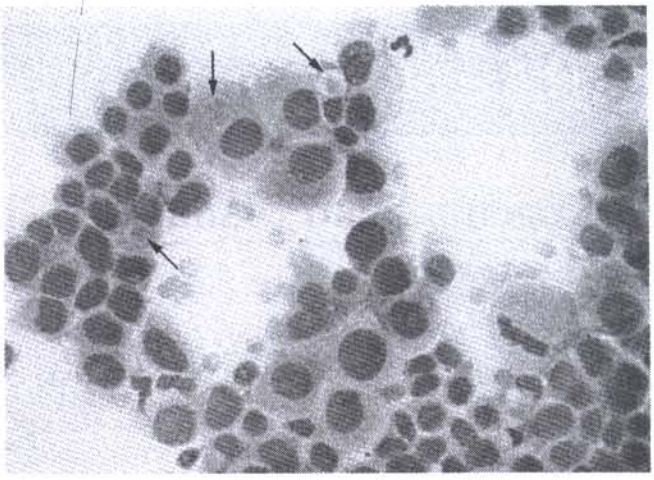


Figure 188-2 Large clustering epithelial cells showing criteria of malignancy from a male neutered Scottie with a urinary bladder mass, note transitional bodies *(arrows)*. Sample obtained via traumatic catheterization. (20×, Diff Quick stain.)

Although radiation therapy may also play a role in the management of TCC, survival times are not reported.[16] Surgical palliation for TCC obstructing the urethra ranges from ureterocolonic anastomosis to tube cystostomy. Ureterocolonic anastomosis has been described but this procedure is commonly associated with neurologic and gastrointestinal complications secondary to hyperammonemia, metabolic acidosis, and uremia, as well as chronic pyelonephritis, and survival times following this procedure ranged from only 0 to 5 months.[17] A tube cystostomy is a much simpler and better tolerated procedure that allows pets to survive an average of 3 months beyond when they would have been euthanized for urethral obstruction.[18] With disadvantages limited to recurrent urinary tract infections and occasional mechanical complications (e.g., tube is pulled out, animal chews through tube), the tube cystostomy is an excellent palliative option.

PROSTATE

Prostatic tumors are rare in dogs and are even less common in cats. Older, neutered, or intact dogs are typically affected. The most common histologic types are prostatic adenocarcinomas (ADC) and TCC, with many tumors having features of both.[19] Clinical signs include stranguria, hematuria, weight loss, tenesmus, rear limb lameness/pain, lumbar pain, and polyuria/polydipsia. Important differentials to consider are benign prostatic hypertrophy, prostatic cyst, prostatic abcess, and prostatitis. Prostatic carcinomas are aggressive; the majority of dogs

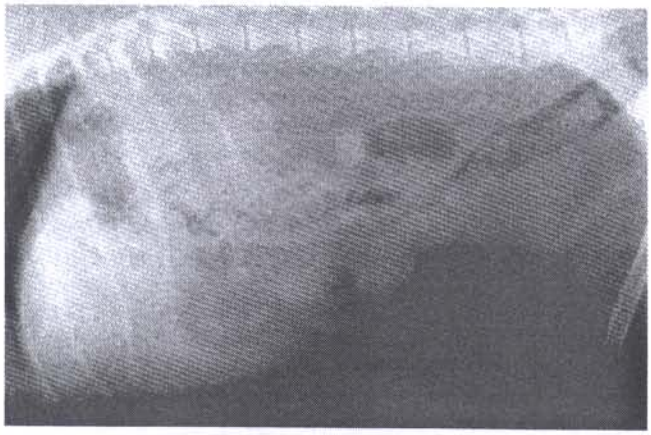


Figure 188-3 Lateral abdominal radiograph of a male neutered sheltie dog with prostatic carcinoma, note the irregular proliferative changes along the ventral aspects of lumbar vertebral bodies 5 through 7. (Courtesy David Biller, Kansas State University.)

have metastatic disease at the time of diagnosis. Metastases may be seen in the regional lymph nodes, vertebral bodies, or lungs.

Diagnostic evaluation should begin with a rectal examination. A neoplastic prostate is usually asymmetric, fixed, and firm. Careful rectal palpation for intrapelvic lymph node enlargement is also warranted. The CBC, chemistry profile, and urinalysis do not usually have pathognomonic findings; however, malignant cells may be observed occasionally in the urine sediment. As with any evaluation for metastatic disease, three view thoracic radiographs are recommended. The finding of mineralization in the prostate on abdominal radiographs or ultrasound is suggestive of neoplasia. Other areas that should be examined closely on abdominal radiographs and/or ultrasound include sublumbar lymph nodes and lumbar vertebrae (Figure 188-3), as these are common areas for metastases. Samples for cytologic examination may be collected via traumatic catheterization, prostatic massage, or transrectal needle aspiration. Although ultrasound guided aspiration of the prostate provides an accurate sampling technique, there is a possibility of seeding the tumor with this procedure.[7] Cytology is often diagnostic for malignancy but histologic examination remains the gold standard for diagnosis. Tissue may be obtained surgically or via ultrasound-guided biopsy, but caution is warranted as ultrasound-guided techniques may result in tumor seeding.

Curative treatment has not been identified for prostatic carcinomas. Castration is not beneficial. Palliative therapies including either tube cystostomy or piroxicam (0.3 mg/kg orally once daily) may provide up to 6 months of survival. The role of radiation therapy for the treatment of prostatic cancer is under investigation and seems promising, but the actual value of this therapy in prolonging survival is undefined. The overall prognosis for animals with prostatic neoplasia is guarded.

PENIS AND PREPUCE

The prepuce is affected by tumors that occur on haired skin elsewhere (e.g., mast cell tumor, squamous cell carcinoma). As with other cutaneous sites, evaluation of regional lymph nodes (i.e., inguinal and sublumbar lymph nodes) is an important component of the diagnostic examination. For the majority of penile and preputial tumors the diagnostic evaluation and treatment is the same as for other locations. Mast cell tumors tend to be more aggressive when arising on the prepuce, and thus even lower grade mast cell tumors in this location may require systemic chemotherapy for effective management.

The most common penile neoplasm is transmissible venereal tumor. This round cell tumor rarely metastasizes, is readily diagnosed via cytology, and is usually curable with vincristine (0.5 mg/m^2 IV weekly).[20] The number of treatments required varies between cases. Lesions tend to resolve within 2 weeks of the first treatment, but therapy should be continued for a minimum of 2 doses beyond complete visible resolution. Lesions that are resistant to chemotherapy may be successfully treated with radiation therapy.

TESTICLE

Testicular tumors are the second most common tumor of the male dog but are extremely rare in cats. Middle-aged to older dogs (9 to 11½ years) are affected. The three main histologic types seen include Sertoli cell, seminoma, and interstitial cell tumor. These tumors occur with roughly the same frequency, but cryptorchid individuals have 13.6 times greater risk of developing a Sertoli cell tumor or seminoma, and animals can be affected at a younger age. Roughly 25% to 50% of Sertoli cell tumors are functional and can cause hyperestrogenemia. The Sertoli cell tumor is also the type most likely to metastasize, usually to regional lymph nodes, but still with a low rate of 2% to 14%.

Although most testicular tumors are incidental findings on physical examination, clinical signs may include decreased libido, signs of prostatomegaly (e.g., stranguria or tenesmus), and inappetance and/or weakness secondary to anemia. Asymmetric testicles, scrotal or inguinal swellings, prostatomegaly, or signs of hyperestrogenism including alopecia, gynecomastia, a pendulous prepuce, and a poor haircoat may be seen on physical examination. Both testes are palpated simultaneously to compare size, shape, and firmness. A rectal examination should also be performed on these dogs; prostatomegaly secondary to estrogen-induced squamous metaplasia (Figure 188-4) is common.

Evaluation of dogs with testicular tumors should include a CBC with a platelet count and evaluation of regional lymph nodes via radiographs and/or ultrasonography with fine needle

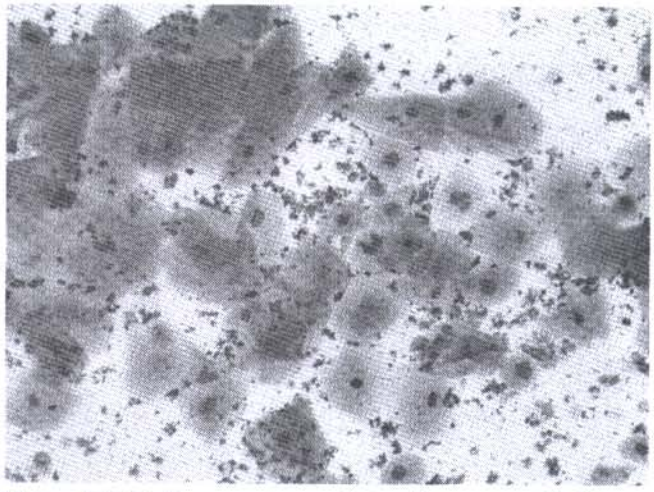


Figure 188-4 Squamous metaplasia of prostatic cells from a mixed-breed cryptorchid dog with a Sertoli cell tumor. Sample acquired via traumatic catheterization, debris in background is lubricating jelly. (20×, Diff Quick stain.)

aspiration if indicated. Bone marrow suppression is a rare complication of hyperestrogenism. This syndrome is characterized initially by thrombocytopenia and neutrophilic leukocytosis, which ultimately progresses into pancytopenia. As pulmonary metastases are extremely rare, thoracic radiographs may not be cost effective as a staging test; however, they may be indicated for evaluation of concurrent disease in these older patients.

Castration is curative for most testicular tumors. Scrotal ablation may be necessary if the tumor is fixed to scrotal skin. If the affected testicle is cryptorchid caution is warranted during surgery as the testicle may be friable. Any enlarged lymph nodes should be biopsied and ideally excised at the time of surgery. Cisplatin has been reported to be of benefit in a small number of dogs with metastatic disease.[21] Radiation has been used to treat sublumbar lymph node metastases in patients with seminoma.[22] If estrogen-induced myelosuppression has occurred, the patient may require months of hematologic support; some dogs with such myelosuppression never recover.

VAGINA AND VULVA

Tumors of the vagina and vulva are the second most common reproductive tumors in female dogs but are extremely rare in cats. Most are benign smooth muscle tumors that arise within the vestibule and occur in older intact dogs, with an increased incidence in nulliparous bitches. Histologic terminology used for these benign tumors includes leiomyoma, fibroleiomyoma, fibroma, or polyp, depending on the amount of connective tissue present in the mass. Lipomas may also be seen in this area. Malignant tumors are rare, with leiomyosarcoma the most likely. Transmissible venereal tumors may also occur (Figure 188-5).

Tumors may be intraluminal or extraluminal. Intraluminal tumors are often associated with stranguria; owners may see the mass protrude during urination or defecation. Other possible clinical signs include bleeding, discharge, dysuria, and licking. Extraluminal tumors are usually slow-growing perineal masses. Diagnostic evaluation of any straining dog should include a rectal and vaginal examination. For intraluminal masses, cytology can often be performed from an impression smear made by gently scraping the mass with a gloved fingertip. Fine needle aspirates can be performed on extraluminal masses or on intraluminal masses that do not exfoliate with the digital technique. Other diagnostic tests include vaginoscopic exam to determine the local extent of disease as well as abdominal radiographs and/or abdominal ultrasound to evaluate for lymph node involvement.

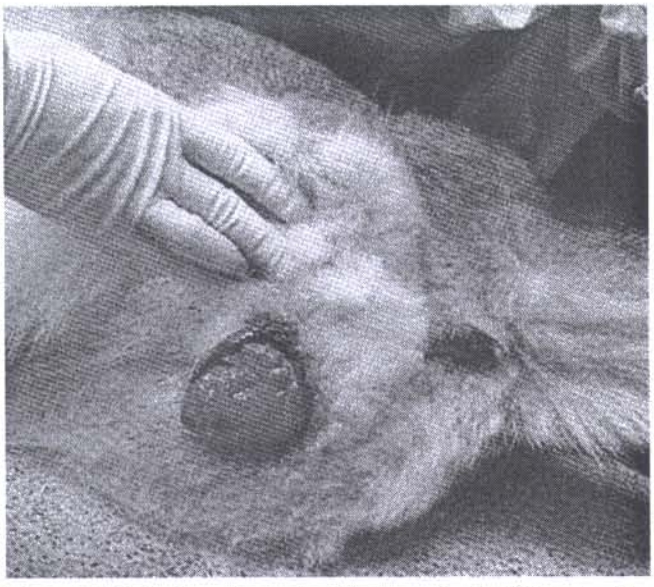


Figure 188-5 Large, irregular friable vaginal TVT protruding from vulva of mixed breed intact dog.

Chemotherapy with vincristine as described above is the treatment of choice for bitches with TVT, for all other types of vaginal tumors surgical resection and OHE is usually curative. OHE is recommended for these hormonally responsive tumors as recurrence is likely in dogs treated with mass removal only. Excise intraluminal tumors at the pedicle; wide excision is not needed. Approach extraluminal tumors via dorsal episiotomy; these tend to be well encapsulated and are easy to resect.

UTERUS

Uterine tumors are rare in dogs and cats, likely because the vast majority of female dogs and cats under veterinary care within the United States have undergone OHE. In dogs the majority of uterine tumors are mesenchymal; 85% to 90% are leiomyomas and 10% are leiomyosarcomas. German shepherd dogs may be overrepresented in the literature due to the well-described syndrome of renal cystadenocarcinomas and associated uterine leiomyomas.[23] As expected with their benign nature, most uterine tumors in dogs are slow-growing, non-invasive into surrounding structures, and not metastatic. In cats uterine adenocarcinoma is the most common primary tumor of the uterus, a disease associated with an aggressive biologic behavior and widespread metastases.

Although clinical signs in dogs may be organ-related, such as vaginal discharge or evidence of pyometra, uterine tumors are more commonly an incidental finding. Cats may have specific signs of discharge or suspected pyometra, or they may have signs related to metastatic disease (e.g., pulmonary distress, lymphadenopathy, anorexia).

Diagnostic evaluation of animals with suspected uterine tumors should include a minimum database to establish overall metabolic status as well as thoracic and abdominal radiographs and abdominal ultrasound. A technique that may be useful in imaging uterine tumors if ultrasound is unavailable is compression radiography.[24] This procedure employs the use of a radiolucent device (e.g., a wooden or plastic spoon or paddle) to apply pressure to the area of interest during the making of a radiograph, increasing visualization of the region by moving overlying structures out of the way. Ovariohysterectomy is often curative for dogs, but due to the aggressive biologic behavior in cats OHE alone is unlikely to provide long-term control. Although the efficacy of chemotherapy in both dogs and cats remains largely unknown, one case report describes the successful use of OHE followed by epirubicin in a young dog with a uterine carcinoma.[25] Thus anthracycline based chemotherapy may be efficacious in the rare cases of uterine malignancy.

OVARY

Similar to uterine neoplasia, ovarian tumors are rare in dogs and cats, again in part related to the high rate of neutering in companion animals. Asymptomatic ovarian tumors are most commonly found during routine OHE in older animals; an important differential in this situation are ovarian cysts. However, as some ovarian tumors are malignant, any abnormal ovary should be submitted for histologic examination.

Specific clinical signs associated with ovarian tumors include a palpable mass, signs of ascites, or systemic effects of hormone production. These tumors may attain a large size prior to detection. Three categories of ovarian tumors are seen, depending on the cell of origin of the neoplasm: epithelial, germ, and sex-cord stroma.[26] All three of these categories include benign and malignant forms. The malignant forms may metastasize to the peritoneum and can cause a malignant effusion; metastases are also seen in the lymph nodes, liver, and lungs.

In dogs, roughly one half of ovarian tumors fall into the epithelial category and include the histologic diagnoses of papillary adenoma, cystadenoma, papillary adenocarcinoma, and undifferentiated adenocarcinoma. These tumors can occur bilaterally, are rarely functional, and have malignant forms with a metastatic rate of approximately 50%. Epithelial tumors are rare in cats.

Germ cell tumors make up roughly 10% of ovarian neoplasms in dogs, are rarely bilateral or functional, have a metastatic rate of 10% to 30%, and may be seen in young as well as older animals. These tumors are further categorized into three histologic types: dysgerminomas, teratomas and teratocarcinomas. Dysgerminomas (i.e., ovarian seminomas) arise from undifferentiated germ cells and have a similar histologic appearance to their testicular counterpart. Teratomas are made up of more than one germ cell layer (ectoderm, mesoderm, and/or endoderm) and the majority are well differentiated. Teratocarcinomas have differentiated and undifferentiated components; metastatic lesions are composed of the undifferentiated components and have been reported in the abdomen, lung, mediastinum, and bone. In cats approximately 15% of ovarian tumors are dysgerminomas; these may occur bilaterally and are malignant.

Sex-cord stromal tumors make up 35% to 50% of ovarian tumors, are rarely bilateral, are functional in approximately 50% of cases, and have a metastatic rate of less than 20%. These tumors can produce estrogen and progesterone. Clinical signs seen may be related to estrogenic effects (e.g., vulvar enlargement, vaginal discharge, persistent estrus) or progesterone effects (e.g., pyometra). The most common sex-cord stromal cell tumor is the granulosa cell tumor; this is the only tumor in this category that can metastasize. Less commonly, the benign thecoma or luteoma may be diagnosed. In cats germ cell tumors make up roughly 50% of ovarian tumors; greater than 50% of these are malignant. The most common histologic type in cats is granulosa cell tumors, and hyperestrogenism is commonly seen.

Diagnostic evaluation of dogs or cats with ovarian tumors should include a minimum data base, thoracic radiographs, and abdominal radiographs or ultrasound. If ascites is present, cytologic examination of the fluid may be diagnostic for malignancy. The ultrasonographic characteristics of ovarian tumors in dogs has been reported, with the tumors ranging from solid to cystic in appearance.[27] Uterine changes (i.e., findings consistent with cystic endometrial hyperplasia or pyometra) were commonly found with sex-cord stromal tumors.

Treatment of ovarian tumors relies primarily on OHE and carries, in general, an excellent prognosis. In the rare cases of peritoneal metastases or malignant ascites, intracavitary chemotherapy may be of benefit.[28]

MAMMARY GLAND

Mammary gland tumors (MGT) are the third most common tumor overall in cats and one of the most common tumors in female dogs. Older females of either species are more likely to develop these tumors. Breeds at risk include Siamese; Poodles; English, cocker, and Brittany spaniels; English setters; and fox and Boston terriers. A hormonal etiology is well described for dogs and is likely for cats. Ovariohysterectomy can greatly decrease the risk of developing mammary gland tumors. Dogs spayed before their first estrus have a risk of 0.5%, after their first estrus the risk jumps to 8%, and after their second estrus the risk goes to 26%. There is no protective effect if dogs are spayed after their third estrus cycle. Estrogen and progesterone receptors have been identified in dog and cat MGT; for dogs the less well differentiated the tumor the more likely the tumor is to be hormone receptor negative. Prolonged administration of estrogens to dogs does not increase the incidence of MGT, although progesterone administration may result in benign nodule formation. However, there is an association between the use of megestrol acetate and the development of MGT in cats.[29]

On physical examination, animals may have single or multiple nodules associated with the nipple or the gland itself. Benign lesions tend to be small, well-circumscribed, and firm on palpation. The caudal mammary glands are most often involved in dogs; feline tumors occur with equal frequency in all glands. MGT may be freely movable or adherent to the skin or abdominal wall. They may be ulcerated (Figure 188-6), inflamed and edematous, or associated with discharge from the nipple. Differentials for MGT include other neoplasms (e.g., mast cell tumors, squamous cell carcinoma), mastitis, lobular hyperplasia, and fibroepithelial hyperplasia in cats.

Diagnostic evaluation of animals with mammary neoplasia should include a CBC, chemistry profile, and urinalysis. Cytologic evaluation of the mass is warranted. Although cytology cannot generally differentiate benign from malignant lesions, it can be helpful in ruling out other differentials. Also, cytology may be diagnostic if strong criteria of malignancy are present. Thoracic radiographs are important to evaluate for pulmonary metastatic disease and sternal lymphadenopathy. Pleural effusion, a common occurrence in cats with metastatic MGT, may also be identified. Assessment of inguinal, sublumbar, mesenteric, and pelvic lymph nodes is an important component of thorough staging. These nodes can be evaluated via physical and rectal examination, fine needle aspiration, and abdominal radiographs, or ultrasound. Biopsy of the mammary mass, typically excisional, will provide a definitive diagnosis.

In dogs 50% of MGT are benign, most often fibroadenomas (i.e., benign mixed tumor). The most common types of malignancies in dogs are solid carcinomas, followed by tubular adenocarcinomas; only about 3% are sarcomas and 1% are inflammatory carcinomas. Of the 50% that are malignant, 50% will recur or metastasize following the first surgical resection. Poor prognostic factors for survival in dogs with MGT include histologic type (poorly differentiated tumors,

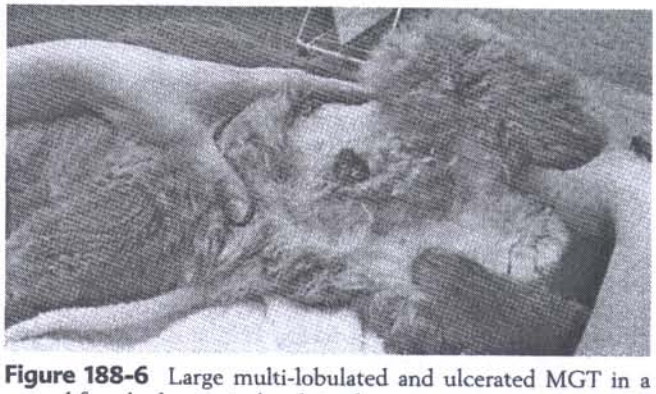


Figure 188-6 Large multi-lobulated and ulcerated MGT in a spayed female domestic shorthaired cat.

sarcoma, and inflammatory carcinomas have a worse prognosis), tumor size greater than 3 cm, lymph node involvement, histologic evidence of lymphatic or vascular invasion, minimal to no lymphocytic infiltration into the tumor, ulceration, and distant metastases.

The majority of feline MGT are malignant, most often adenocarcinomas, and they exhibit highly metastatic behavior. Prognosis depends primarily on tumor size at the time of diagnosis. Tumors less than 2 cm in diameter are associated with survival times over 3 years, whereas tumors larger than 3 cm are associated with survival times of 4 to 6 months. The type of surgery performed (see below) has been shown to be prognostic for disease free interval but not for survival time.

Surgery is the mainstay of treatment of MGT in dogs and cats. A major contraindication to surgery is in the case of inflammatory carcinomas, as it is virtually impossible to remove the entire tumor and regrowth may occur within days of the surgery. In dogs with MGT the goal of surgery is to remove the entire tumor by the simplest procedure possible. For example, a "lumpectomy" is acceptable for a small (less than 1 cm diameter) and superficial mammary nodule, whereas lesions 1 to 2 cm in diameter may require a mammectomy. If masses are present in multiple glands, they may be resected individually or in a chain mastectomy, again choosing the surgery based on the easiest way to remove all affected tissue. As malignant MGT do rarely express estrogen or progesterone receptors, there is theoretical benefit to spaying the pet; however, no controlled studies have shown an actual therapeutic benefit of OHE at the time of mammary tumor excision. OHE may be recommended at the time of mastectomy to prevent ovarian or uterine diseases in the future. As described above, the majority (75%) of canine mammary gland tumors can be cured with surgery alone. In cats, full chain mastectomy (i.e., removal of all five glands on one side without removal of underlying musculature) is recommended, with bilateral staged mastectomy for bilateral disease. Cats with minimal resections reportedly had recurrent disease sooner than cats with a full mastectomy but had similar survival times. Radiation therapy is not routinely used for this disease in dogs or cats.

Little information is available regarding the efficacy of chemotherapy for canine or feline MGT. In dogs with malignant mammary tumors and the presence of poor prognostic factors, a doxorubicin or doxorubicin/cyclophosphamide protocol is the conventional treatment. Recently, a 5-FU/cyclophosphamide protocol was shown to be of benefit in a small case series. Additionally, piroxicam has been shown to have some effect against this disease and may be particularly indicated for inflammatory carcinomas. Since the vast majority of feline mammary tumors are malignant and metastatic, chemotherapy postoperatively is recommended. As in dogs, single agent doxorubicin or a doxorubicin-based protocol is used. 5-FU should not be administered to cats as the drug is associated with neurotoxicity.

CHAPTER • 189

Paraneoplastic Syndrome

Frédéric P. Gaschen
Erik Teske

Paraneoplastic syndromes (PNS) result from indirect effects of tumors due to the production and release of biologically active substances such as hormones, growth factors, and cytokines. The immune system may be affected, and autoimmunity, immune complex production, or immune suppression can occur. Occasionally, PNS may have a higher morbidity than the original tumor itself.

PNS are divided in different categories depending on their target organ. They include endocrinopathies, disorders of hematopoiesis and hemostasis, neuromuscular disorders, and cutaneous syndromes. Cancer cachexia is usually treated separately as it affects multiple organ systems.

A timely detection of PNS is essential for several reasons: (1) they may be the first clinical manifestation of tumor, and early diagnosis may improve the prognosis for the underlying neoplasia; (2) the severity of the PNS can reflect the activity of the tumor cells, and give information on the progressive or regressive nature of the tumor; (3) the clinical signs caused by a PNS could be falsely interpreted as direct effects of the tumor itself or side effects of treatment, and lead to false prognostic considerations; (4) finally, PNS may affect the general condition of the animal, and significantly alter the prognosis of a specific tumor.

GENERAL MANIFESTATIONS OF CANCER

Cancer Anorexia-Cachexia

The cancer anorexia-cachexia syndrome (CACS) affects more than one half of all human cancer patients and represents the most common paraneoplastic disorder. A decline in body weight of more than 10% in these patients negatively influences survival, in part due to secondary infections and wound healing complications.[1,2] In addition to CACS, anorexia and weight loss are often compounded by the side effects of treatment in cancer patients. Although no comparable epidemiologic data are available in small animal oncology, CACS is also recognized in canine and feline cancer and is likely to adversely affect prognosis.

Anorexia, nausea, and weight loss clinically characterize CACS. In contrast to wasting due to severe starvation, a massive decrease in muscle protein mass accompanies body fat depletion in CACS. In addition to wasting, this syndrome is frequently accompanied by changes in food perception (taste, smell), which diminishes the pleasure of eating. The metabolic alterations associated with CACS are, at least in part, mediated by the production of substances such as IL-1β, TNF-α, IL-6, IFN-γ, and serotonin by both the tumor and the host

immune system.[1] The pathophysiologic mechanisms triggered by these cytokines include alterations in carbohydrate, fat, and protein metabolism as well as in energy expenditure.

Several studies have investigated the metabolic alterations associated with lymphoma in dogs. Abnormalities in *carbohydrate metabolism* include an increased concentration of insulin and lactate in response to an intravenous glucose challenge[3], which does not resolve when complete clinical remission following doxorubicin chemotherapy is achieved.[4] Moreover, intravenous infusions with lactated Ringer's solution seem to exacerbate this aberration and should therefore be avoided in canine lymphoma patients.[3] The authors of these studies concluded that an insulin receptor or post-receptor defect is present in dogs with lymphoma, and that hyperlactatemia is the result of preferential anaerobic glucose metabolism by lymphoma cells. Large amounts of lactate produced by anaerobic glycolysis in tumor cells are then reconverted into glucose via the hepatic Cori cycle, which creates a futile energy-consuming cycle for the host.[2]

Abnormalities in *lipid metabolism* associated with CACS result in severe loss of body fat. Decreased lipoprotein lipase activity impedes the extraction of fatty acids from plasma lipoproteins by adipocytes. Moreover, increased hormone-dependent lipase activity, which acts in concert with a recently isolated lipid mobilizing factor in some tumors, contributes to lipolysis and lipid mobilization.[5] In dogs with lymphoma, lipoprotein profiles were found to be altered and did not improve following complete remission with doxorubicin therapy.[6]

Studies on *resting energy expenditure* (REE) in cancer patients have yielded disparate results. Although some tumors in humans are associated with an increased REE, others are not. Similarly, despite a decreased REE observed in canine lymphoma patients, dogs with osteosarcoma (OSA) were found to have a higher REE before limb amputation than healthy controls.[7] In addition to the abnormalities in glucose metabolism, an altered expression of uncoupling proteins has recently been postulated to be an important determinant in the increase in REE associated with cancer. Uncoupling proteins are mitochondrial membrane proteins that impede the coupling of respiration to ADP phosphorylation, which results in the generation of heat instead of ATP.[5]

The effects of CACS on *protein metabolism* encompass both increased protein catabolism and decreased protein synthesis and result in significant muscle atrophy. Dogs that suffer from OSA were found to have a negative nitrogen balance following limb amputation.[7] In these animals, the rate of protein synthesis was only 72.4% that of healthy dogs, whereas the urinary nitrogen excretion was 65% greater.[7] The role of cytokines, such as TNF-α, IL-6, and IFN-γ, as mediators of muscle catabolism and abnormal protein metabolism has been called into question, and these substances may merely serve as markers of these phenomena. Moreover, a recently isolated circulatory skeletal muscle proteolysis-inducing factor (PIF) is thought to play a central role in eliciting cancer-associated protein catabolism. Indeed, human cancer patients with severe weight loss were found to frequently excrete PIF in their urine.[5]

The objectives of nutritional support in cancer patients are to limit the adverse effects of CACS and enhance immune system function as well as the response to and tolerance of cancer therapy. Recently, a diet rich in polyunsaturated omega-3 fatty acids was found to have beneficial effects on the disease-free interval and survival of dogs with stage-III lymphoma treated with doxorubicin.[8] This fish-based diet was also associated with a more rapid decline in circulating levels of the inflammatory cytokines IL-6 and TNF following treatment. Moreover, insulin resistance and hyperlactatemia diminished to a greater extent and more rapidly in dogs fed with this diet than in control animals.[8] In addition to aspects of diet composition, current treatment recommendations for CACS in human patients emphasize the advantages of gastrointestinal over parenteral nutritional support.[1]

The metabolic alterations responsible for CACS are usually present in cancer patients long before clinical signs of CACS are recognized. This implies a need for early nutritional support. In persistently anorectic animals, naso-esophageal, esophagostomy, or gastrostomy tubes are recommended to administer food safely and provide adequate nutrients. Most pharmacologic interventions aimed at prevention of weight loss in human cancer patients have thus far been largely unsuccessful and are unlikely to be beneficial in veterinary cancer patients.[1,2]

Fever

Although common in human cancer patients, fever is rarely a genuine PNS. In patients with neutropenia, fever is often the consequence of an infectious process. Paraneoplastic fever is generally suspected in human patients who are not neutropenic, and those affected by certain neoplasms, including renal cell carcinoma, hepatoma, and non-Hodgkin's diseases.[1] The pathomechanisms of paraneoplastic fever include the elaboration of pyrogenic cytokines by the tumor and/or host immune system. In particular, IL-1, IL-6, and TNF may act as endogenous pyrogens on the thermoregulatory center of the anterior hypothalamus. Despite the lack of studies on the prevalence of paraneoplastic fever in dogs and cats, numerous case reports and experience indicate that it also occurs in small animals.

HEMATOLOGIC PARANEOPLASTIC SYNDROMES

Tumors, or their metastases, can have profound effects on hematopoietic cell lines by infiltration of the bone marrow. Further suppression of the bone marrow can be caused by treatment with cytostatic drugs. In addition to these direct effects on the bone marrow, mechanisms involved in PNS sometimes have even more serious effects on hematopoiesis, which may be better understood when data from ongoing research on hematopoietic growth factor are available.

Anemia

Anemia is one of the more common PNS in dogs and cats. Although exact figures are not available for all tumor types, anemia has been reported to occur in 30% to 40% of dogs with malignant lymphoma and up to 69% of those with splenic hemangiosarcoma. Different mechanisms are involved: anemia of chronic disease, immune-mediated hemolytic anemia, myelophtisis, blood loss, and microangiopathic hemolytic anemia.[9]

Anemia of chronic disease (ACD) is caused by shortening of the erythrocyte life span and is a mild, normocytic-normochromic, nonregenerative anemia. It is not associated with particular types of cancer and its cause is unknown. The characteristic features of ACD are disordered iron metabolism as manifested by a low serum iron, decreased serum transferrin, decreased transferrin saturation, increased serum ferritin, increased reticuloendothelial iron stores, and reduced iron absorption.[9] In humans, erythropoietin production is usually normal but the responsiveness of erythroid progenitor cells to the hormone is impaired by inflammatory cytokines. The anemia is mild and disappears after treatment of the tumor.

When *immune-mediated hemolytic anemia* (IMHA) occurs as a PNS in dogs and cats, it is usually associated with hematopoietic tumors, especially lymphoid malignancies and less frequently with solid tumors. Cross-reacting antibodies against cell-membrane antigens or direct interference with the immune system through suppressor T-cells lead to a premature destruction of red cells by the reticuloendothelial system.

The anemia can be acute or chronic, mild or severe and is regenerative in most cases. The most common clinical signs are lethargy, weakness, pale mucous membranes, icterus, hepatosplenomegaly, hemoglobinuria, and anorexia. Diagnosis is made by a direct antiglobulin test for detection of erythrocyte-bound immunoglobulin (IgG and IgM) and complement (C3). Treatment with corticosteroids, with or without immunosuppressive agents such as azathioprine or cyclophosphamide, has been evaluated mainly in dogs with primary idiopathic IMHA, but not in cancer patients. Elimination of the primary tumor remains as the most important factor for control of the IMHA.

Blood loss anemia associated with paraneoplastic gastroduodenal ulceration occurs with mast cell tumors and gastrinomas as well as primary gastrointestinal neoplasms. The anemia is initially regenerative but becomes nonregenerative, microcytic, and hypochromic, accompanied by decreased serum iron concentration and increased iron-binding capacity. Blood loss anemia occurs with some renal tumors and with any tumor in which bleeding occurs, such as splenic or hepatic tumors. Treatment should be directed at the primary tumor. Supportive treatment with transfused blood and oral ferrous sulfate is usually not necessary in animals with chronic blood loss, unless they undergo surgery for the tumor.

Microangiopathic hemolytic anemia is usually associated with microvascular tumors but can occur with any tumor that leads to disseminated intravascular coagulation (DIC). Fragmentation of erythrocytes can be caused by abnormal vascular structures with fibrin deposits, fibrin threads formed in the course of DIC, pulmonary intraluminal tumor emboli, or narrowing of pulmonary arterioles by intimal proliferation.[10] Hemangiosarcoma is the most frequent tumor associated with this type of anemia in dogs.

Erythrocytosis

Erythrocytosis, or polycythemia, is a rare PNS in dogs and cats. It is usually associated with primary or secondary tumors of the kidney, but it has also been documented in dogs with nasal fibrosarcoma, bronchial carcinoma, and cecal leiomyosarcoma. In contrast to primary eryrhocytosis (polycythemia vera), in which there is a neoplastic disorder of the erythroid cell lines in the bone marrow, the cause of secondary erythrocytosis is an increased level of erythropoietin. Possible mechanisms are ectopic erythropoietin production by the tumor,[11] increased erythropoietin production by the kidney in response to hypoxia of the kidney caused by tumor compression, and increased production of so-called *hypoxia-inducible transcription factors*, which stimulate erythropoietin production.[12] The clinical signs result from hyperviscosity of the blood and dilatation and decreased perfusion of small blood vessels, which result in tissue hypoxia, bleeding, polyuria, and thrombosis.

Leukocytosis

Increased peripheral granulocytosis without evidence of infection or leukemia has been reported to occur in association with several tumor types in humans but less frequently in the dog and cat. The excessive leukocytes are mature neutrophils and there are usually no clinical signs. In the dog, neutrophilic leukocytosis has been reported as a PNS with renal carcinoma, malignant lymphoma, metastatic fibrosarcoma, rectal adenomatous polyps, and pulmonary carcinoma. It has been described in a cat with dermal tubular adenocarcinoma. The diagnosis is made by exclusion of other causes of leukocytosis and resolution of the leukocytosis after removal of the tumor. Differentiation from a coexistent chronic myelogenous leukemia can be difficult. In paraneoplastic leukocytosis the tumor itself produces colony-stimulating factors (CSF). With the help of immunohistochemical staining techniques and reverse transcription polymerase chain reactions, the presence and production of both granulocyte-CSF (G-CSF) and granulocyte-macrophage-CSF (GM-CSF) have been demonstrated in tumor tissue in the dog, while in the cat only G-CSF could be demonstrated.[13,14]

Hypereosinophilia is a rare manifestation of cancer. Although it has been found with T-cell lymphoma,[15] mammary carcinoma, and oral fibrosarcoma, it is usually associated with disseminated mast cell tumors. Thoracic and abdominal eosinophilic effusions may accompany the peripheral blood eosinophilia.[16] The hypereosinophilia appears to be a response to cytokines such as IL-2 and IL-5. It is associated with disseminated, metastatic disease and hence signifies a poor prognosis.

Thrombocytopenia

Thrombocytopenia is one of the most common hemostatic abnormalities in cancer patients. It has been reported to occur in 10% to 36% of dogs with solid cancers and up to 50% of animals with malignant lymphoma.[17,18] Myeloproliferative neoplasms are responsible for 20% of the cases of thrombocytopenia in cats. Several different mechanisms may be responsible for thrombocytopenia in cancer patients. The life span of platelets can be shortened, especially in animals with metastatic tumors. Proposed mechanisms for this include binding of platelets to abnormal endothelium of blood vessels in tumors such as hemangiosarcomas, and accelerated removal from the circulation because of tumor-stimulated microaggregation of the platelets or because of binding of tumor proteins to the platelets. Immune-mediated thrombocytopenia (ITP) is another frequent cause of depletion of platelets in animals with cancer. It may result from anti-platelet antibody production or cross-reactivity between platelet and tumor antigens. Another cause of increased platelet destruction is microangiopathy, which leads to fragmentation of both red cells and platelets. Thrombocytopenia can also be the result of decreased platelet production caused by massive tumor infiltration of the bone marrow. Clinical signs of thrombocytopenia do not usually become evident until the platelet count decreases below 30,000/µL. Treatment of thrombocytopenia associated with cancer should be directed at removal of the tumor. ITP is treated with immunosuppressive drugs such as corticosteroids.

Thrombocytosis

Thrombocytosis (platelet counts above 500,000/µL) is a very common PNS in humans but is rare in dogs and cats. It has been described in animals with osteosarcoma, gingival carcinoma, chronic myeloid leukemia, bronchoalveolar carcinoma, and metastatic squamous cell carcinoma. It can cause thrombotic or hemorrhagic tendencies, but in most cases there are no clinical signs. The mechanism leading to the thrombocytosis is still unclear. Although elevated levels of IL-6, GM-CSF, and G-CSF have been found in some human patients, the levels were generally lower than required for *in vitro* induction of megakaryocytic differentiation. There may be other thrombopoietins in affected patients that have not yet been identified.[19] For the diagnosis of thrombocytosis as a PNS, other causes of thrombocytosis such as vinca alkaloids, splenectomy, iron deficiency, and myeloproliferative disorders should be ruled out.

Thrombocyte Hyperaggregability

Functional changes in platelets have also been demonstrated in patients with cancer. Hyperaggregation of platelets was demonstrated in a study of 59 dogs with cancer.[20] Proposed explanations for hyperaggregation include (1) an increase in serum factors that induce platelet aggregation, (2) a change in plasma membrane lipid composition, and (3) increased numbers of younger platelets, which have a higher activity. Platelet hyperaggregability may not only lead to thromboembolism but may also aid metastasis by the release of factors influencing stroma and blood vessels.

Pancytopenia

In dogs, bone marrow aplasia can be caused by administration of estrogens and by estrogen-producing tumors such as Sertoli cell tumors of the testis and granulosa cell tumors of the ovary. Although the exact pathomechanism is unknown; estrogens may not directly damage the bone marrow granulocyte-macrophage progenitor cells. A myelopoiesis-inhibitory factor produced by canine thymic stromal cells is probably a mediator of the bone marrow suppression.[21] The prognosis is guarded, for the pancytopenia is often irreversible in spite of removal of the tumor. In addition to large individual differences in sensitivity to estrogens, age is a major factor that influences the prognosis.[22]

Coagulation Disorders

Coagulation disorders often develop in late stages of aggressive malignancies. The mechanism of this cancer-related hypercoagulability is not completely understood. It has been postulated that tumor-specific physiologic changes such as decreased oxygenation (tumor hypoxia) stimulate expression of blood-clotting regulators such as tissue factor and plasminogen activators, by both tumor cells and host cells.[23] In dogs and cats, however, disseminated intravascular coagulation (DIC) is the most frequent clinical abnormality and is probably caused by a complex of factors. As in humans, coagulation-activating substances can be produced by tumor cells. Hemangiosarcoma can release tissue thromboplastin into the circulation causing increased platelet aggregation. Tumor necrosis factor (TNF), produced by inflammation-activated macrophages, can change the endothelium of blood vessels, which increases the tendency for intravascular coagulation. The DIC-induced depletion of coagulation factors and the inhibitory properties of fibrinogen degradation products may cause hemorrhagic diathesis. DIC is often associated with hemangiosarcomas, thyroid carcinomas, and mammary gland carcinomas. Hemostatic abnormalities occurred more frequently with canine mammary carcinomas in the presence of extended tumor necrosis, inflammatory carcinoma, infiltration of the stroma by tumor cells, and distant metastases.[24]

Hyperproteinemia

Hyperproteinemia occurs as a PNS more often in animals with multiple myeloma or chronic lymphatic leukemia (CLL).[25,26] In approximately 75% of cases of multiple myeloma there are monoclonal immunoglobulins, usually IgG or IgA, which can be secreted in large quantities, producing paraproteinemia. Incomplete molecules, heavy or light chains, may also be secreted. The light chains have molecular weights ranging from 20,000 to 25,000 Daltons and are readily excreted in the urine. They are referred to as *Bence Jones proteins* and in patients with multiple myeloma are either only kappa type or only lambda type. Excretion of Bence Jones proteins occurs in about 30% to 40% of dogs with monoclonal gammopathy. In many dogs with CLL, serum globulin concentrations are normal, but in most a monoclonal gammopathy is revealed by serum protein electrophoresis. IgM is the most frequent paraprotein and these monoclonal gammopathies are described as *Waldenström's macroglobulinemia*. Bence Jones proteinuria can also be found. Hyperviscosity in these patients results from the protein-protein interactions of large, long molecules with high intrinsic viscosity, such as IgM M-components, or from high concentrations of specific IgG or IgA M-components, which have a tendency to form multimolecular aggregates. It rarely or never occurs in patients with light-chain-only myeloma, because of the small molecular size of Bence Jones proteins.

Multiple clinical signs of variable severity are associated with paraproteinemia. Bleeding disorders occur as the result of poor platelet aggregation and release of platelet factor III secondary to platelet coating by immunoglobulins. Prolongation of PT and APTT sometimes occurs as the result of interference by the immunoglobulins with the function of coagulation factors. There may be an increased susceptibility to infections because of severe depression of immunoglobulin levels.

Serum hyperviscosity causes sludging of blood and tissue hypoxia, which may lead to a plethora of clinical signs. Both the increased vascular volume and bleeding tendencies may lead to ocular changes, including distended and tortuous retinal vessels, cysts of the pars plana, papilledema, and retinal hemorrhage and detachment. These changes can result in acute blindness. Severe central nervous system deficits (dementia with concurrent deficiency in midbrain or brainstem reflexes) were reported in 11% of dogs with myeloma. The cause of cardiac disease or failure associated with hyperviscosity is thought to be the large volume of hyperviscous blood. It is rare in the dog, more frequent in the cat. In patients with hyperviscosity of the serum, plasmapheresis may be necessary to reduce paraprotein concentration.[27] Therapy consists of treating the underlying cause of hyperproteinemia, multiple myeloma or CLL, with chemotherapy.

ENDOCRINE MANIFESTATIONS OF CANCER

Hormonally active tumors can arise in endocrine tissues, including the parathyroid glands, adrenal cortex and medulla, and pancreatic islet cells, as well as in tissues of nonendocrine origin. PNS associated with primary endocrine neoplasia are discussed in more detail in the section dealing with endocrine disorders. The following paragraphs focus on PNS due to ectopic hormone production by neoplasms of nonendocrine tissues.

Hypercalcemia of Malignancy

Hypercalcemia is a relatively uncommon problem in small animals, diagnosed more often in dogs than in cats. Numerous disorders are associated with increased serum calcium concentrations, and the general approach to and differential diagnosis of hypercalcemia is discussed in detail in Chapter 237. The most common cause of hypercalcemia in dogs is hypercalcemia of malignancy (HM), which is diagnosed in 57% to 67% of hypercalcemic dogs (Figure 189-1).[28,29] In contrast, neoplasia is diagnosed in only 30% of hypercalcemic cats.[30]

The central mechanism of HM is the promotion of bone resorption by osteoclasts and subsequent release of calcium into the circulation. Patients with primary hyperparathyroidism are predictably affected with HM resulting from increased parathormone (PTH) levels. Interestingly, a variety of tumors originating outside of the parathyroid glands cause increased serum calcium concentrations. The most widely documented mechanism of tumor-associated hypercalcemia is humoral hypercalcemia of malignancy due to the synthesis of PTH-related peptide (PTHrP) by neoplastic cells. PTHrP shares structural homology with PTH in the first 13 amino acids of its N-terminal portion, which bind to the PTH receptor with an affinity equal to that of PTH and result in similar biologic effects.[31]

Other mechanisms of HM are more complex and have not been investigated in much depth in dogs and cats. They include tumor production of various substances that stimulate bone resorption, including cytokines, notably interleukin-1, and growth factors such as transforming growth factor beta (TGF-β). Furthermore, a recently elucidated novel pathway for HM involves the production of soluble forms of receptor activator of nuclear factor kappa B ligand (RANKL), a membrane-associated protein capable of stimulating the activity of osteoclasts by binding to a receptor on their surface. Hypercalcemia occurs when the interactions between ligand, receptor, and their natural inhibitors allow osteoclastic activation to predominate.[32]

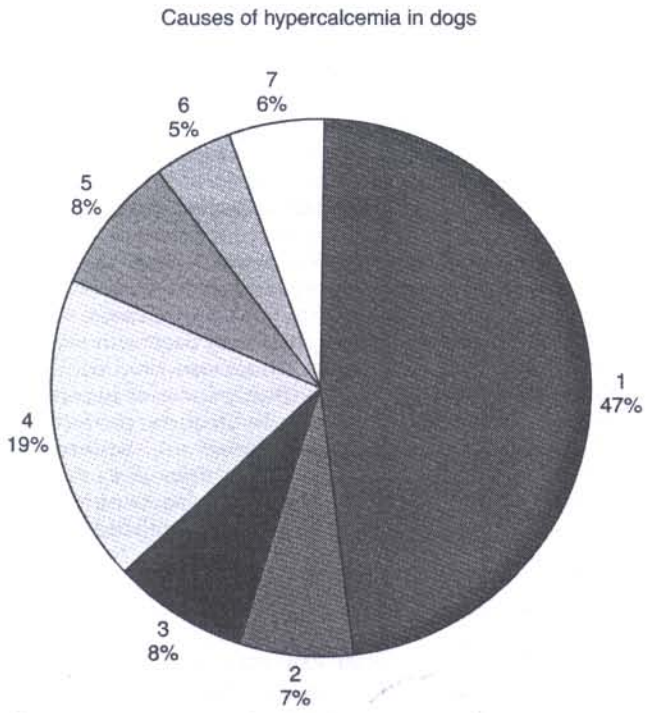


Figure 189-1 Causes of hypercalcemia in 86 dogs. 1. lymphoma; 2. anal gland adenocarcinoma; 3. other neoplasias (2 mammary tumors, 1 of each anaplastic carcinoma, lung tumor, malignant histiocytosis, osteosarcoma, thymoma); 4. hypoadrenocorticism; 5. renal disease (2 acute, 2 chronic renal failure); 6. miscellaneous (primary hyperparathyroidism, vitamin D intoxication, panniculitis); 7. no diagnosis. (Compiled from references 28 and 29.)

HM in dogs is most frequently associated with lymphoma (10% to 40% of all cases), anal sac adenocarcinoma (ASAC, 25% to 53% of all cases), and multiple myeloma (15% to 20% of cases). In ASAC, a linear correlation was found between serum concentrations of calcium and PTHrP, attesting to the central etiological role of PTHrP in causing hypercalcemia by this tumor. No such correlation could be detected in dogs with lymphoma, suggesting that PTHrP is only partially responsible for HM in this neoplasia.[33] In canine lymphoma, hypercalcemia occurs most frequently in dogs with T-cell lymphomas and anterior mediastinal masses. In canine multiple myeloma, hypercalcemia is thought to be the result of local processes that increase bone resorption in the immediate proximity of neoplastic foci. HM is less prevalent in cats and has been associated with a variety of tumors, the most frequent of which are lymphoma and a variety of carcinomas. In squamous cell carcinomas, HM was most often detected in cases involving the mandible with radiographic evidence of bone lysis.[30]

The most significant effects of hypercalcemia are those exerted on the kidneys. Furthermore, dogs with HM are more frequently azotemic than those with parathyroid-dependent hypercalcemia.[34] Decreased responsiveness of the distal tubules to antidiuretic hormone (ADH) and subsequent polyuria and polydipsia are early features of hypercalcemia in dogs. Moderate to severe hypercalcemia may lead to decreased renal plasma flow and glomerular filtration rate, which significantly decrease renal function. In addition, parenchymal calcium salt deposition leading to nephrocalcinosis can compound azotemia.[34]

Clinical signs observed in hypercalcemic dogs are relatively nonspecific and include inappetence or anorexia, polyuria and polydipsia, weakness, vomiting, twitching and shaking, and weight loss. In cats, hypercalcemia also causes anorexia and lethargy, but the frequency of polyuria and polydipsia, and gastrointestinal signs is markedly lower than in dogs. Moreover, signs of lower urinary tract disease were observed in approximately one quarter of hypercalcemic cats and were probably associated with calcium oxalate urolithiasis, although there was not always a clear explanation for their appearance.[30]

Once spurious hypercalcemia has been ruled out, several parameters may provide useful diagnostic clues in elucidating the cause of hypercalcemia. These include serum phosphorus and ionized calcium concentrations, as well as circulating levels of PTH and PTHrP. Typically, dogs and cats with HM have increased serum ionized calcium, normal or low serum phosphorus, low PTH and increased PTHrP concentrations. In addition to these specific laboratory parameters, a systematic search for malignancy should be undertaken, including a meticulous clinical examination, CBC, chemistry profile, imaging of both body cavities, and bone marrow cytology.

Treatment of hypercalcemia of malignancy includes symptomatic therapy to avert or curtail complications of hypercalcemia as well as treatment of the primary disease. A detailed review of therapy is available in Chapter 181. Among the particularities for the treatment of HM, glucocorticoids may hamper diagnosis, especially in lymphoma, and should be avoided until a diagnosis is reached. Alternatively, in cases with a high level of suspicion of lymphoma, the administration of cytostatic drugs with few side effects, such as L-asparaginase may result in both diagnostic confirmation and resolution of hypercalcemia.

The prognosis is generally guarded to poor in animals with HM and depends greatly on the prognosis of the primary neoplasia. Relevant factors are the rapidity of onset, duration, and severity of hypercalcemia, and the degree of renal involvement. In dogs with lymphoma, hypercalcemia has been identified in the past as a negative prognostic factor. However, several studies have demonstrated that the shorter survival is only due to the frequent association of HM with T cell tumors in these dogs.

Hypoglycemia

Hypoglycemia is recognized infrequently in dogs and only rarely in cats. The most common cause of hypoglycemia is insulin-producing islet cell pancreatic tumor. Diagnosis and therapy of insulinomas and associated hypoglycemia are described in detail in Chapter 240. Hypoglycemia associated with other neoplasia is unusual PNS in humans[1] and small animals. In dogs, it has been described in association with hepatoma, hepatocellular carcinoma, intra-abdominal leiomyoma or leiomyosarcoma, and hemangiosarcoma of the liver and spleen.

Paraneoplastic hypoglycemia is probably caused by tumor production of insulin-like growth factors (IGFs) or somatomedins, a family of peptide hormones normally produced in the liver under growth hormone regulation.[1] Increased levels of IGF-II have been documented in hypoglycemic humans with various cancers as well as in one dog with leiomyoma of the gastric wall.

Treatment of hypoglycemia caused by non–islet cell cancers optimally resides in the surgical removal of the neoplasm. However, management of hypoglycemia is also essential. If signs of neuroglycopenia are present, treatment includes the immediate administration of glucose and glucagon infusions,[35] followed by feeding of diets with complex carbohydrates. Low doses of corticosteroids (0.5 to 1 mg/kg/day) can be administered to curtail further hypoglycemic episodes.

Miscellaneous Endocrine Paraneoplastic Syndromes

The syndrome of inappropriate ADH secretion (SIADH) is characterized by hyponatremia, serum hyposmolality, and urine hyperosmolality in the absence of renal function disorders or

adrenal dysfunction. Only very rare clinical cases of paraneoplastic SIADH in dogs have been reported. SIADH probably occurs very exceptionally in dogs and cats but should be considered when typical laboratory findings are observed.

GASTROINTESTINAL MANIFESTATIONS OF CANCER

Gastroduodenal Ulceration

Although gastroduodenal ulceration is not a very frequent problem in small animals, the diagnostic workup of gastric and/or duodenal ulcers includes a thorough search for neoplasia. Beside primary gastrointestinal tumors, the presence of mast cell tumor (MCT) and gastrinoma must also be ruled out. The latter two stimulate gastric acid secretion through histamine release and activation of histamine-type 2 (H2) receptors, or binding to the gastrin receptors on the basal wall of the gastric parietal cells, respectively.

Mast cell tumor is a common neoplasm in dogs and accounts for up to one fifth of all skin and subcutaneous tumors in that species. MCT can be difficult to differentiate clinically from other skin tumors as they sometimes mimic the appearance and the indolent behavior of benign subcutaneous tumors such as lipomas. Mast cell granules contain biologically active substances such as histamine, heparin, and proteolytic enzymes, and canine MCT have been associated with a variety of complications of which gastrointestinal ulceration is probably the most frequently encountered.

To date, two studies have investigated the role of hyperhistaminemia associated with MCT in a total of 28 dogs.[36,37] Although only 10 of 28 dogs with MCTs confirmed histologically had gastrointestinal signs at initial presentation, plasma histamine concentrations were increased in 21 animals, mostly those with macroscopically evident MCT. An inverse relationship between plasma histamine and gastrin concentrations was documented in one study, providing indirect evidence for gastric hyperacidity secondary to hyperhistaminemia.[36] Severe hyperhistaminemia and increasing histamine levels following surgery represent a negative prognostic factor in dogs with MCT.[37] Dogs affected with MCT should receive treatment with an H2 receptor blocker such as ranitidine, famotidine, or cimetidine at the time of diagnosis.

Gastrinomas are rare pancreatic islet cell tumors that secrete excessive amounts of gastrin.[38] A discussion on diagnosis, biologic behavior, and treatment of gastrinoma can be found in the section on pancreatic tumors.

RENAL MANIFESTATIONS OF CANCER

In human cancer patients, glomerular disorders may be associated with non-renal neoplasia, especially in the elderly. Neoplasia is also an important differential diagnosis in dogs and cats with glomerulonephritis due to the potential for tumor-related immune complexes to be deposited in the renal glomeruli. In addition, hypercalcemic nephropathy can affect dogs and cats with paraneoplastic hypercalcemia (see above).

CUTANEOUS PARANEOPLASTIC SYNDROMES

PNS affecting the skin are rare in dogs and cats and mostly affect older animals.

Superficial necrolytic dermatitis (SND) is a condition reported rarely in dogs and cats.[39] Other names previously used to describe this disorder are *necrolytic migratory erythema, hepatocutaneous syndrome,* and *diabetic dermatopathy*. Cutaneous lesions associated with SND include erythema, crusting, exudation, ulceration, and alopecia without severe pruritus. These lesions may involve the face, anogenital region, and pressure points on the trunk and extremities. Additionally, marked crusting, fissuring and ulceration of the footpads is observed in most dogs with SND, and secondary infections with bacteria, yeast, or dermatophytes are common. Histopathologic examination typically reveals epidermal parakeratosis, inter- and intracellular edema, degeneration of keratinocytes in the upper epidermis, and hyperplastic basal cells. Plasma amino-acid concentrations were severely decreased (as low as 30% of the normal plasma concentrations) in all dogs affected with SND that were examined. Underlying conditions observed in dogs with SND include glucagon-producing pancreatic tumors, hepatic disease, and diabetes mellitus. Dogs with SND often have a poor to guarded prognosis. Treatment is aimed at fighting the primary cause if it can be identified. Surgical removal of pancreatic tumors has been associated with resolution of SND and intravenous administration of amino-acid solutions has been effective in prolonging survival in some cases.

Nodular dermatofibrosis is a rare paraneoplastic disorder typically affecting middle-aged to older German shepherd dogs (GSD) with hereditary multifocal renal cystadenocarcinomas. Skin nodules are typically small (2 to 5 mm), very firm, and round. They can easily be overlooked initially and grow slowly. Most are located subcutaneously on the limbs and head region, are freely mobile, and consist of densely packed collagen fibers.[40] At the time of diagnosis, abnormal kidneys are detected on abdominal palpation in 60%, and on radiographs in more than 85% of dogs. Additionally, uterine tumors can be detected in a high proportion of affected bitches. The prognosis is poor due to renal disease and no curative treatment is known for this disorder. The syndrome seems to be inherited as an autosomal dominant trait in some GSD families.[40]

NEUROMUSCULAR MANIFESTATIONS OF CANCER

Neurologic paraneoplastic disorders occur in less than 1% of human cancer patients and encompass diseases affecting the brain, cerebellum, peripheral nerves, and neuromuscular junction.[1] Neurologic PNS are also infrequently reported in dogs and cats, and clinical relevance is limited to the peripheral neuropathies, myasthenia gravis, and polymyositis.

Myasthenia gravis (MG) has been reported in up to 50% of dogs affected with thymoma.[41] Among the associated clinical signs, megaesophagus was present in many reported cases and was frequently associated with aspiration pneumonia. Detection of circulating auto-antibodies against the acetylcholine receptor (AchR) and, to a lesser degree, the edrophonium (Tensilon) test and electromyography with repetitive nerve stimulation were helpful in confirming the diagnosis. Megaesophagus is a negative prognostic factor that significantly shortens median survival in dogs with thymoma.[41] Surgical removal of the tumor is associated with improvement of the clinical signs, although anti-AchR titers do not always significantly decrease. Conservative treatment using immunosuppressive doses of glucocorticoids and/or cholinesterase inhibitors may be attempted in cases in which surgery is not an option (see Chapter 192).

Peripheral neuropathy has been reported in association with a variety of tumors in dogs, including multiple myeloma, lymphoma, and various carcinomas and sarcomas. The disease is likely due to auto-antibodies targeting antigens shared between the tumor and the peripheral nerves. Expected clinical signs are weakness and progressive paraparesis to tetraparesis, characterized by lower motor neuron type disease. Polyneuropathy, a generally rare and subclinical disease, may

be present. Besides screening tests for cancer, electrodiagnostics (such as electromyography and motor nerve conduction studies) may also be of value.

MISCELLANEOUS SYNDROMES

Hypertrophic Osteopathy

Hypertrophic osteopathy (HO) is a well-documented paraneoplastic disorder in dogs and occurs only rarely in cats. HO is characterized by progressive periosteal hyperostosis that occurs on the bones of distal extremities and occasionally on other long bones of the appendicular skeleton. The disease is associated with chronic space-occupying lesions located in the thorax or, rarely, in the abdomen. These include a variety of intrathoracic tumors as well as non-neoplastic processes such as abscesses, granulomas, foreign bodies, and parasites. The pathogenesis of HO is still largely unknown but is believed to be associated with irritation of the vagal and/or intercostal nerves and subsequent enhanced blood flow to the distal extremities.

Animals with HO are typically presented with a history of shifting leg lameness and reluctance to move especially if several limbs are affected. Frequently, a painful swelling of the distal extremities is clinically detected. At the time of diagnosis of HO, clinical signs attributable to the primary disease process are usually discrete. The diagnosis of HO is confirmed on radiographs and should be followed by a search for a space-occupying intracavitary process. The focus of treatment of HO is the removal of the thoracic or abdominal lesion. Administration of steroidal or non-steroidal anti-inflammatory drugs may be useful in the management of pain associated with HO.

SECTION X

Nervous System

CHAPTER • 190

Neurologic Manifestations of Systemic Disease

Michael Podell

GENERAL PRINCIPLES

Systemic diseases can induce a variety of neurologic manifestations that affect the central (CNS) and peripheral nervous system (PNS) in small animals. In theory, identification of a systemic illness as the underlying cause of the neurologic sign(s) is diagnostically simple, with historical signs that suggest a multi-organ problem that can be quickly identified with appropriate laboratory tests. In reality, when the neurologic signs are the sole manifestation of the illness, or when an unrelated, coincidental metabolic disease is present, the diagnosis of a systemic disease as the underlying cause can be challenging. Manifestation of a metabolic encephalopathy should be taken as a warning sign of organ deterioration or failure. The purpose of this chapter is to help clinicians identify the presence of a systemic disease associated with preceding neurologic signs and to realize the potential neurologic complications associated with systemic illnesses. The goal is to develop an efficient diagnostic plan to provide rapid reversal of many of the neurologic signs resulting from the metabolic derangement before permanent deficits occur.

Metabolic-induced neurologic disorders (MIND) of the CNS (metabolic encephalopathies, ME) or PNS (myopathies and/or neuropathies) are syndromes that are not due to primary structural problems of that part of the nervous system. The underlying mechanisms are either the inability to generate energy, to use energy in a normal fashion, changes in baseline excitability of the membrane potential, or direct toxic effects. A common mechanism of pathogenesis is the cascade phenomenon related to excessive glutamate neurotransmission in the brain, known as excitotoxicity[1] (Figure 190-1). As extracellular glutamate uptake increases in the brain secondary to hypoxia, ischemia, hypoglycemia, and other metabolic disturbances, calcium channels open to raise intracellular calcium concentration, leading to neuronal death. Differential sensitivity exists, however, between patients, and within the nervous system of each patient. This selective vulnerability is most apparent in the brain. Here, the more metabolically active regions are most susceptible to injury, so that gray matter is more vulnerable than white matter, and within the gray matter, layers 3, 5, 6 of the neocortex, and portions of the hippocampus, amygdala, thalamus, basal ganglia, and cerebellum are highly sensitive to the effects of metabolic derangement. Although the brain makes up only 2% of body mass, it receives 20% of the cardiac output and oxygen supply of the body, with 75% of this oxygen consumed by the gray matter for aerobic glycolysis.[2] Over 60% of the body's glucose is used in the brain, with the majority of this energy used to preserve normal ionic gradients responsible for maintaining the delicate balance of excitation and inhibition of the nervous system.

In general, the clinical signs of MIND are initially diffuse, non-fixed in time, and reversible. The onset of clinical signs of ME ranges from peracute (e.g., hypoxia) to chronic (e.g., hepatic encephalopathy). Waxing-waning behavior changes are the predominant early clinical signs in the majority of small animal ME. Aimless wandering, non-directional circling, and disorientation are common early changes.[3] As the disease progresses, clinical signs progress in a rostral (cerebrocortical) to caudal (brain stem) fashion. Over time, animals can develop stupor or coma with untreated ME. Oculomotor abnormalities are common and range from symmetric, reactive miosis in early ME, to symmetric, fixed mydriasis with prolonged hypoxia. Marked motor abnormalities are unusual early in the course of ME, with the exception of epileptic seizure activity. As more brain stem involvement occurs, ataxia and paresis can be seen. Respiratory pattern irregularities are common with ME. Diffuse cortical disease can result in an irregular cycle of hyperventilation followed by apnea (Cheynes-Stokes respiration). The presence of ataxic breathing (very irregular inspiratory and expiratory pattern) indicates caudal brain stem involvement, a poor prognostic sign.

In the PNS, similar mechanisms, as seen in the brain, are responsible for loss of function. Long and large diameter nerve fibers are affected first via disruption in axonal transport of integral substances necessary for nerve viability. Nerves will then undergo a dying back process, with degeneration of the axons in a distal to proximal fashion.[4] The clinical signs include a chronic systemic disease, preferential lower and pelvic limb involvement, sensory loss prior to motor loss, muscle wasting, and slow return to normal with treatment. In contrast, in myopathies, the proximal muscles are typically affected, muscle mass is preserved, and muscles may be painful. Since muscle contraction and relaxation are both energy dependent activities, failure to maintain normal ionic gradients is a common mechanism for myopathies associated with systemic illness.

Five major classifications of systemic diseases are listed in Box 190-1. Examples of the more common systemic diseases associated with neurologic manifestations in the cat and dog are presented with emphasis placed on the pathophysiology and identification of the disease process.

FUEL DEPRIVATION

Oxygen Deprivation

Hypoxic-ischemic encephalopathy is the result of loss of cerebral oxygen supply either through decreased arterial oxygen tension (PaO_2 <50 mm Hg), or reduced to absent cerebral blood flow. Irreversible brain injury occurs within 20 seconds after anoxia, and 2 to 4 minutes after hypoxia-ischemia. Moreover, in dogs, a PaO_2 less than 45 mm Hg is sufficient to cause heart failure and systemic hypotension, thus exacerbating the condition with cerebral perfusion deficit.[5] This circulatory collapse cascade phenomenon in acute hypoxia is due to a primary CNS-induced reflex depression of cardiac function. In this setting, a common cause of hypoxia-ischemia in small animals is an anesthetic complication. Other causes for acute respiratory insufficiency include pneumonia, pulmonary thromboembolism, pneumothorax, and bronchospasm. Surviving animals may initially be comatose with fixed dilated pupils, leading to dementia, cortical blindness, and motor abnormalities. Since the degree of necrotic neuronal death is

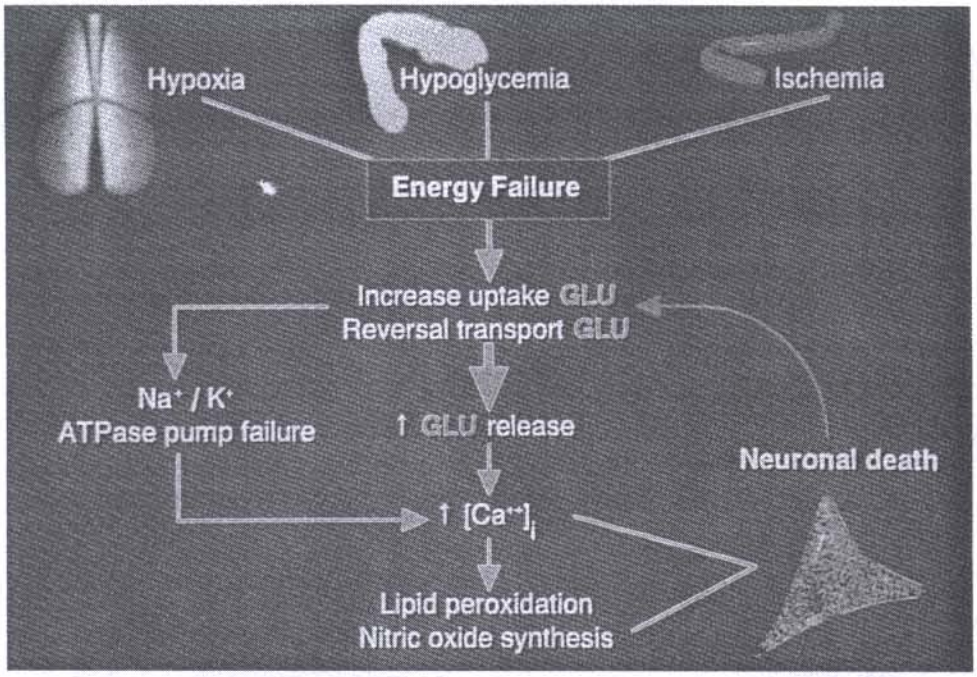


Figure 190-1 Schematic diagram of glutamate (GLU)-induced excitotoxicity secondary to fuel deprivation of the brain.[1]

Box • 190-1

Classification of Systemic Diseases With Neurologic Manifestations

I. Fuel deprivation
  A. Oxygen
    1. Hypoxia
      a) Primary pulmonary disease
      b) Decreased O_2 transport
      c) Secondary heart failure
    2. Vascular disease
      a) Ischemia
        (1) Decreased peripheral vasomotor tone (shock)
        (2) Decreased cardiac disease
        (3) Thromboembolic disease
      b) Hemorrhage
        (1) Vessel rupture secondary to hypertension
        (2) Coagulopathies
        (3) Vasculitis
  B. Glucose utilization (hypoglycemia)
    1. Increased uptake
      a) Hyperinsulinemia
        (1) Islet cell tumors
        (2) Insulin overdose
      b) Non-islet cell neoplasia (hepatoma, leiomyoma)
      c) Excessive metabolism (sepsis, breed or activity-related)
    2. Decreased output or metabolism
      a) Primary liver disease
      b) Malnutrition
      c) Thiamine deficiency
    3. Increased uptake of amino acids by extrahepatic tissues

II. Water and ionic imbalances
  A. Water
    1. Hypoosmolar states (retention of free water)
      a) Hyponatremia
    2. Hyperosmolar states (loss of free water)
      a) Hypernatremia (diabetes insipidus)
      b) Hyperglycemia (diabetes mellitus)
  B. Ions (excess or deficiency)
    1. Potassium
    2. Calcium

III. Endogenous neurotoxins
  A. Renal failure
  B. Hepatic failure
  C. Endocrine disease
    1. Adrenal
      a) Cortisol and mineralcorticoid dysregulation
        (1) Hyperadrenocorticism (Cushing's disease)
        (2) Hypoadrenocorticism (Addison's disease)
      b) Adrenergic dysregulation
        (1) Pheochromocytoma
    2. Thyroid
      a) Hypothyroidism (myxedema, neuromyopathy)
      b) Thyrotoxicosis

IV. Exogenous neurotoxins
  A. Sedative depressant drugs (e.g., antiepileptic drugs)
  B. Plant toxicity and poisons
  C. Heat stroke

V. Remote neurologic manifestations of cancer
  A. Metastases to the nervous system
  B. Vascular accidents and infection
  C. Adverse effects from therapy
  D. Paraneoplastic syndromes

proportional to the lack of oxygen, the prognosis is greatly dependent upon the total duration of the hypoxic-injury. The longer the duration of hypoxia, the greater the chance for brain stem signs to occur.

Therapy consists of reversal of the underlying event and supportive care to reintroduce energy to the brain by instituting proper ventilation and oxygenation, maintenance of normal hydration, and early enteral nutritional support. Steroid therapy does not improve neurologic recovery in people,[6] and in general, increases metabolic demand on the body, produces adverse effects, and has minimal benefit to the brain. Many animals may become functional pets over time and take several weeks to recover.

Cerebrovascular disease that results in focal lesions often is related to underlying systemic illness in the cat and dog.[7] Historical signs may be vague initially (e.g., lethargy, inappettance), leading to acute, focal cerebrocortical signs. Thromboembolic disease from sepsis, tumor metastasis, atherosclerotic disease, and hemorrhage from systemic causes of hypertension have been documented.

Glucose Deficiency

Hypoglycemia is a common cause of neurologic signs associated with systemic diseases. The brain requires an average of 100 g of glucose/day to function. Blood glucose below 40 mg/dL induces a stress response to release counter-regulatory hormones and induce gluconeogenesis. Progressive and/or persistent hypoglycemia results in cerebrovascular constriction, thus reducing oxygen delivery. Eventually, neuronal cell death occurs. Neuroglycopenic effects range from behavior changes (e.g., hiding) and weakness early and progress to tremors, partial and generalized seizures, blindness, and unresponsiveness.

The most common causes of hypoglycemia in small animals are increased uptake or decreased output. Increased uptake is seen with insulinoma, non-islet cell tumors, excessive exogenous insulin, and excess metabolism in certain toy and sport breed dogs. Most dogs with pancreatic islet cell tumors have clinical signs for several months with multiple episodic events interspersed with normalcy. In addition to neuroglycopenic signs, affected dogs may develop weakness secondary to a paraneoplastic peripheral neuropathy[8] and lacunar infarcts related to cerebral microangiopathy.[9] No correlation exists between severity or frequency of clinical signs, degree of hypoglycemia, and survival time post-treatment.[10] Non-islet cell tumors that arise from the liver, smooth muscle, and other areas can produce insulin-like growth factor or other counter-regulatory hormones, which results in reversible hypoglycemia once the tumor is removed.[11]

Insulin overdosing is a serious complication of diabetes mellitus management. This problem appears to be more common in heavier cats receiving more than 6 U per injection of insulin, regardless of type.[12] Persistent cortical blindness and epileptic seizures after restoration of euglycemia may occur. Initial treatment is an IV bolus of 50% dextrose at 1 g/kg over 3 to 5 minutes, followed by continuous rate infusion of a dextrose containing solution to maintain blood glucose more than 80 mg/dL. Thiamine supplementation should be provided to allow for proper mitochondrial aerobic glycosis to occur.

Thiamine Deficiency

Thiamine (vitamin B1) is essential for the oxidative decarboxylation of pyruvic acid in the Kreb's cycle. Failure to complete this cycle will result in decreased gluconeogenesis. Thiamine deficiency occurs in cats and dogs fed primarily diets of overcooked meats or fish that contains thiaminase, or with prolonged anorexia. Clinical signs are related to a progressive, bilateral, symmetric polioencelomalacia, which predominantly involves the subcortical gray matter. Cats can initially develop central vestibular disease, head tremor, mydriasis, and cervical ventroflexion, which may progress to opisthotonus, coma, and death. In dogs, ataxia, paresis, vestibular signs, and seizures have been observed. Parenteral administration of thiamine (10 to 20 mg IM for cats; 25 to 50 mg IM for dogs) will resolve clinical signs early in the course of the disease.

WATER AND IONIC IMBALANCES

Hypoosmolality with Hyponatremia

Hyponatremic encephalopathy is the result of an osmotic shift between extracellular fluid and brain cells, which results in a net movement of water into the brain, with its associated cerebral edema. Although the cause of hyponatremia may differ depending on the patient's volume status, the clinical signs are more dependent on the onset of the osmolar shift. Acute hyponatremia (hours) can lead to pressure necrosis of the cerebral hemispheres after an expansion of at least 5%, followed by brain herniation.[13] Little intracranial compensation can occur during the acute stage. With chronic (days) hyponatremia, the brain compensates with a loss of cation to lower intracellular osmolality with minimum water gain. Animals may exhibit little to no clinical signs. A rapid correction in serum sodium of at least 20 mEq/L of hyponatremia (<130 mEq/L) over 24 to 48 hours can lead to a potentially fatal demyelination of the brain stem, known as *central pontine myelinolysis*.[14]

Sodium replacement with 0.9% NaCl in volume depleted patients is calculated by the following equation:

$$\text{Na Deficit (mEq)} = 0.3 \times \text{BW kg} \times (\text{Normal Na} - \text{Patient Na})^{15}$$

Appropriate volume correction is simultaneously administered. The goal is to raise serum sodium at a rate of 6 to 12 mEq/L per day.

Hyperosmolality

Acute plasma hypoosmolarity leads to shifting of intracellular water into the extracellular space, which results in disruption of the neuronal ionic gradients, cell shrinkage, progression to brain shrinkage, and potentially leading to tearing of arachnoid blood vessels, with intracranial bleeding. With chronic hyperosmolar shifts, the brain adapts by *de novo* synthesis of idiogenic osmoles to increase intracellular osmolarity. Rapid correction of the resultant hypernatremia can lead to cerebral edema, as the brain is now hyperosmolar to the plasma.

Common causes of plasma hyperosmolality with neurologic signs include central (CDI) or nephrogenic diabetes insipidus (free water loss) and diabetes mellitus (hypotonic fluid loss). Antecedent clinical signs include intense polydipsia and polyuria. Since CDI may cause similar neurologic signs indirectly through fluid shifts or directly from a pituitary mass, brain imaging is recommended after diagnosis of CDI in all dogs.[16]

Neurologic complications associated with diabetes mellitus related to CNS changes related due to hyperosmolality, electrolyte imbalances, and metabolic acidosis and to PNS changes with chronic inability to maintain Na-K ATPase activity in the nerve membranes. Diabetic neuropathy is typically a subclincal, electrophysiologic phenomenon in the dog[17] but results in a pronounced tibial neuropathy in the cat. These cats have a marked, symmetric plantigrade stance with pelvic limb weakness. Many cats will improve after sustained euglycemia.

Initial correction of hypernatremia to replace total body water can be calculated with the following formula:

$$\text{Water deficit} = \text{BW (kg)} \times [(\text{Patient Na}/\text{Normal Na}) - 1]^{15}$$

The deficit should be given over a 48-hour period to prevent cerebral edema starting with 0.45% NaCl/2.5% dextrose solution. A 5% dextrose in water solution can be used if serum sodium is not declining adequately.

Ionic Imbalances

Potassium and calcium imbalances have a direct effect on muscle membrane stability. Hypokalemia (≤3.0 mEq/L) from excessive urine loss or dietary depletion decreases membrane excitability, which leads to episodic weakness, cervical ventroflexion, and bizarre postures in the cat[18] (Figure 190-2) but can also be seen in the dog. Clinical signs resolve with appropriate potassium supplementation. Oral potassium gluconate supplement at an initial dose of 5 to 10 mEq/day is preferable, as parenteral supplementation may exacerbate the hypokalemia through volume expansion and enhanced potassium diuresis.

Generalized weakness with or without tetanic muscle contractions are commonly seen with hypocalcemia (ionized calcium <5.0 mg/dL in dogs and <4.5 mg/dL in cats) due to increased membrane excitability. The more acute the onset, the more severe the clinical signs, with progression to status epilepticus possible. Initial treatment consists of 10% calcium gluconate IV at dosage of 0.5 to 1.5 mL/kg over 10 to 20 minutes while heart rate is monitored.[19] Identification and treatment of the underlying cause is essential to prevent recurrence.

ENDOGENOUS NEUROTOXINS

The blood-brain barrier is a highly specialized, integrated network of capillaries and glial cells to maintain the internal environment of the brain and cerebrospinal fluid. Certain endogenous neurotoxins and/or consequences of systemic diseases have been identified to alter the brain's neurochemical balance by either bypassing the blood-brain barrier or through direct changes in neurotransmitter activity.

Uremic Encephalopathy

Neurologic clinical signs associated with acute or chronic renal failure can be seen when glomerular filtration rate decreases below 10% to 20% of normal. Extensive data suggests that parathyroid hormone is the putative neurotoxin.[20] Clinical signs in cats and dogs include depression, stupor, myoclonic movements, generalized weakness, and partial and generalized seizures. Animals may not have prolonged antecedent mental depression prior to more pronounced neurologic signs, as seen in people.[21] Calcitriol (1,25 dihyroxyvitamin D, 1.5 to 3.5 ng/kg/day), by lowering parathyroid hormone serum concentration, reverses the neurologic depression in the majority of chronically treated uremic small animals.[20] Attention to blood pressure control should also be provided.

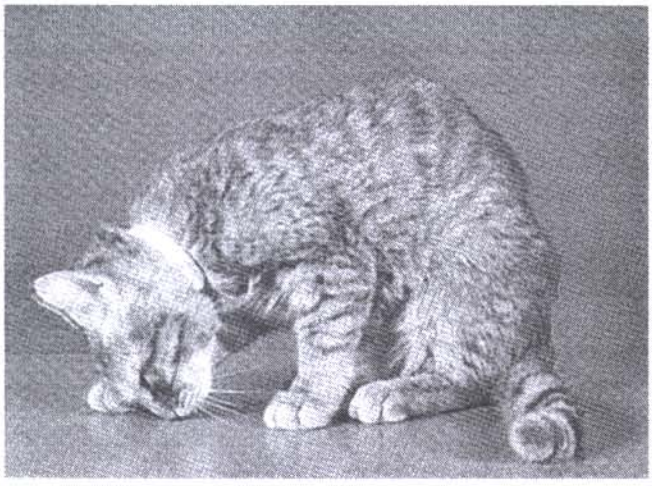


Figure 190-2 Cervical ventroflexion in a 2-year-old female spayed DSH cat with hypokalemic polymyopathy secondary to potassium-losing nephropathy.

Hepatic Encephalopathy

Advanced congenital or acquired liver disease can produce a complex of neurologic signs, known as hepatic encephalopathy (HE). Waxing-waning bizarre, unpredictable behavior, dementia, progressive loss of arousability, myoclonus, and seizures can all occur. Clinical signs can worsen after protein digestion. Although most animals with HE will have an elevated plasma ammonia concentration, there is minimal correlation between the severity of clinical signs and ammonia level. Irish wolfhound pups can exhibit hyperammonemia of a metabolic and non-hepatic origin, with a low likelihood of a portosystemic shunt (PSS) if the ammonia level is less than 120 mumole/L.[22] There are several potential pathophysiologic causes of the neurologic syndrome of HE, which include (1) hyperammonemia, (2) synergistic neurotoxins, (3) altered monoamine (tryptophan) and "false" neurotransmitter synthesis, (4) alterations in amino acid neurotransmitters, and (5) increased cerebral concentrations of an endogenous benzodiazepine.[23] Recent studies demonstrated increased cerebrospinal fluid concentrations of tryptophan, tryptophan metabolites, glutamine, and quinolinic acid in dogs with naturally occurring PSS as compared with control dogs. The results support the theory of an increased flux and metabolism of tryptophan through the CNS serotonin metabolic pathway as a contribution to the neurologic complications with PSS and ensuing encephalopathy in dogs.[24]

Medical therapy for HE is directed to the reduction of by-products of protein metabolism and subsequent neurotoxins. Initial medical therapy includes a low-protein diet, antibiotic therapy to reduce ammonia producing bacteria, lactulose to decrease production and absorption of ammonia, and H_2-blockers as needed to treat for gastrointestinal bleeding. Surgical correction of congenital porto-caval shunts is most successful in dogs less than 2 years of age for reduced mortality[25] and neurologic morbidity. Generalized seizures may persist post-ligation despite lack of other evidence of HE.[26] The recommended antiepileptic drug therapy for these dogs is either potassium bromide at an initial maintenance therapy at 40 mg/kg/day or gabapentin at 20 mg/kg/day with increases to 60 to 80 mg/kg/day divided TID as needed. Both of these drugs are renal excreted, non-protein bound drugs with good antiepileptic properties in the cat and dog. Bromide therapy should be used with caution in the cat due to the potential for induction of an allergic induced asthmatic reaction.[27] Continuous rate infusion of sodium bromide at 600 to 1200 mg/kg/24 hours for 1 day is an alternative method to rapidly raise bromide serum concentrations to a therapeutic range.[28] Benzodiazepine therapy should be avoided to prevent potentiation of inhibitory neurotransmission in the brain. Sarmazenil, a benzodiazepines antagonist and partial inverse agonist, at 3 to 8 mg/kg IV ameliorated neurologic signs in dogs with experimentally induced HE secondary to PSS.[29]

Thyroid Diseases

Primary hypothyroidism is a common endocrinopathy of the older dog with multiple neurologic manifestations. The most severe form is myxedema, associated with bradycardia, hypothermia, dementia, stupor or coma, generalized lower motor neuron weakness, and possible seizures. Concurrent complications of hyponatremia, hypoventilatory hypoxia, and cerebral ischemia make this a life-threatening condition. Treatment consists of gradual rewarming, correction of serum sodium and osmolarity, steroid therapy (prednisolone sodium succinate 10 mg/kg IV BID for 24 hours), and injectable

levothyroxine replacement (5 ug/kg IV once), followed by maintenance thyroid supplementation. Marked improvement is usually seen within 24 hours.

Chronic, progressive peripheral or central vestibular disease can also occur in hypothyroid dogs.[30] These dogs are typically older (more than 7 years), with progressive ataxia and head tilting as primary signs. Other clinical syndromes are related to motor unit dysfunction. Generalized lower motor neuron weakness with exercise intolerance can be the result of hypothyroid neuro-myopathy. Concurrent or separate signs of megaesophagus and facial and/or laryngeal paralysis may be present. Many, but not all, dogs will improve with appropriate thyroid supplementation.[31]

Thyrotoxicosis (hyperthyroidism) in cats can produce multiple neurologic abnormalities. Predominant behavior changes include irritability, hyperactivity, aggression, and reduced sleep cycles. Some cats may exhibit a paradoxic "apathy," characterized by excessive dullness. Progressive neuromuscular weakness with cervical ventroflexion, exercise intolerance, and loss of jumping ability can be seen with more advanced disease, and associated muscle wasting. Signs are reversible with appropriate treatment of the underlying hyperthyroid condition.

Adrenal Diseases

Adrenal hormone excess or deficiency has been associated with a variety of neurologic disturbances. Signs attributed to hypoadrenocorticism (Addison's disease) include episodic, progressive lethargy, dullness, tremors, vomiting, and possible acute collapse.[32] Glucocorticoid deficient hypoglycemia may exacerbate these signs. Rapid reversal of neurologic signs is seen with mineral- and/or glucocorticoid replacement and restoration of metabolic homeostasis.

Cushing's disease (hyperadrenocorticism) can produce CNS and PNS abnormalities through direct or indirect mechanisms. Direct compression of a pituitary macroadenoma onto the brain results in early signs of dullness and dementia, with progression to obtundation, tetraparesis and ataxia, visual impairment, and seizures. Up to 35% of dogs with pituitary dependent Cushing's with a visualized (CT or MRI scan) tumor of more than 4 mm may develop neurologic signs.[33] Cerebrovascular accidents may also occur, secondary to systemic arterial hypertension or thromboembolic disease. In the PNS, an irreversible progressive fibrosing myopathy can occur, regardless of duration, severity, or onset of treatment with canine Cushing's disease. A progressive stiff gait leading to inability to flex the limbs is characteristic of this condition.

Pheochromocytoma can induce neurologic signs in approximately 10% of clinically symptomatic dogs.[34] Generalized weakness, pelvic limb weakness, focal forebrain signs, and seizures may develop. Signs can be the result of direct intracranial metastasis or secondary intracranial hemorrhage due to hypertension.

EXOGENOUS NEUROTOXINS AND INJURY

A variety of environmental or iatrogenic substances will produce diffuse forebrain disturbances. More common conditions are toxic reactions to antiepileptic drugs, rodenticides, and heat stroke. Removal of the inciting cause and appropriate supportive care are often corrective.

Neurologic Complications of Cancer

More neurologic complications secondary to systemic cancer are being observed with the advancement of diagnostic and treatment capabilities in veterinary oncology. These complications can be serious to life-threatening, may be diagnostically challenging, yet early treatment can be quite beneficial to the patient. Moreover, the nervous system problems are unique to the rest of body, in that small lesions can create major clinical signs (as compared with the liver), heterogeneous function is present, barriers must be kept intact for proper function, and damage to CNS tissue has limited capacity to repair itself, so that clinical signs may be irreversible.[35]

Direct and extensional metastases to the nervous system are the most common neuro-oncologic complications in the cat and dog. Hemangiosarcoma, mammary and thyroid carcinoma, and melanoma, spread preferentially to the end-arterial vasculature of the gray-white matter regions of the cerebrum.[36] Clinical signs are related to tumor location and the secondary effects. Dogs with intracranial extension of nasal carcinoma may present only with CNS signs. Chemo- and radiation therapy can directly or indirectly affect the nervous system. Paraneoplastic disorders are due to autoimmunity as a result of tumor cells expressing "onconeural" antigens identical or antigenically related to molecules normally expressed by neurons or other receptors.[37] In small animals, the primary paraneoplastic syndromes recognized are related to PNS disease, including neuropathy (e.g., secondary to insulinoma, carcinoma, sarcoma) and myasthenia gravis (e.g., secondary to thymoma, osteogenic sarcoma).

CHAPTER 191

Brain Disease

Dennis P. O'Brien
Todd W. Axlund

"All the most acute, most powerful, and most deadly diseases, and those most difficult to be understood ... fall upon the brain."
Hippocrates

For as long as people have been aware of disease, they have been frustrated by brain disease. Recent advances in brain imaging and molecular approaches to understanding disease hold the promise of changing these concerns. This chapter will outline the diagnostic approach to brain disease and discuss the major diseases of dogs and cats that primarily affect the brain.

RESPONSE OF THE BRAIN TO DAMAGE

The nervous system has relatively few ways to respond to damage, and the complexity of neurologic signs depends upon the localization of that response within the nervous system. Because neurons are excitable cells, one potential response to disease is excessive discharge of these cells. The most dramatic example of this is seizure activity. Conversely, if the disease destroys the neurons of a functional system, there will be a loss of function of that system. For example, the destruction of a cranial nerve nucleus in the brain stem will lead to paralysis of the muscles innervated by that nerve. If the system that is lost happens to be an inhibitory pathway, then the system that is no longer inhibited may show an exaggerated response. The classic example of such disinhibition is the exaggerated reflexes seen with upper motor neuron (UMN) loss. When dealing with higher brain functions, such responses can be complex. For example, the paradoxical aggression sometimes seen with benzodiazepines or barbiturates in dogs may represent a disinhibition of aggressive behavior.

In addition to local effects, a disease process in the brain can produce generalized effects secondary to increased intracranial pressure. Because the calvarium is a rigid structure, the three major components within it (brain, cerebrospinal fluid [CSF], and blood) are confined to a fixed volume. Any increase in one of these components would then have to be accompanied by a decrease in one of the others (the Monro-Kellie doctrine). A gradual increase in volume of one component, such a slowly progressive hydrocephalus, can be compensated for to some extent, in this case by atrophy of brain tissue. More acute disease would not allow time for compensatory atrophy, and even chronic disease, such as a brain tumor, will eventually exceed the ability of the other components to compensate. The result is increased intracranial pressure. With increasing intracranial pressure, generalized forebrain signs will develop, even if the inciting cause is a localized process such as neoplasia. As intracranial pressure increases, blood pressure will increase to maintain cerebral perfusion. This can sometimes result in a reflex increase in vagal tone and bradycardia (the Cushing's response). Vomiting may also occur.

Continued increases in intracranial pressure will lead to herniation. Brain tissue can herniate laterally under the falx cerebri, or it can herniate caudally under the tentorium or through the foramen magnum. Tentorial herniation leads to a progressive rostral-caudal deterioration of neurologic status when the midbrain, pons, and terminally the medulla are compressed. The progression can be rapid or can evolve slowly over a mater of hours or even days. Herniation is most commonly associated with forebrain lesions, such as neoplasia or trauma. Increased pressure arising below the tentorium (e.g., a cerebellar tumor) will cause herniation of the cerebellum through the foramen magnum, mimicking the terminal events of tentorial herniation without any of the earlier signs.

Neurologic Examination

Regardless of whether the signs reflect focal damage or diffuse disease, the first step in diagnosing any neurologic disease is to localize the lesion. The neurologic exam requires care to perform, but it is the most cost-effective diagnostic procedure available. A neurologic exam form can be used to ensure a complete exam and to accurately record observations (Figure 191-1). Even in cases with obvious brain disease, a complete neurologic exam should be done to rule out multifocal disease. The focus of this chapter is on the aspects of the neurologic exam that are important for evaluating brain function: (1) observation of behavior, posture, and gait; (2) postural reactions; and (3) cranial nerves. Although not technically a part of the neurologic exam, a fundic exam should be considered. Because the retina and optic nerve are basically extensions of the brain, the clinician should take advantage of the one place where they can look directly at the nervous system (Figure 191-2). A disease process visualized in the fundus is likely to be the same process producing signs elsewhere in the nervous system.

History and Behavior Because changes in behavior or episodic events like seizures will be important clues to brain disease, an adequate history is essential. The clinician must elicit descriptions of the animal's behavior that will allow identification of the changes without leading the client. Clients will misinterpret the nature of many neurologic signs, including seizures, so they should be encouraged to describe what they observed rather than their conclusions. Many clients have access to video cameras, and a tape of an episodic event can be useful in determining the nature of the episode.

If allowed to freely roam the exam room, the animal's behavior can be observed while a history is being taken. Looking at how an animal interacts with the environment assesses the mental status. A normal animal will be aware and observant of its surroundings. How the animal interacts with its owner or other people should be noted. Any spontaneous noises or movements may be used to see if the pet is attentive to these stimuli. The odors of the exam room floor can also be an interesting stimulus to many animals. An animal that is lethargic or obtunded will withdraw from its surroundings unless stimulated. A stuporous animal responds only to strong or noxious stimuli, and the response may not be at all appropriate.

NEUROLOGICAL EXAMINATION FORM

UNIVERSITY OF MISSOURI

VETERINARY MEDICAL TEACHING HOSPITAL

DATE: _____

***= MINIMUM EXAM**

Animal's Name_____

Owner's Name_____

Age_____ Sex_____

Species _____ Breed_____

***HISTORY:**

Presenting Complaint:

Onset: Peracute (min-hrs) ☐ Acute (day-week) ☐ Chronic (week-months) ☐

Progression: Slow ☐ Fast ☐ Static ☐ Improving ☐ Waxing & waning ☐

Seizures or behavioral abnormalities (Dementia, aggression, head pressing, circling, pacing, etc.):

***OBSERVATION:**

Mental status: Alert ☐ Depressed/lethargic ☐ Stuporous ☐ Comatose ☐ Demented ☐

Involuntary movement: None ☐ Tremors: Intention ☐ Resting ☐ Myoclonus ☐ Fasciculation ☐

Posture: Normal ☐ Head tilt: Left ☐ Right ☐ Torticollis: Left ☐ Right ☐ Dorsal ☐ Ventral ☐

Wide-based stance ☐ Falling ☐ direction_____

Decerebrate rigidity ☐ Decerebellate rigidity ☐ Schiff-Sherrington ☐

Gait: Normal all 4 ☐ Mono-paresis ☐ limb_____ Hemi-paresis: Left ☐ Right ☐

Thoracic limb paresis ☐ Paraparesis ☐ Quadriparesis ☐

Thoracic limb paralysis ☐ Paraplegia ☐ Quadriplegia ☐

Circling: Left ☐ Right ☐ Either direction ☐

Ataxia: Proprioceptive ☐ Vestibular ☐ Cerebellar ☐

Thoracic limbs ☐ Pelvic limbs ☐ All four limbs ☐ Truncal ☐

POSTURAL REACTIONS

N = normal, D = delayed or weak, A = absent

Left	Response	Right
Thoracic limb N☐ D☐ A☐	*Proprioception (Knuckling)	Thoracic limb N☐ D☐ A☐
Pelvic limb N☐ D☐ A☐		Pelvic limb N☐ D☐ A☐
Thoracic limb N☐ D☐ A☐	*Hopping	Thoracic limb N☐ D☐ A☐
Pelvic limb N☐ D☐ A☐		Pelvic limb N☐ D☐ A☐
N☐ D☐ A☐	Hemi Standing/walking	N☐ D☐ A☐
N☐ D☐ A☐	Visual Placing	N☐ D☐ A☐
N☐ D☐ A☐	Tactile Placing	N☐ D☐ A☐
N☐ D☐ A☐	Extensor Postural Thrust	N☐ D☐ A☐
N☐ D☐ A☐	Righting	N☐ D☐ A☐

Thoracic limbs		Pelvic limbs
N☐ D☐ A☐	Wheelbarrowing	N☐ D☐ A☐

Student **Clinician** **Fee**

Figure 191-1 Neurologic examination form.

CRANIAL NERVE EXAM

N = normal A= absent/abnormal (describe)

Left	Reflex or Response	Right
	Olfaction (I) N☐ A☐	
N☐ A☐	Vision (II)	N☐ A☐
N☐ A☐	*Menace response (II, VII)	N☐ A☐
N☐ A☐ Direct N☐ A☐ Consensual	*PLR (II, III) Direct / Consensual	N☐ A☐ N☐ A☐
N☐ Y☐ I☐	Pupil size & Anisocoria (II, III, Sympathetics) mYdriasis or mIosis	N☐ Y☐ I☐
N☐(absent) Present☐	Other Horner's Signs (Sympathetics)	N☐(absent) Present☐
N☐(absent) L☐ X☐ M☐	Strabismus: III-ventroLateral, IV- eXtorsion (outward rotation), VI-Medial Positional ☐:	N☐(absent) L☐ X☐ M☐
N☐(present) Absent☐	*Physiologic nystagmus (Doll's eye) (III, IV, VI, VIII)	N☐(present) Absent☐
N☐(absent) H-L☐ R☐ O-L☐ R☐ V☐ P☐	Pathologic nystagmus (VIII) Horizontal, rOtary (Left or Right) Vertical or Pendular, Positional ☐:	N☐(absent) H-L☐ R☐ O-L☐ R☐ V☐ P☐
N☐ A☐	*Masticatory muscle mass (V)	N☐ A☐
N☐ A☐	*Palpebral (Ophth V, VII)	N☐ A☐
N☐ O☐ X☐ D☐	Facial Sensation (V: if absent check branch: Ophthalmic, maXillary or manDibular)	N☐ O☐ X☐ D☐
N☐ A☐	Facial muscles (VII)	N☐ A☐
N☐ A☐	Hearing (VIII)	N☐ A☐
N☐ A☐	*Gag reflex / swallowing, eating, voice (IX, X, XII)	N☐ A☐
N☐ A☐	Trapezius / brachiocephalicus (XI)	N☐ A☐
N☐ A☐	Tongue: paralysis, atrophy, fasciculations (XII)	N☐ A☐

SPINAL HYPERESTHESIA

Absent /Present	Localize
Cervical A☐ P☐	
Thoracic A☐ P☐	
Lumbar A☐ P☐	
Sacral A☐ P☐	

SPINAL REFLEXES

0 = absent, 1+ = decreased,
2+ = normal, 3+ = increased,
4+ = very exaggerated, clonus or crossed extension

Left	Reflex or Response	Right
	Triceps (C7-T2 - radial)	
	Extensor Carpi Radialis (C7-T2 - radial)	
	*Thoracic limb withdrawal (C6-T2 - radial, ulnar, median, musculocutaneous)	
Superficial N☐ weak☐ A☐ Deep (if no SP) N☐ weak☐ A☐	Thoracic limb pain perception	Superficial N☐ weak☐ A☐ Deep (if no SP) N☐ weak☐ A☐
	*Patellar (L4-L6 - femoral)	
	Cranial Tibial (L6-S1 – peroneal)	
	Gastrocnemius (L6-S1- tibial)	
	Pelvic limb withdrawal (L6-S1 - sciatic)	
Superficial N☐ weak☐ A☐ Deep (if no SP) N☐ weak☐ A☐	Pelvic limb pain perception	Superficial N☐ weak☐ A☐ Deep (if no SP) N☐ weak☐ A☐
N☐ A☐	Perineal reflex & sphincter tone (S1-S3 - pudendal)	N☐ A☐
N☐ A☐ Ends:	Panniculus (T3-L3 & C8-T1)	N☐ A☐ Ends:

PALPATION: Normal ☐ Abnormal ☐ (muscle atrophy, spasms, rigidity, peripheral hyperesthesia, etc - describe.)

BLADDER & BOWEL FUNCTION:

*Voluntary urination: Yes☐ No☐ N/A(not assessed)☐

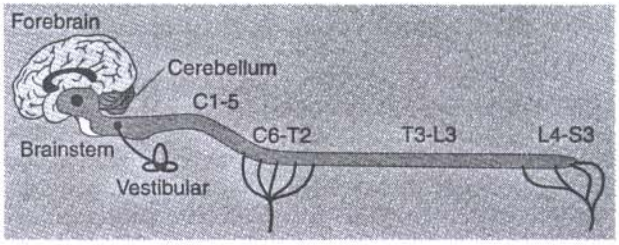
*Incontinence: No☐ Urinary☐ Fecal☐

Bladder size: Small☐ Large☐ N/A☐

Bladder expression: Difficult☐ Easy☐ N/A☐

TAIL MOVEMENT/TONE: Normal☐ Abnormal☐

***LESION LOCALIZATION/SUMMARY:**



***DDx:**

***Plan:**

Figure 191-1—Cont'd Neurologic examination form.

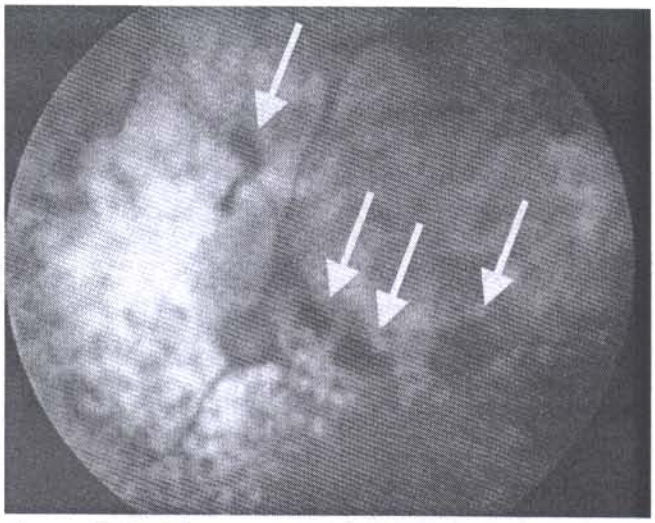


Figure 191-2 The retina is a direct extension of the brain. Thus retinal hemorrhages (*arrows*) in this dog with histoplasmosis suggest the same process is occurring within the brain. (Photo courtesy Dr. Elizabeth Giuliano.)

A comatose animal does not respond even to noxious stimuli. A demented animal may appear alert, but its response to its environment will be inappropriate.

Because a tendency to circle can reflect asymmetrical damage to the brain, the direction the animal turns when it reaches a corner should be noted. If the animal is not clearly circling but has a bias toward turning one direction, the clinician should set up situations in which a turn in the opposite direction is required and see if the animal does so effortlessly. The character of the circling can provide clues to the localization. Forebrain disease tends to produce larger, wandering circles (sometimes the animal only makes a turn when it reaches a place where it cannot continue forward). Typically the circling will be toward the side of the forebrain lesion. Brain stem disease will more commonly produce tight circling or a tendency to lean against the wall with one side. The direction can be variable with brain stem lesions.

Abnormal Movements While observing the animal's behavior in the exam room, any abnormal movements should be noted. In addition to the character of the movement, it is important to note when the abnormal movement occurs, whether at rest, when standing still, or when moving.

Tremors are probably the most common abnormal movement because they can be the result of a wide variety of causes. A tremor is a rhythmic oscillation of at least one functional region of the body such as a limb or the head. Tremors can be classified based on the frequency of the tremor, the part of the body affected, and the activity that precipitates the tremor.

Normally a subclinical tremor called the *physiologic tremor* occurs in all muscles. This is a high-frequency tremor (6 to 12 Hz) that disappears when the muscles are at rest. A variety of diseases can produce an enhanced physiologic tremor. Such a tremor is still a high-frequency tremor, and it tends to be most noticeable when the animal is standing quietly (postural tremor).

Goal-directed movements activate an intention tremor. This is seen most clearly in the head when the animal attempts to eat or drink or otherwise tries to fix its attention on something. Such tremors are characteristic of cerebellar disease but may be seen in other conditions such as hypocalcemia. The tremors are courser and slower (3 to 5 Hz) than physiologic tremors.

Myoclonus refers to a brief contraction of a muscle, group of muscles, or occasionally the entire body. Although myoclonus can repeat rhythmically, it does not have the oscillating character of tremors. Instead a rapid jerk occurs, followed by a quiet period (Figure 191-3). Myoclonus is seen most commonly in dogs after distemper infection but can be seen in other conditions such as myoclonic epilepsy, toxicities such as lead poisoning, or metabolic encephalopathies.

Dyskinesia is a general term to describe abnormal movement. The specific dyskinesias described in human neurology, such as chorea, ballism, or athetosis, have not been well characterized in animals. It is important to recognize that in a quadruped, fine motor control is more important in the head and facial muscles than the limbs. For example, star thistle toxicity in horses produces a degeneration of the substantia nigra comparable to Parkinson's disease of humans. The tremors and motor difficulties in the horse, however, are most dramatic in the facial muscles.

Gait and Posture The posture of a normal animal should be square with the feet directly beneath the body and the head straight. A wide-based stance would indicate a problem with proprioception or balance. Unilateral balance or motor problems, usually related to a brain stem or inner ear lesion, may cause the animal to lean toward one side, possibly against a wall for support. With forebrain disease, the animal may tend to curl toward the side of the lesion as they orient toward that direction. With vestibular disease, the head tends to be rotated on the long axis so that one ear is lower than the other. The nose may be kept straightforward or sometimes turned away from the lower ear. Except for the paradoxical vestibular syndrome seen with cerebellar disease, the head tilt will be toward the lesion (Figure 191-4). If abnormal head posture

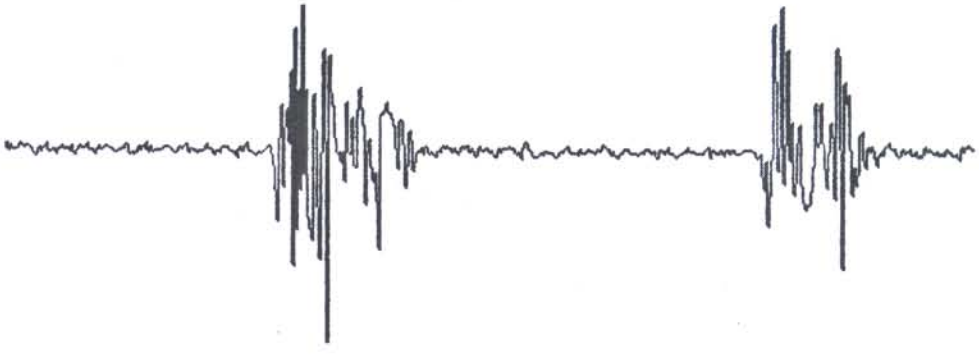


Figure 191-3 Myoclonus is visible as brief bursts of muscle activity in the electromyography (EMG) of a dog with canine distemper.

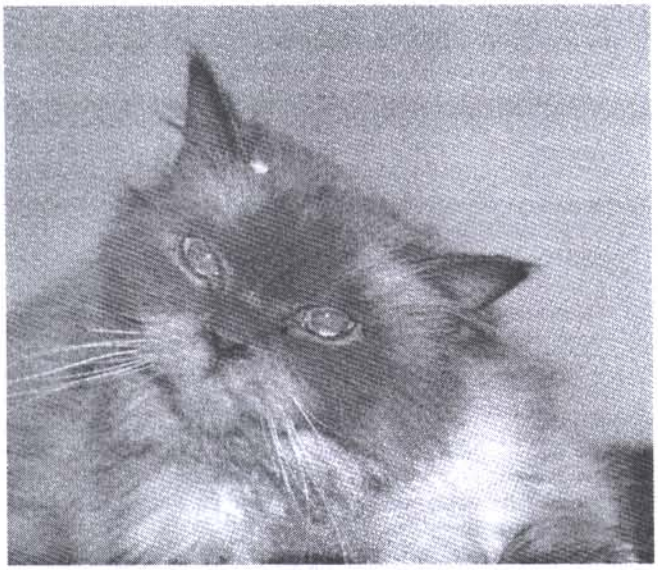


Figure 191-4 With vestibular disease the head is rotated on its long axis with one ear lower than the other. This can be compared with a head adversion shown in Figure 191-17 in which the nose is pulled around toward the flank. (From O'Brien DP: Circling. In August JR, editor: *Consultations in feline internal medicine*, Philadelphia, 1994, WB Saunders Co, p 449.)

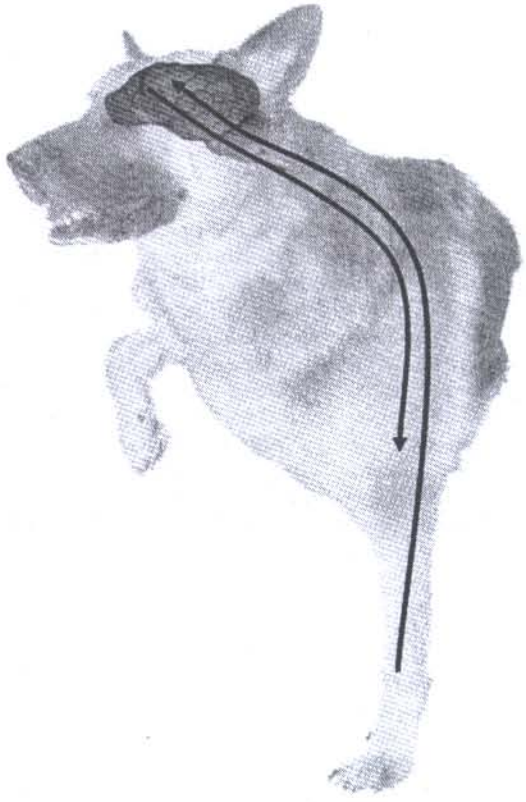


Figure 191-5 Postural reactions, such as hopping, assess the ability of the brain to integrate sensory information and produce a coordinated motor response. The entire circuit (sensory afferents, long tracts, higher integration, and motor efferents) must be functional for a postural reaction to be executed. (From O'Brien DP; Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004.)

occurs in forebrain disease, the head will be pulled around to the side but usually not rotated. This type of head posture is sometimes referred to as an *adversion*, but the direction of the movement is typical toward the side of the lesion. *Dystonia* refers to a sustained abnormal contraction or posturing from basal ganglia disease.

If the animal is stuporous or comatose, it may adopt abnormal postures that help to localize the lesion. A lesion affecting the midbrain will produce decerebrate rigidity. The neck is extended dorsally, and all four limbs are extended. Lesions of the cerebellum can sometimes produce a similar posture (decerebellate posture). The neck and thoracic limbs are extended, but the pelvic limbs are flexed.

The gait can be observed while the animal explores the exam room or while the owner walks the animal on lead. Walking in tight circles or up and down stairs may exacerbate subtle deficits. If an animal is weak from brain disease, it will be a UMN weakness. As a result, the limbs will tend to be stiff and the stride lengthened as opposed to the short, shuffling stride and buckling of the limbs seen with lower motor neuron (LMN) weakness. An animal with cerebellar disease will have normal strength with dysmetria. This is most apparent in the thoracic limbs as a goose-stepping gait, but the pelvic limbs may also show hyperflexion. Typically marked truncal ataxia is also noted as a swaying of the pelvis. Truncal ataxia may also be observed with proprioception deficits, but limb ataxia is different. An animal with proprioception deficits tends to drag the toes and may stand with the foot knuckled under. It misplaces the feet and may cross over or step on itself, especially during tight circles.

Postural Reactions The postural reactions are complex responses requiring integration of sensory information and coordination of motor responses at the brain level (Figure 191-5). Thus they are more involved than simple reflexes but still occur in direct response to a sensory stimulus, usually a perturbation of proprioception or balance. This makes them useful for evaluating brain function and spinal tracts.

Conscious proprioception is evaluated by balancing the animal with one hand under the thorax or abdomen and knuckling one foot under so that the animal bears weight on the dorsum of the paw. Although clinicians are mainly interested in the perception of the sensation, they are looking for a motor response (replacing the foot to a normal position), thus this qualifies as a postural reaction. Proprioception deficits with forebrain disease may not be as obvious as the deficits seen with spinal cord disease. An alternative method for assessing proprioceptive awareness is placing a sheet of paper under one foot and slowly pulling the paper laterally. An animal with proprioception deficits may allow the foot to slide far laterally, even though it may replace the foot when knuckled.

Hopping also assesses proprioception, specifically where the foot is relative to the animal's center of gravity. The required motor response is more complex and thus allows the clinician to assess motor function and sensory perception. A small animal may be held with all its weight on one paw, whereas in a larger animal, only one paw is lifted and the animal pivoted. As the animal moves laterally, it should begin to hop to the side before its center of gravity passes over the paw. Proprioception deficits result in a delayed or absent initiation of the response. Cerebellar disease would result in an exaggerated movement, whereas UMN lesions would result in a weak or absent response.

Hemistanding and hemiwalking are good for comparing strength and coordination on one side of the body versus the other. First, both legs on one side are lifted off the ground

so that the animal has to support all of its weight on one side and strength can be assessed. Then the animal is moved laterally so that it has to walk sideways on one side. This is a sensitive test of the ability of the contralateral forebrain to control those limbs.

Visual placing assesses the animal's ability to use a visual stimulus to coordinate a motor response. As with proprioceptive positioning, the clinician is mainly interested in the sensory perception, in this case, vision. The animal must be small enough to be lifted off the ground, and then it is brought forward and downward toward the edge of a table. The normal response is to reach out and place one or both thoracic paws on the table. Tactile placing can be used to evaluate light touch perception of the thoracic limbs. The procedure is like visual placing, except the animal is blindfolded and the dorsum of the paw lightly touched against the table. Perception of touch in the pelvic limb is evaluated by the extensor postural thrust. The animal is picked up under the axilla and slowly lowered down. The normal response when the paws touch the ground is an extension of the limb and a shuffle to get the feet underneath the body.

The righting response is also a postural reaction. In this case the main sensory modality evaluated is the vestibular system. Proprioception and vision can also play a role, particularly in animals with vestibular deficits. Blindfolding the animal to remove visual compensation will exacerbate a vestibular deficit. Suspending the animal by the pelvis with the head down removes most proprioception clues, and the clinician can assess the animal's ability to orient to gravity. A normal animal will attempt to keep the head upright, whereas an animal with vestibular deficits may curl or move the head regardless of orientation to gravity. Alternatively the animal can be placed in lateral recumbency and allowed to right itself. A normal response would be a rostral-caudal righting, whereby the animal brings up the head, then neck, then shoulders, and sometimes also the pelvis.

Cranial Nerves Because the cranial nerves originate in the brain, careful evaluation assesses the function of not only the nerve itself but also the associated brain areas. Although there can be UMN type of deficiencies in cranial nerves (just as for spinal reflexes), these are difficult to detect in animals. Thus with a few exceptions (see following discussion), a deficiency in a cranial nerve reflects damage either to the nerve itself or the brain area where the nucleus resides. Cranial nerve deficits will generally be ipsilateral to the lesion with the exception of the optic (II) and trochlear (IV)[4] nerves, which may be contralateral. Forebrain lesions may produce a loss of response to sensory information originating from the contralateral side.

The olfactory nerve (I) is the only sensory nerve that does not relay through the thalamus. Instead, it projects to the pyriform cortex and limbic areas such as the septal nuclei and amygdala, areas important in emotional responses. This may explain why odors can have a profound emotional effect. Evaluating olfactory function can be difficult. If the animal investigates an odor, such as concealed food or urine odor on the exam room floor, then they have some olfactory function, but a unilateral loss could not be ruled out. A failure to orient to an odor could reflect a loss of the sense of smell or simply a lack of interest in the odor. Any withdrawal from an odor must be interpreted cautiously, because irritating substances such as alcohol could stimulate pain receptors in the nasal mucosa (carried by the trigeminal nerve [V]).[5]

The optic nerve (II) is evaluated by assessing vision and the pupils. *Vision* refers to the conscious perception of a visual stimulus, so clinicians rely on observing a behavioral response to determine if the animal has perceived the stimulus. The decussation of the optic nerves ensures that all visual information from one side goes to the contralateral visual cortex (Figure 191-6). The most effective way to evaluate vision is by tossing a cotton ball from behind, toward one side or the other, and observing whether the animal tracks the cotton ball (Figure 191-7). By avoiding the area directly in front of

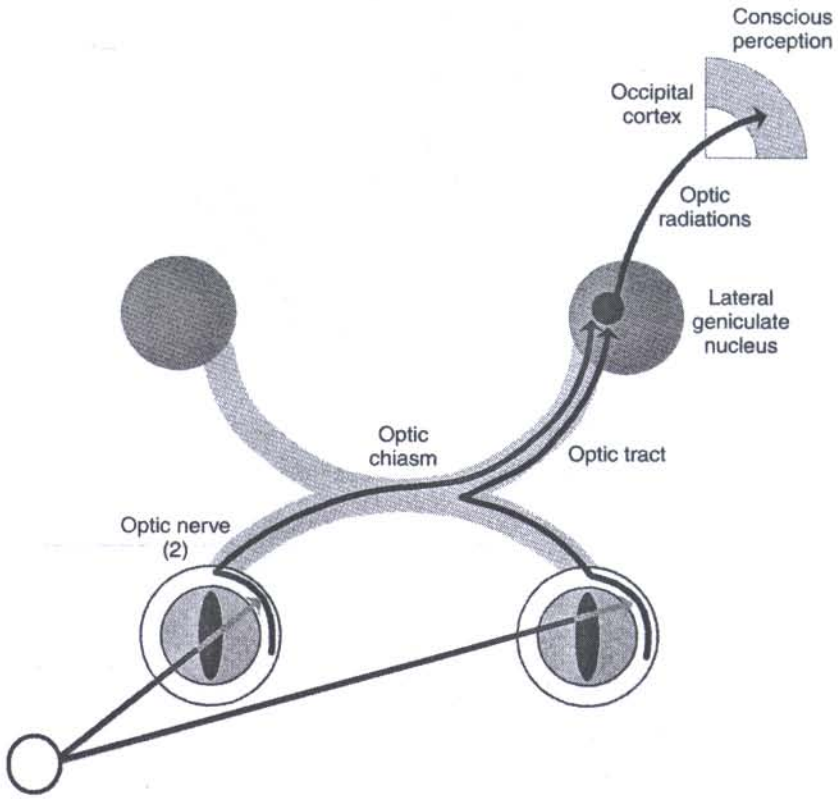


Figure 191-6 The decussation of fibers within the optic chiasm ensures that images from one visual field are transmitted to the contralateral visual cortex.

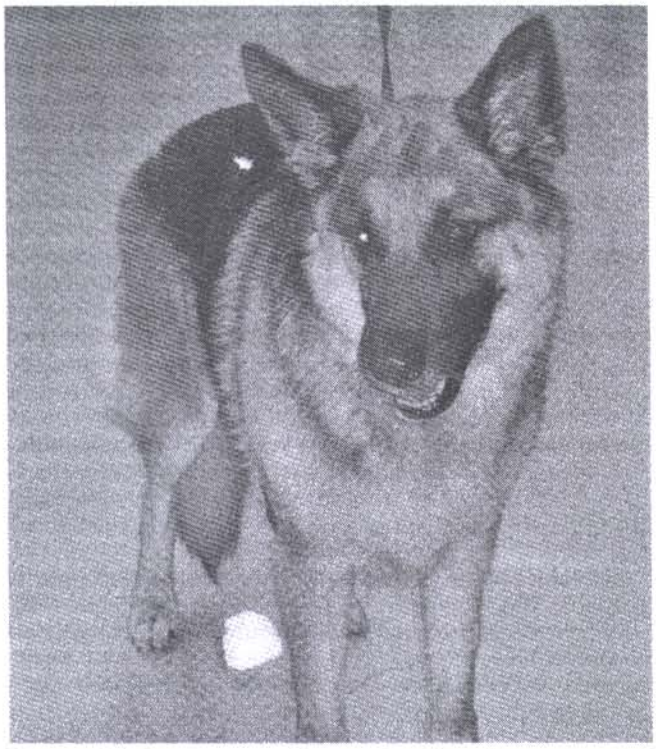


Figure 191-7 Most normal animals will track a cotton ball tossed from behind them. By keeping the cotton ball off to the side, vision in the left and right fields can be independently evaluated.

the animal where stereoscopic vision occurs, it is easier to differentiate loss in one visual field. The cotton ball will not create any noise and will typically surprise the animal enough to elicit some response.

The ability of the animal to negotiate obstacles in the exam room, such as the exam table or a chair, can also assess vision. One eye can be covered to detect unilateral deficits. If the animal appears blind, the room can be darkened to dilate the pupils and the door opened to a bright hallway. If it cannot perceive the doorway, then it is unlikely that the animal has any functional vision. If the animal is small enough to be picked up easily, visual placing can be used to assess vision.

The menace response is an acquired and complex response, not a simple reflex. It is one of the last cranial nerve responses to develop and may not be apparent until the animal is 12 weeks of age. It is best assessed with a quick movement of the hand parallel to the head, starting from behind the ear outside the animal's visual field. By moving parallel to the head, the whiskers can be avoided and fewer air currents are generated. By staying lateral, the stereoscopic field is avoided and one visual field evaluated. Most animals will respond to a quick movement from outside their vision with a blink. Because it is a complex pathway, a menace loss does not precisely localize a lesion without clues from the rest of the examination.

The optic nerve (II) provides the sensory afferents for the pupillary light reflex (PLR). These fibers synapse in nuclei in the midbrain and control the parasympathetic constriction of the pupil via the oculomotor nerve (III). In mammals, crossover in the optic chiasm and the midbrain ensures that both pupils respond together (Figure 191-8). Thus a light in one eye produces a constriction of the ipsilateral eye (direct response)

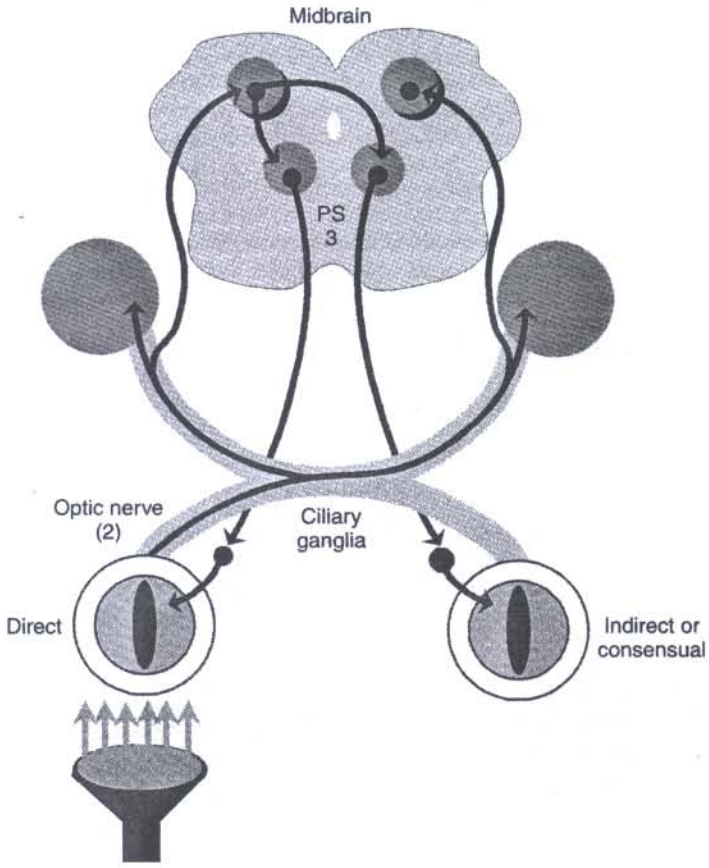


Figure 191-8 Light in one eye activates afferents in the optic nerve *(2)*. These synapse on efferents for the parasympathetic portion of the oculomotor nerve *(PS3)*, which in turn synapse in the ciliary ganglia. Crossover in the optic chiasm and the midbrain ensure that both the ipsilateral (direct response) and contralateral (indirect or consensual response) pupils constrict. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

and the contralateral eye (indirect or consensual response). A unilateral lesion of the retina or the optic nerve distal to the optic chiasm will produce blindness in that eye; thus if the other eye is blindfolded, the animal will have no vision. Shining a light in the affected eye will not produce a response in either pupil. Because the consensual innervation from the unaffected eye would be intact, pupil size and consensual response in the affected eye would be normal. With bilateral disease, both pupils would be dilated and completely unresponsive to light in either eye. A lesion affecting the parasympathetic third nerve, either in the brain stem or peripherally, would cause a dilated pupil in the ipsilateral eye that did not respond to light in either eye. Vision in that eye, however, would be normal, and shining a light in the affected eye would still elicit constriction of the contralateral pupil (consensual response).

The sympathetic innervation of the pupil controls dilation. The first sympathetic fibers to leave the spinal cord at the T1–T2 cord segments run cranially in the vagosympathetic trunk to synapse in the cranial cervical ganglia at the base of the skull. From there, the postganglionic fibers course through the middle ear and into the calvarium, where they join with the ophthalmic branch of the trigeminal nerve and project through the retrobulbar area to innervate the eye. A lesion anywhere along this path can produce the classic signs of Horner's syndrome. The pupil cannot dilate normally in darkness but constricts normally in response to light, so the anisocoria will be most evident in dim lighting. Loss of sympathetic innervation to other structures around the eye would produce enophthalmos, ptosis, elevated third eyelid, and vasodilation.

Eye movements are controlled by the oculomotor (III), trochlear (IV), and abducens (VI) nerves. Damage to one of these nerves results in deviation of the eye (strabismus), because the muscles innervated by the functioning nerves pull the eye away from the denervated muscles. Thus with loss of the oculomotor nerve (III), a ventrolateral strabismus occurs. Trochlear nerve (IV) loss results in an outward rotation of the top of the eye. In an animal with a round pupil like the dog, this can be detected by the position of the vessels in the fundus. The trochlear nerve (IV), like the oculomotor nerve (III), originates in the midbrain, but it is the only cranial nerve to completely decussate. The abducens nerve (VI) originates near the vestibular nucleus in the medulla. Loss of this nerve results in a medial strabismus. The abducens nerve (VI) also innervates the retractor bulbi muscle; thus lesions will abolish retraction of the globe when the cornea is touched. With lesions sparing one or two of the nerves, some eye movement will be apparent even though the eye is deviated. With retrobulbar or cavernous sinus lesions, all three nerves may be lost, resulting in an eye that is positioned normally but unable to move (external ophthalmoplegia).

The doll's eye reflex (physiologic nystagmus or oculocephalic reflex) can be used to induce eye movements, and thus evaluate the vestibular system, and the innervation of the extraocular muscles. The vestibular apparatus detects movement of the head. The vestibular nuclei feed information about the direction and speed of movement to the third, fourth, and sixth nerve nuclei, which move the eyes in the opposite direction at exactly the same speed. This allows the animal to maintain a fixed image on the retina even when the head is moving. Once the eyes have reached the limit of their range of movement in that direction, a center in the pons takes over to quickly flick the eyes back in the direction of the head movement, and the process begins again. Clinicians can observe this physiologic nystagmus by rotating the head to one side at a moderate speed and observing the eye movements. It is often easier to see the eye movements if the eyelid is pulled back to reveal the sclera. Because the pathway between the vestibular nucleus in the medulla and the third and fourth nerve nuclei in the midbrain (the medial longitudinal fasciculus) runs through the area of the reticular activating system, it is also a useful reflex in animals with stupor or coma.

Facial sensation is carried by the three branches of the trigeminal nerve (V). The ophthalmic branch innervates the skin medial to the eye and the cornea. Touching the medial canthus of the eye or the cornea will produce a blink (the palpebral or corneal reflex, respectively) if sensation is present and the motor innervation of the eyelid muscles by the facial nerve (VII) is intact. Because the sympathetic fibers to the eye travel with the ophthalmic branch, Horner's syndrome can accompany the sensory loss. The maxillary branch innervates the skin of the side of the face and the nostrils. A blink can frequently be elicited by touching the dog on the lateral aspects of the muzzle as well. Alternatively, maxillary sensation can be evaluated by touching the inside of the nostril. A normal animal will withdraw the head, but this response is sensitive to altered consciousness and nerve damage. The mandibular branch carries sensation for the skin of the chin and just ventral and rostral to the ear.

The muscles of mastication are innervated by the motor portion of the mandibular branch of the trigeminal nerve (V). Bilateral trigeminal paralysis will result in a dropped jaw and an inability to prehend food. The animal will be able to swallow normally when food is placed into the back of the mouth because pharyngeal function is normal. With unilateral paralysis, the animal will be able to eat normally, and the only sign will be atrophy of the temporalis and masseter muscle on the ipsilateral side.

Facial nerve (VII) palsy results in loss of function of the small muscles of the face. The most obvious sign will be an inability to blink the eye on the ipsilateral side, either spontaneously, in the palpebral and corneal reflex, or in the menace response. The lip and cheek may sag, and food may become lodged in the cheek. The nostrils will not flair with respiration, and cats will not be able to move their whiskers forward. The animal will not be able to lay the ear back, and in droop-eared dogs the ear will sag further. With chronic denervation, the muscles may contract, producing a grimacing facial expression.

Because the parasympathetic innervation of the lacrimal glands is also carried by the facial nerve, a dry eye may accompany the loss of blinking, predisposing the eye to exposure keratitis. Tear production can be evaluated by the Schirmer's tear test. The facial nerve also conveys taste sensation from the rostral two thirds of the tongue. Taste can be evaluated by touching the lateral aspect of the tongue just behind the canine tooth with a cotton tip soaked in a bitter substance like atropine. If the animal can taste, it immediately begins to salivate and lick. Taste from the caudal one third of the tongue is carried in the glossopharyngeal nerve but is more difficult to evaluate in animals. Finally, sensation from the skin in the concave surface of the pinna is carried by the facial nerve.

The vestibular portion of the eighth cranial nerve transmits information about the position of the head relative to gravity and head movement from the inner ear. The vestibular nuclei use this information to control eye movements (discussed previously) and maintain balance. Acute unilateral lesions affecting the vestibular apparatus will cause profound disruption of balance. The imbalance in vestibular input between the two sides creates the perception of spinning, leaning, or both. In response to this, the animal will be anxious and may be nauseated and vomit. It will lean and may even roll toward the side of the lesion. There will be a head tilt toward the affected side, sometimes dramatically. If able to walk, affected animals may circle or lean against a wall for balance. When lifted off the ground, they may curl toward the side of the lesion with the contralateral limbs extended and the ipsilateral limbs flexed.

Spontaneous nystagmus occurs because the imbalanced vestibular input creates a perception that the animal is spinning when it is not. With peripheral vestibular disease, the nystagmus may be horizontal or rotary with the fast phase away from the lesion. With time, the animal can compensate even if vestibular function does not return on the affected side. The disorientation and rolling will subside within a few days, and within 1 week the nystagmus may stop. Often signs like nystagmus can be precipitated again by rolling the animal onto its back or quickly extending the neck with the nose pointed toward the ceiling. Blindfolding will exacerbate the balance problems. With time, a residual head tilt may be the only sign that the vestibular system has not recovered completely. When the head is tilted, the eye position appears normal. If the clinician straightens the animal's head, the eye ipsilateral to the lesion will deviate ventrally. This is referred to as a *positional strabismus*.

Because no asymmetry exists in the vestibular afferents, bilateral vestibular lesions do not produce the classic vestibular signs of nystagmus, head tilt, and circling. Instead the animal is wide based and apprehensive. It may hug the ground, refusing to move. Head movements are exaggerated. The doll's eye response is absent, and when blindfolded the animal has deficient righting responses.

The auditory portion of the eighth cranial nerve mediates hearing. Like vision, *hearing* refers to the conscious perception of a sensory stimulus and is assessed by observing the response to a noise such as clapping or a squeaky toy. When assessing the animal's ability to orient to a sound, it is important to avoid vibrations, shadows, or air currents that might provide a nonauditory cue. Animals with unilateral hearing loss may orient abnormally, turning away from a sound, but some can locate sound accurately even with unilateral hearing loss. The brain stem auditory evoked response (BAER) can detect unilateral damage to the cochlea or auditory pathways, but only a behavioral response truly tests hearing.

Swallowing entails coordination of the tongue, pharynx, larynx, and esophagus. The glossopharyngeal nerve (IX) and cranial branches of the vagus nerve (X) innervate the pharyngeal muscles and carry sensory information from the caudal tongue and pharynx. Damage to these nerves would affect the ability to swallow but not the ability to prehend food. Clinicians can use the gag reflex to assess pharyngeal function by placing the finger or a tongue depressor on the caudal aspect of the tongue. A normal animal will gag and swallow, whereas an animal with glossopharyngeal paralysis will not respond. An animal with unilateral damage may still be able to swallow, but it will choke, gag, or lose food through the nostrils. Regurgitation of swallowed food occurs with disorders of esophageal motility. The vagus nerve (X) is the major nerve of the esophagus. Contrast radiography may be necessary to evaluate esophageal motility.

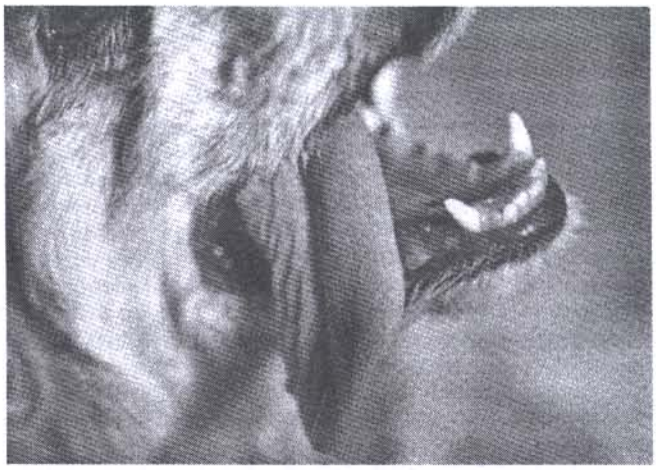


Figure 191-9 Unilateral hypoglossal paralysis interferes with swallowing. The ipsilateral half of the tongue will atrophy, and the tongue will deviate. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

The larynx is also innervated primarily by the vagus nerve (X) through the cranial and recurrent laryngeal nerves. Unilateral paralysis produces laryngeal hemiplegia and inspiratory stridor. Because the left recurrent laryngeal nerve follows a longer course through the thorax, that side is more susceptible to some disease processes, such as dying back neuropathies. Observing the movement of the vocal folds under light sedation will confirm paralysis. Voice change and dysphagia may also accompany laryngeal paralysis.

The spinal accessory nerve (XI) may contribute to some of the laryngeal and pharyngeal muscles, but it primarily innervates the trapezius, brachiocephalicus, and sternocephalicus. Denervation of these muscles is difficult to detect clinically.

The intrinsic and extrinsic muscles of the tongue are supplied by the hypoglossal nerve (XII). Unilateral damage will denervate the ipsilateral muscles and result in deviation of the tongue (Figure 191-9). Bilateral lesions abolish tongue movement, preventing normal prehension and swallowing.

Localizing the Lesion

Once a neurologic exam has been performed, that information is synthesized to localize the lesion. For localization purposes, the brain can be divided into four broad areas: (1) the forebrain (cerebrum and diencephalon), (2) the midbrain, (3) the pons and medulla, and (4) the cerebellum (Figure 191-10). It is often possible to further localize within these areas, but placing the lesion within one of the broad divisions is sufficient to have

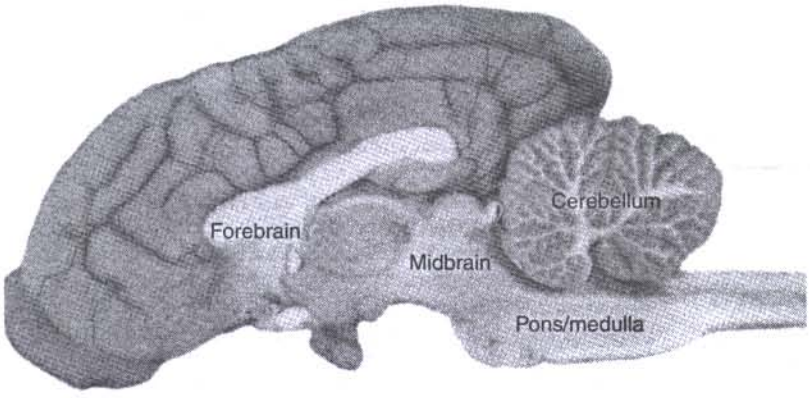


Figure 191-10 For purposes of localization, the brain can be divided into four areas: the forebrain, midbrain, pons and medulla, and cerebellum. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

a reasonable list of differential diagnoses and diagnostic plan. When localizing the lesion, the first question the clinician must answer is whether the signs reflect focal, diffuse, or multifocal disease. A focal lesion is suspected if strong lateralization to the clinical signs occurs (e.g., circling, focal onset seizures, lateralized cranial nerve deficits). A focal lesion suggests localized damage to the brain as might occur from a neoplasia, vascular disease, or localized infection. A metabolic or toxic insult or a degenerative process would be expected to affect the brain more generally and not preferentially affect one side or the other. Although symmetrical forebrain signs suggest a diffuse disease process, they do not rule out focal disease. Focal disease can produce diffuse signs through mechanisms like obstructive hydrocephalus and increased intracranial pressure. Every effort should be made to explain the clinical signs based on a single lesion. If a single lesion cannot explain some signs; multifocal disease is suspected. For example, a single lesion cannot explain an animal that has both seizures (cerebral cortex) and unilateral facial palsy (medulla or facial nerve).

Cerebellum The cerebellum receives input from higher motor command centers and sensory feedback from proprioceptive afferents and the vestibular system. It uses this information to coordinate movement and help maintain balance. The connections to and from the cerebellum via the cerebellar peduncles form a large part of the pons. A disease affecting the cerebellum or its peduncles will produce dysmetria, tremors, and vestibular signs. Dysmetria is most noticeable in the thoracic limbs as a goose-stepping gait (Figure 191-11) but will also be apparent as a wide base, truncal swaying, and exaggerated flexion of the pelvic limbs. The tremors of cerebellar disease are coarse tremors that disappear at rest. In acute cerebellar disease the tremors can be almost constant and the most dramatic manifestation of dysfunction. In more chronic disease, such as congenital cerebellar deficits, the tremors may be more subtle and only noticeable when the animal attempts to make a directed movement such as eating (intention tremors). The cerebellum works intimately with the vestibular system to control balance and eye movements. Lateralized lesions, such as in one cerebellar peduncle, can produce head tilt, imbalance, and horizontal or rotary nystagmus similar to a peripheral vestibular lesion. With cerebellar disease, the direction of the head tilt (away from the lesion) and nystagmus (fast phase toward the lesion) are the opposite direction as in peripheral vestibular disease. This is referred to as *paradoxical vestibular syndrome*. With more diffuse disease of the cerebellum, a vertical nystagmus can be present as in central vestibular disease. In either case the animal may also lose its balance, especially in response to quick movements, such as shaking the head or sudden turns. Severe cerebellar lesions can produce decerebellate posturing, extension of neck, and thoracic limbs with flexion of the pelvic limbs. Because the menace response is a learned motor response and the cerebellum plays an important role in motor learning, animals with cerebellar disease may lose the menace response.

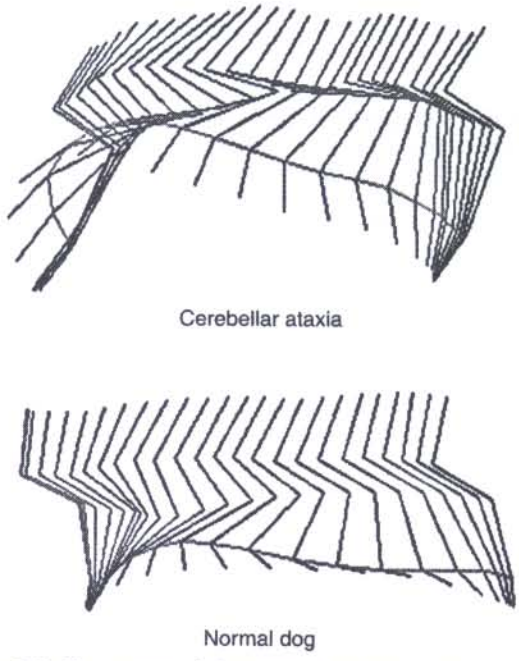


Figure 191-11 Lesions of the cerebellum disrupt the control of movement, resulting in dysmetria. This is most obvious as a goose-stepping gait in the thoracic limbs demonstrated by this stick figure representation of the limb in a Chinese crested dog with multiple system degeneration compared with a normal littermate. The line connecting the limb positions follows the trajectory of the carpus. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

Pons and Medulla The pons and medulla are the most caudal portions of the brain stem (Figure 191-12). The sensory and motor tracts of the spinal cord traverse these areas as well; thus lesions in this area can produce deficits in these long tracts similar to cervical spinal cord disease. Lateralization to the weakness or proprioception deficits would be common, and the side affected would depend on where the lesion was relative to the decussation of that particular tract. Because the respiratory centers reside in the medulla, an animal with a lower brain stem lesion producing complete paralysis would die from respiratory compromise. In addition to respiration, other autonomic centers reside in the brain stem, although clinical signs associated with their malfunction may not be as readily apparent.

Cranial nerve deficits are the signs that point most directly to a brain stem lesion. In isolation, such deficits could reflect a peripheral nerve lesion or small focal brain stem disease. Multiple nerve deficits or concurrent long tract signs (e.g., hemiparesis, proprioception deficits) point toward brain stem involvement. Cranial nerves V to XII arise from the pons and medulla. They all remain ipsilateral, and thus a lateralized deficit will be on the side of the lesion. The facial nerve (VII), vestibulocochlear nerve (VIII), and nerves controlling the pharynx, larynx, and tongue (IX, X, XII) run laterally from the brain stem out their respective foramina. Thus a lesion on the lateral aspects of the brain stem, such as a meningioma of the cerebellopontine angle, may affect combinations of these nerves (Figure 191-13). The trigeminal nerve (V) originates from the pons in close proximity to these nerves but runs rostrally to exit retrobulbar. The abducens nerve (VI) also runs rostrally from the medulla to innervate the lateral rectus and retractor bulbi muscles. A lesion produces a medial strabismus.

Midbrain In addition to the nuclei of cranial nerves III and IV, the midbrain contains important motor nuclei and serves a major role in regulation of consciousness (Figure 191-14). The red nucleus is the origin of one of the major UMN tracts in quadrupeds, and damage to this nucleus in the midbrain will cause paresis or paralysis. Because the vestibulospinal tracts originate in the medulla and would be spared by a midbrain lesion, their excitatory effects on extensors of the limbs and neck would be unopposed by the normal inhibitory effects of the rubrospinal tracts. Thus midbrain lesions can produce decerebrate rigidity, a posture with dorsal extension of the neck and extension of the limbs. Because the respiratory

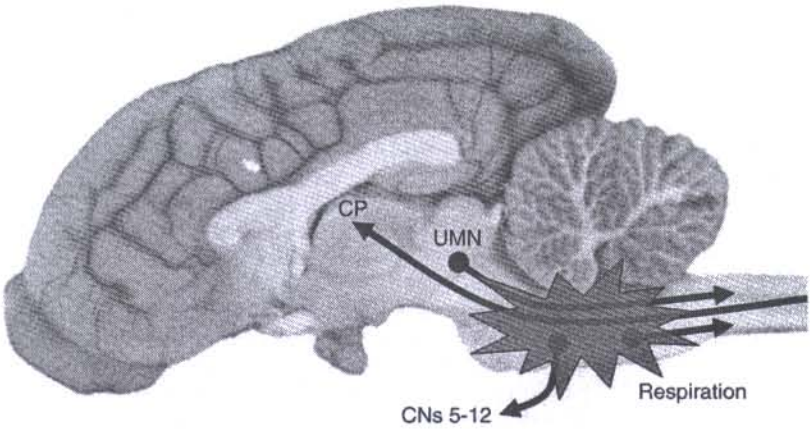


Figure 191-12 Lesion of the pons and medulla can affect cranial nerves V to XII, proprioception, and motor tracts. Severe lesions cause death by affecting respiratory centers. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

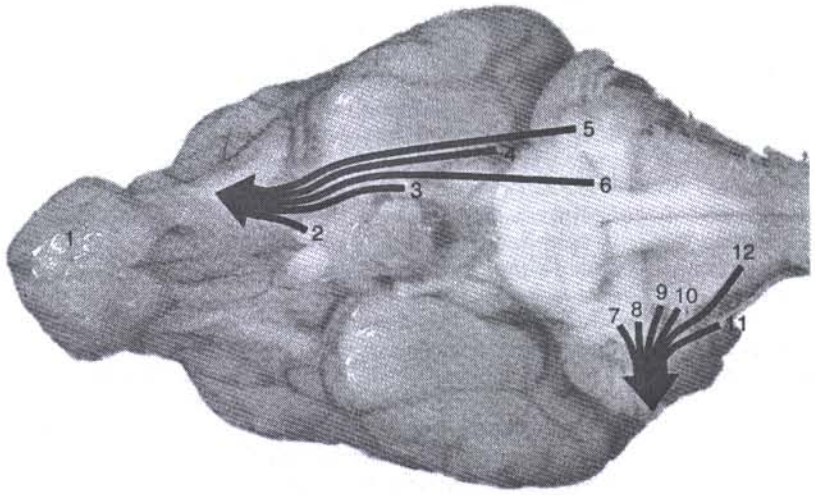


Figure 191-13 The cranial nerves form two anatomic clusters. Cranial nerves VII to XII run laterally from the brain stem and could be affected by a lesion such as a meningioma of the cerebellopontine angle. Cranial nerves II to V course rostral below the forebrain to exit in the retrobulbar area. Thus lesions in the cavernous sinus or retrobulbar area could affect combinations of these nerves. The olfactory nerve *(1)* crosses the cribriform plate and projects directly to the limbic areas. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

centers reside more caudally in the medulla, the animal can continue to breathe even if completely paralyzed from a midbrain lesion. Conscious proprioception tracts must also course through the midbrain on their way toward higher centers. Thus deficits in postural reactions may be apparent with a midbrain lesion if the animal is still capable of voluntary movements.

Lesions below the midbrain may produce complete paralysis and respiratory compromise but may not directly alter consciousness or behavior. The midbrain marks the beginning of the reticular activating system (RAS), a group of loosely defined areas that project from the cranial pons, midbrain, and hypothalamus to the cerebral cortex and regulate consciousness and goal-directed behavior. Lesions of the midbrain will affect these functions (see following discussion).

The trochlear nerve (IV) innervates the dorsal oblique muscle. Deficits result in outward rotation of the eye and, because the trochlear nerve is the only cranial nerve to completely decussate, a midbrain lesion will produce strabisms in the contralateral eye. In animals with round pupils such as the

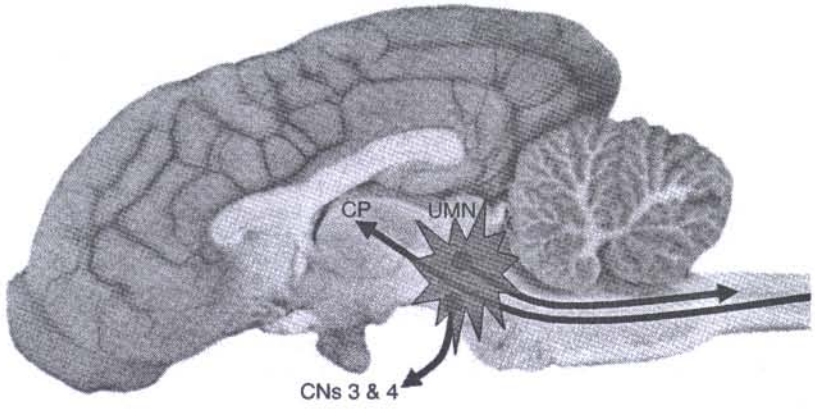


Figure 191-14 Lesions of the midbrain affect cranial nerves III and IV. Damage to the origin of upper motor neurons (UMNs) in the red nucleus can lead to decerebrate rigidity and damage to the reticular activating system (RAS) will affect consciousness. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

dog, this can only be detected by looking at the orientation of the vessels in the fundus. Because the trochlear nerve will seldom be damaged without affecting other cranial nerves, this is usually not an issue. The oculomotor nerve (III) innervates the remaining extraocular muscles. Damage results in ventrolateral strabismus and loss of the normal doll's eye response in the ipsilateral eye. The third nerve also contains the parasympathetic fibers to the pupil. Damage to these fibers will produce mydriasis and loss of the PLR, although vision is unaffected.

Forebrain The forebrain encompasses the cerebral cortex, basal nuclei, thalamus, and hypothalamus. These areas mediate higher brain functions such as personality and learned behavior, motor planning, sensory processing, and emotional, endocrine, and autonomic functions, respectively. The olfactory (I) and optic (II) nerves are also primarily forebrain nerves. All the nerves of the eye and extraocular muscles (II, IV, VI), along with the trigeminal nerve (V), course rostrally along the floor of the calvarium to exit through their retrobulbar foramina. Thus a lesion in the area of the cavernous sinus may produce deficits in combinations of these nerves and affect the overlying forebrain. These nerves can also be affected after they exit the calvarium by retrobulbar lesions.

Although the pupilomotor fibers of the optic nerve project to the midbrain to control the PLR, the main projection of the optic nerve to the forebrain mediates vision. Lesions of the optic tract, lateral geniculate nuclei, or occipital lobes can produce a loss of vision with normal PLR (central blindness). If unilateral, the vision loss is limited to the contralateral visual field.

In addition to vision, other sensory modalities such as conscious proprioception or hearing are relayed through the thalamus to the appropriate area of the cerebral cortex. Thus the ability of the animal to respond meaningfully to a sensory stimulus may be disrupted by lesions of the appropriate thalamic nuclei or region of the cerebral cortex. Like the PLR, some other simple responses such as the startle response to a loud noise or the dazzle response to a bright light are mediated at a subcortical level. Vision appears to be the most sensitive to diseases such as hypoxia that diffusely affect the forebrain. The olfactory nerve projects directly to the olfactory bulbs and from there to the limbic areas of the forebrain, thus bypassing the thalamus. Olfactory deficits, however, are difficult to detect in animals.

The hypothalamus controls endocrine function through the pituitary gland. It also regulates a variety of other homeostatic functions such as body temperature, osmolality, and autonomic functions. Together with limbic areas, the hypothalamus is also involved in learning and memory, goal-directed behaviors, and emotions.

Epileptic seizures are caused by abnormal electrical activity in the cerebral cortex; thus they should be considered an unambiguous sign of forebrain disease. Either focal damage to the cortex or diffuse metabolic effects can produce seizures (see Chapter 48).

Alterations of consciousness and behavior are hallmarks of forebrain disease. The traditional view of regulation of consciousness is that the RAS in the brain stem projects to the cerebral cortex and "activates" it to produce normal consciousness (Figure 191-15). This concept is useful when considering causes of stupor and coma. Such profound alterations of consciousness can result from either a lesion in the brain stem affecting the RAS nuclei, the projections pathways of these systems toward the cortex, or diffuse disease affecting the cerebral cortex. Lesions of the brain stem caudal to the RAS can render the animal quadriplegic without necessarily disrupting consciousness.

The function of these RAS systems, however, is more complex than just turning on or off the cerebral cortex. Different nuclei and neurotransmitter systems are responsible for different aspects of attention, arousal, and goal-directed behavior. One of the main projections from the RAS nuclei to the cerebral cortex is the medial forebrain bundle—a tract running from the midbrain through the lateral hypothalamus to project diffusely to the cortex and limbic forebrain. Brain damage can lead to complex behavioral abnormalities, which are a manifestation of functional subsystems of behavior operating without direction toward a goal.[1,2]

Sensory neglect refers to a loss of meaningful response to stimuli in multiple sensory modalities without a lesion in the classic sensory pathways or a significant depression of consciousness. With unilateral lesions of the medial forebrain bundle or cerebral hemisphere, these signs can be limited to one side (hemineglect or hemi-inattention).[3] Unilateral loss of hearing and proprioception with tumor of the medulla would not fit the definition of hemineglect. The classic sensory pathways are affected in this example, and other sensory modalities, such as vision, are unaffected. Likewise, a comatose animal has simply severely altered consciousness and not neglect.

Hemineglect provides the most interesting illustration of the difference between sensory neglect and loss of consciousness or classic sensory or motor pathway lesions. The decussation of sensory and motor pathways means that all sensory information originating from the right half of the animal's perceptual world goes to left forebrain, and all control of motor activity directed toward the right side of that world originates from the left forebrain. The reader should note that this motor control extends beyond simply control of the right limbs. The activation of the left cortex is necessary for the animal to direct its attention and behavior toward the right half of

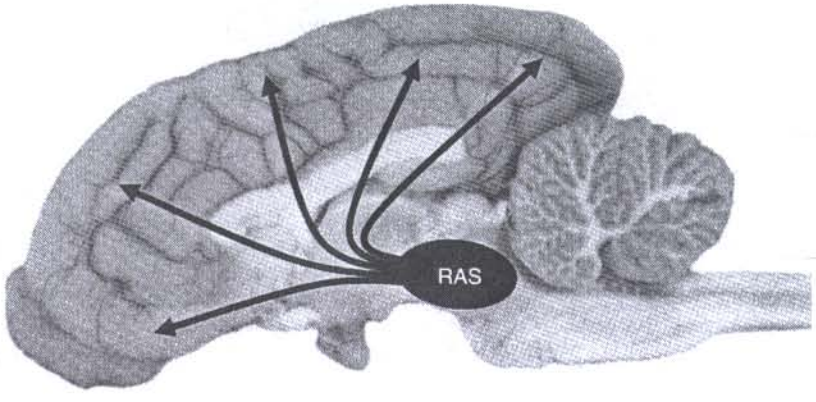


Figure 191-15 The nuclei of the reticular activating system (RAS) in the rostral brain stem project to the cerebral cortex and regulate attention and goal-directed behavior. Lesions of either the cortex or the RAS can affect consciousness. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

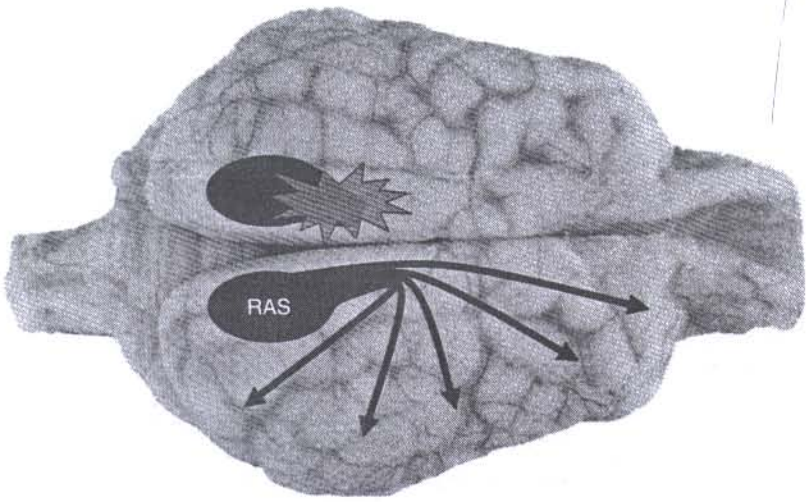


Figure 191-16 The RAS nuclei project to the ipsilateral cortex. A focal lesion of the RAS or diffuse cortical disease on one side will produce hemineglect. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

the world (Figure 191-16). Thus a unilateral lesion may be immediately apparent as a tendency to circle (Figure 191-17). Such circles can be large, wandering circles where turning only occurs when the animal reaches a corner or other obstacle that requires a decision. Because all their attention is directed toward the side of the world associated with the functional cortex, they orient and turn in that direction (i.e., they circle toward the side of the lesion).[1,4]

Conversely, they neglect all sensory information arising from the side contralateral to the lesion. They do not track cotton balls or menace in the contralateral visual field. They have deficient conscious proprioception and postural reactions on that side. They do not orient to sounds in that direction but may turn a circle in the opposite direction to localize the sound. Noxious stimuli may produce arousal, but no meaningful behavior (e.g., biting the clinician) will be directed toward the source of the pain.[1,4,5]

In humans the difference between neglect and simple sensory deficits is readily illustrated by asking the patient to perform tasks such as drawing a picture (they would only draw the half corresponding to the functional half of the brain).[3] In animals this splitting of the world into neglected and normal halves is most apparent at feeding time. A hungry animal with sensory neglect will eat the food from half the food bowl (Figure 191-18). Olfactory inputs would tell them that food is around, but they will not eat from the neglected half because they cannot direct their attention toward that side of the world.[1,4,5]

The red nucleus in the midbrain is responsible for generating the gait in quadrupeds, and the corticospinal system is less important than in humans. Postural reactions require

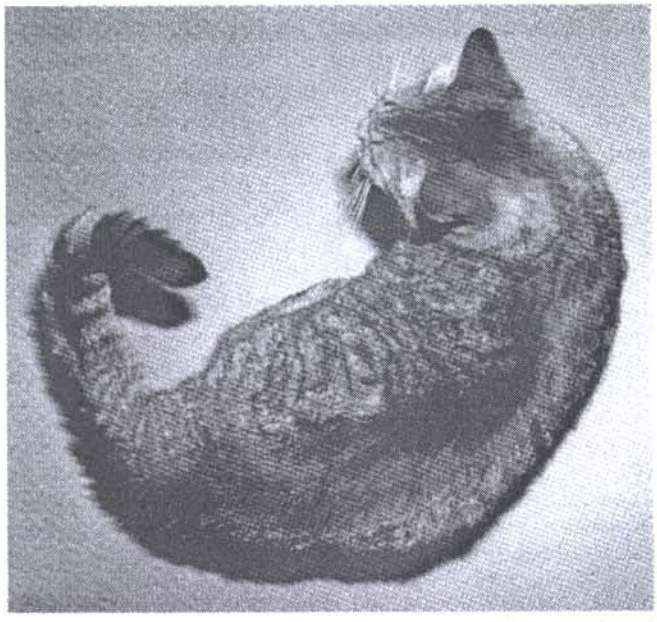


Figure 191-17 With forebrain lesions the animal may curl and circle toward the side of the lesion. In contrast to vestibular disease (see Figure 191-4), the ears are level but the nose is pulled around toward the flank (adversion). (From O'Brien DP: Circling. In August JR, editor: *Consultations in feline internal medicine*, Philadelphia, 1994, WB Saunders Co, p 449.)

Figure 191-18 An animal with hemineglect will eat the food from half the food bowl. Even though still hungry, the dog cannot direct its attention toward the food contralateral to the lesion. (From O'Brien DP. Comparative Neurology http://www.cvm.missouri.edu/academic/neurology/vm604, 2004).

forebrain control and may be deficient, but an animal with bilateral forebrain damage that is not severe enough to produce stupor may still be able to walk relatively normally. The walking, however, may not be directed toward any meaningful goal; instead the animal may pace aimlessly. As in the hemineglect cases, it may not respond to sensory stimuli. In the extreme case, it will not even be aware of the fact that it has walked into a corner and will continue to push forward, head pressing against the corner.

Forebrain lesions disrupt higher control, releasing some subcortical behaviors from their normal regulation.[2] For example, dogs and cats have a bite reflex whereby they will turn and snap at anything that touches them around the mouth. Normally this reflex is regulated by higher centers, activated when needed, such as in a fight, and inhibited when not needed, as in nuzzling the owner. Like a spinal reflex, it can be exaggerated when released from inhibition, and the animal with forebrain disease may snap without warning or emotion when touched around the mouth. In contrast to sensory neglect, where the animal ignores all stimuli, some brain-damaged animals develop magnet responses, whereby they compulsively orient and move toward a stimulus. These orienting responses are subcortical responses released from normal forebrain control and become autonomous. Emotional responses such as rage or fearfulness are also subcortical, and it is not unusual for a demented animal to respond excessively (e.g., when restrained).

Many behaviors such as sleeping and feeding are goal-directed behaviors that can be disrupted by forebrain disease. The same way the animal cannot direct its attention toward external stimuli, it cannot respond to internal needs to accomplish these behaviors. Thus it may be insomniac or anorexic.[1,2] Learned behaviors, such as tricks or housebreaking, may also be lost with forebrain disease. The micturition response is mediated in the pons, thus the animal is able to empty its bladder but is unable to regulate when micturition occurs.

DIFFERENTIAL DIAGNOSES

Once the lesion has been localized, a list of differential diagnoses can be generated and a diagnostic plan developed. The signalment provides the first clues to organizing the differential list. Congenital and hereditary diseases will be much more frequent in young, purebred animals. Although infectious diseases, traumatic injury, and toxicities can occur anytime, young animals are more likely to be affected. Some diseases, such as idiopathic epilepsy, will have their onset in young adulthood. With increasing age neoplasia, metabolic encephalopathies, and degenerative diseases become increasingly common. Breed predilections are most noticeable in hereditary diseases. Tables of breed predilections are available.[6,7]

Onset and progression of signs is the other important clue to ordering the differential diagnosis list (Figure 191-19). A congenital malformation would be present from birth and relatively static, although some, such as hydrocephalus, could progress over time. An acute onset of signs would be expected with vascular disease, trauma, most toxins, and many infectious, inflammatory, and metabolic diseases. Some infectious and inflammatory or metabolic diseases will be chronic and progressive, as will most neoplastic or degenerative conditions.

Finally the neurologic exam will suggest the type of disease process. Some diseases will have predilection for specific parts of the brain (see following discussion). Generally, lateralized neurologic signs such as circling, hemiparesis, or unilateral cranial nerve deficits suggest a localized disease process such as an infection, vascular disease, neoplasia, or traumatic injury. Likewise, focal onset seizures would suggest localized cortical damage, although idiopathic epilepsy can rarely produce focal seizures.[8,9] Infectious and inflammatory, vascular, or metastatic neoplasia would be the most likely to produce multifocal signs. A metabolic or toxic insult should not affect the brain asymmetrically, and diffuse, symmetrical signs would be expected. Because the cerebral cortex is the most metabolically demanding part of the brain, forebrain signs tend to predominate. As discussed in the introduction, however, a localized disease process can result in diffuse forebrain signs through increased intracranial pressure.

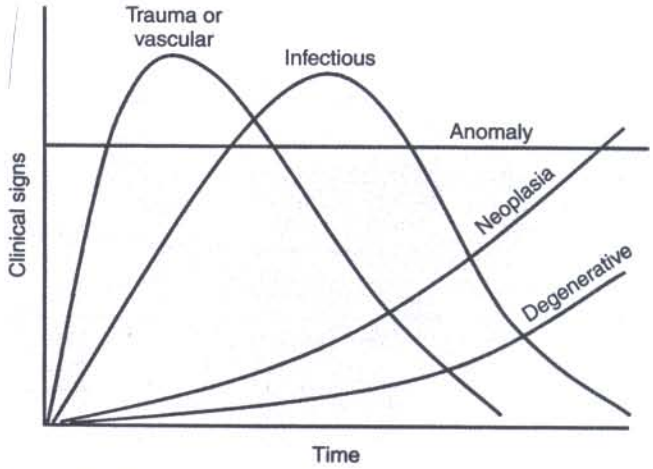


Figure 191-19 The progression of signs over time provides important clues to the underlying cause. A mental "sign-time graph" can help to categorize diseases. (From Lorenz M, Kornegay JN: *Handbook of veterinary neurology*, ed 4, Philadelphia, 2004, WB Saunders Co.)

DIAGNOSTIC APPROACH TO BRAIN DISEASE

When considering the diagnostic approach to diseases affecting the brain (Figure 191-20), the clinician must weigh cost, availability, risks, and potential yield. The value of a thorough history and neurologic examination should never be underestimated. Even if advanced imaging reveals a clear lesion, if that lesion does not correspond to the localization on the neurologic examination, its significance needs to be questioned.

Routine clinical pathology is the most readily available, most cost-effective, and least invasive procedure. Even though the yield may be low with focal disease, it is still an important minimum data base for any ill animal, and in cases with diffuse disease, ruling out a metabolic cause is essential. A complete blood count (CBC) may suggest infectious causes and provide clues to other causes. It is important to recognize, however, that a normal blood count does not rule out encephalitis as a cause. Serum biochemistry profile and urinalysis will be essential to rule out energy deficiencies, electrolyte disturbances, or accumulation of endogenous toxins. Particularly with diffuse forebrain signs or seizures, a liver function test such as bile acids or ammonia tolerance should be included. If inborn errors of metabolism are suspected, urine assays for abnormal metabolites may be necessary. Assays for specific exogenous toxins, such as lead or organophosphates, may be indicated if signs and history suggest likely candidates, but a screen for all possible neurotoxins is not feasible. Because neurologic signs can accompany endocrine diseases such as hypothyroidism and hyperadrenocorticism, endocrine function

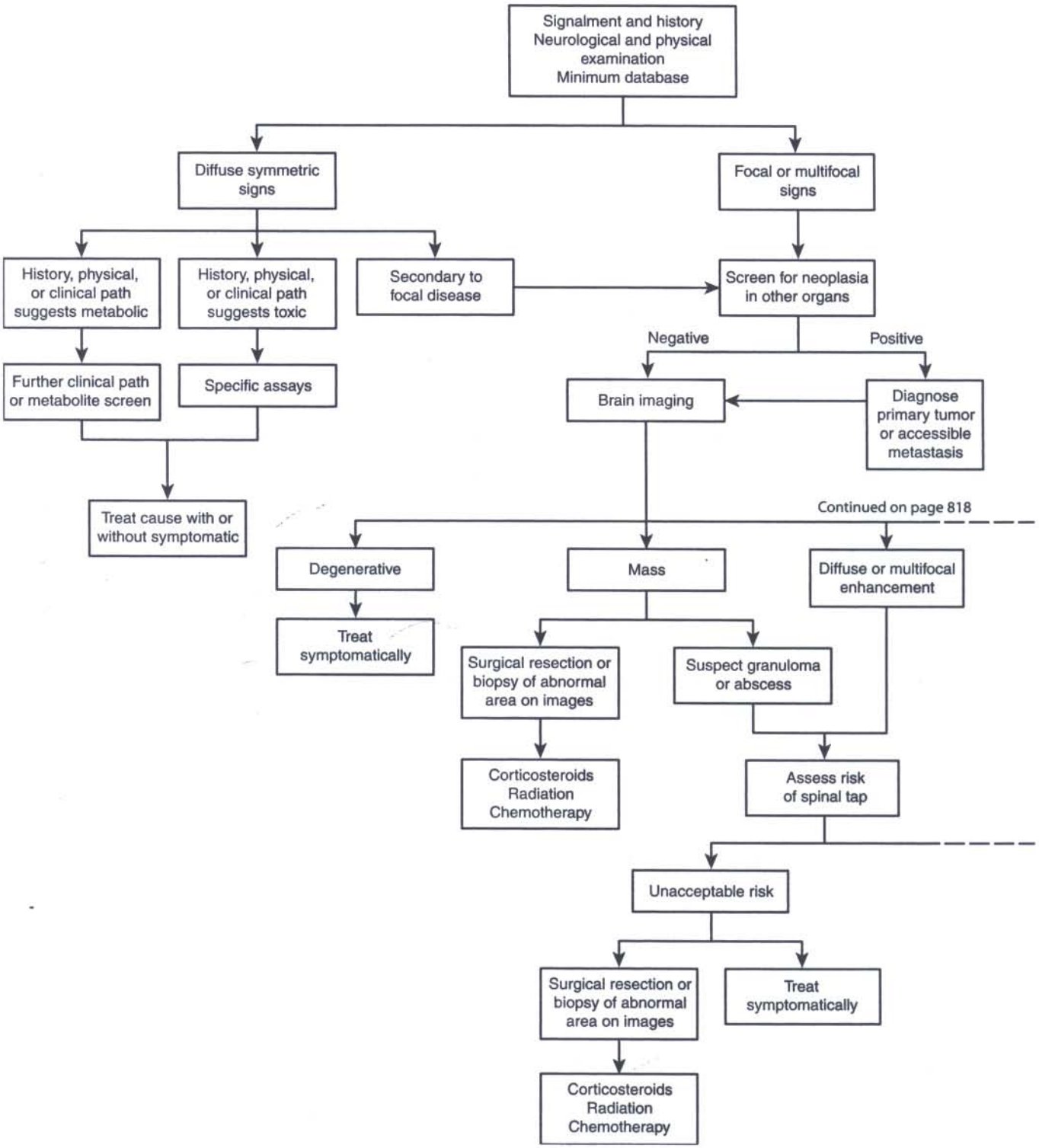


Figure 191-20 Diagnostic approach to brain disease.

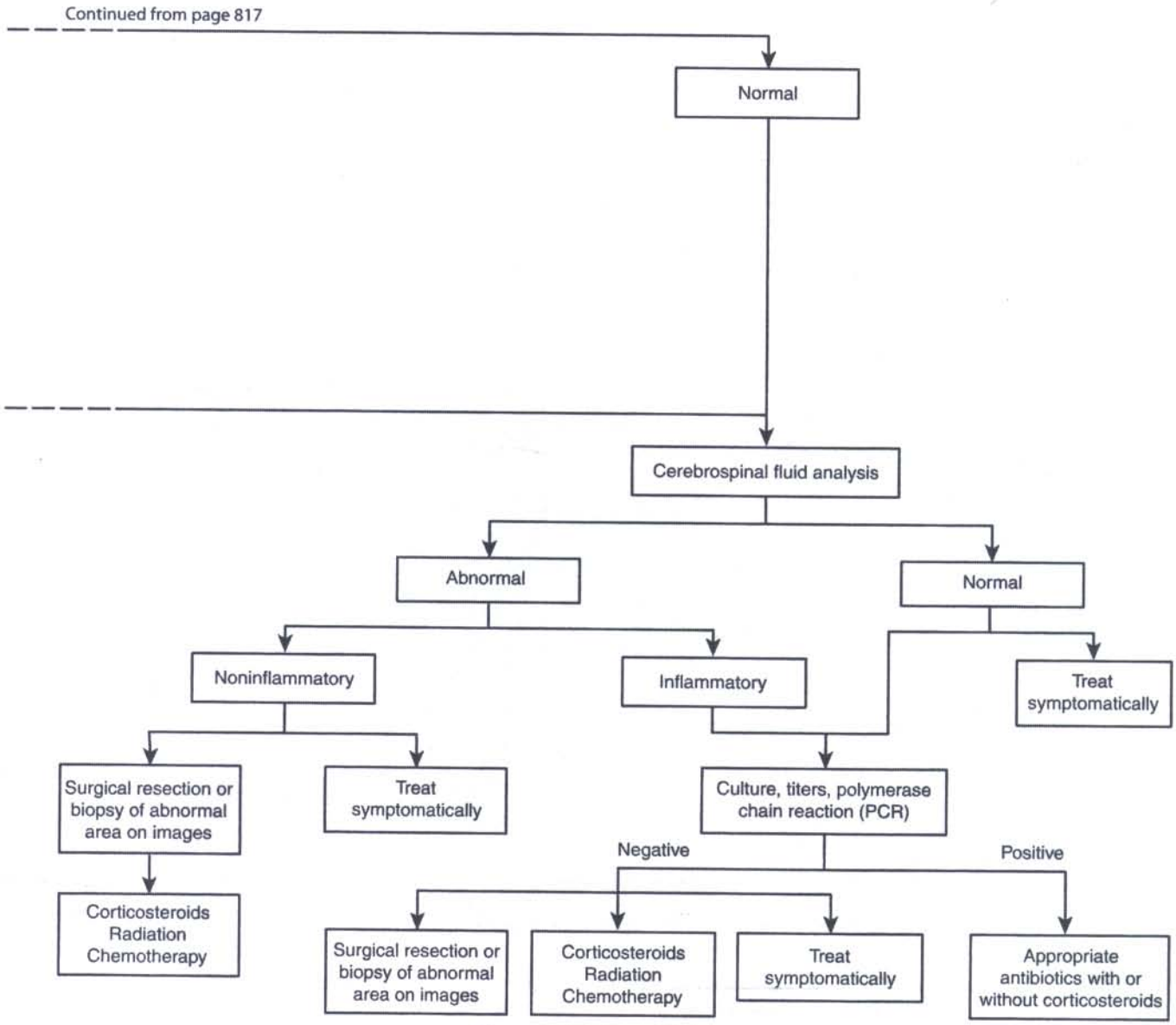


Figure 191-20—cont'd

tests should be considered if the clinical signs and signalment warrant. Thoracic and abdominal imaging will be important, particularly in geriatric animals, to rule out metastatic or cardiac disease.

The increasing availability of advanced brain imaging techniques for animals has revolutionized the practice of neurology. Although advanced imaging is expensive, the high return usually justifies the expense. Routine skull radiographs are of very limited value in diagnosing brain disease, because only the skull can be imaged without invasive contrast studies. The superimposition of the structures on radiographs makes interpretation difficult. Ultrasound imaging of the brain, although useful, is only an option when an open fontanelle or craniotomy provides an acoustic window.

Computed tomography (CT) and magnetic resonance imaging (MRI) allow detection of structural changes of the brain itself (Figure 191-21).[10,11] CT is more readily available and less expensive. CT relies on traditional radiographic principles; thus the image consists of similar graded densities, with bone being white and air black. The attenuation of the x-rays will be similar to that of the gamma rays used in radiation therapy, so CT images are used to calculate dose delivery. Only cross-sectional images are acquired, although computer reconstructions can generate sagittal or dorsal planes. CT has the advantage of being able to image bone, which is useful in diseases such as osteochondrosarcomas of the skull. The ventricular system is readily appreciated on CT, but fine anatomic detail is often not visible. Edema may be visible as a reduced density of the parenchyma, whereas other processes, such as acute hemorrhage or calcification, produce an increased density. CT resolution is limited by the attenuation of the x-rays by the surrounding skull. The petrosal bones at the base of the skull are dense, thus limiting the quality of CT images of the area below the tentorium.

MRI uses magnetic resonance of charged particles to generate radio waves that can then be detected and reconstructed into an image in any plane desired. The MRI unit generates a large magnetic field through the brain, which aligns charged particles with the field. It then conducts a sequence of radio wave pulses through the brain while a radio frequency detector listens for the echo from the interaction of those pulses with the charged particles and the magnetic field. The hydrogen ion (proton) generates a large portion of the radio wave signal in most MRI sequences, and because water contains a high proportion of free protons, the MRI can be thought of as imaging free water content. This is particularly useful in the nervous system, where marked differences exist in water density between gray matter, white matter, edema, and the ventricular system. In contrast, bone generates little signal. By altering the sequence used, different weight is given to the signals producing different contrasts between the tissues. In a T1-weighted image, water in the ventricular system is black and white matter is light, whereas in a T2-weighted image, the ventricles appear white and the white matter dark. Edema is readily apparent as an increase signal on T2 images. An in-between sequence (proton density) decreases the contrast between the ventricles and the brain, but increases contrast between gray and white matter, revealing fine anatomic detail. More advanced techniques such as FLAIR (fluid attenuated inversion recovery), MRI spectroscopy, and MRI angiography can also be useful for special applications. One disadvantage of MRI is that it cannot be used when metal implants are present.

For both CT and MRI, the initial evaluation is for differences in density and signal in the brain parenchyma, which may be readily apparent as asymmetry. Even without clear differences within the parenchyma, a mass effect may produce a shift of the midline structures or distortion of the ventricles. Contrast agents are available for both imaging modalities. After IV injection,

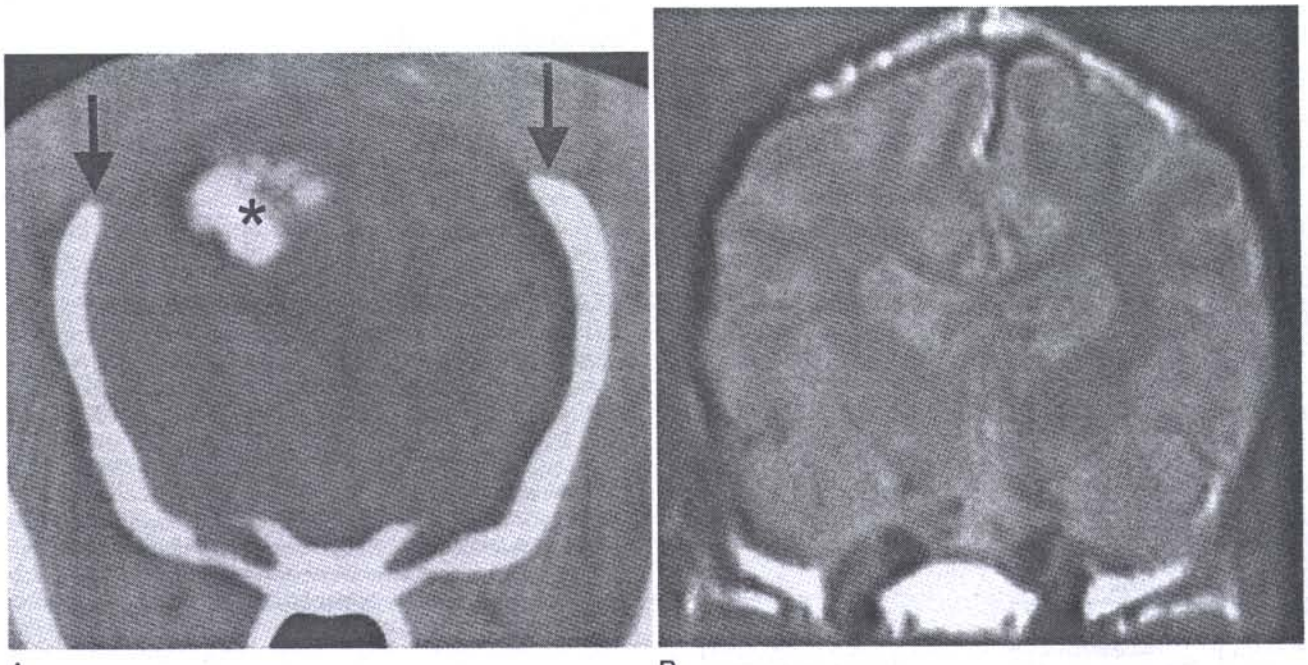


Figure 191-21 A, Computed tomography (CT) scans are more readily available and can image many intracranial diseases. Bone is readily visible as in this recurrent osteochondrosarcoma *(asterisk)* after a prior craniectomy *(arrows)*. B, Magnetic resonance image (MRI) provides much greater detail, especially in the caudal fossa. This proton density image of normal brain clearly delineates gray and white matter.

the blood-brain barrier would normally exclude such agents from the brain. Breakdown of this barrier by neoplasia or inflammation will result in accumulation and contrast enhancement of the lesion. Contrast enhancement is most apparent on the T1-weighted MRI.

Although advanced imaging may provide an unprecedented view of the nervous system, it still may not provide a definitive diagnosis. Brain biopsy is not commonly used as a diagnostic procedure in veterinary medicine, except when accompanying tumor resection. Imaging-guided biopsy techniques will decrease the morbidity associated with biopsy and increase the availability.

Because a mass lesion producing increased intracranial pressure significantly increases the risk of complications of a spinal tap, imaging should be recommended before performing the tap. The CSF is most useful in inflammatory disease but can provide clues to other diseases such as an increased protein with neoplasia. In some cases, such as cryptococcosis, the organism may be found in the CSF. More commonly, the CSF simply confirms inflammation in the central nervous system (CNS). Then auxiliary tests are necessary to make the definitive diagnosis. Cultures of the CSF are rarely positive, but the importance of ruling out a treatable condition warrants the expense if the CSF analysis, and signs are compatible with bacterial meningoencephalitis. Most infectious diseases will be identified by titers on the serum, CSF, or both. Although some titers such as the antigen titer for cryptococcosis are highly reliable, most are highly subjective. It is hoped that the increasing availability of PCR testing for infectious agents will relieve the problems clinicians have interpreting titers.

Electrodiagnostic tests allow functional testing of the nervous system. The electroencephalogram (EEG) is used primarily to confirm epileptic activity in the brain in suspected seizure cases. It is particularly useful in cases of status epilepticus to confirm that seizure activity has been stopped. The brainstem auditory evoke response (BAER) is used primarily to assess cochlear function, but can also assess brain stem conduction. Somatosensory and visual evoked potentials can assess function of these systems.

Response to therapy can be an important diagnostic tool, particularly when financial or other factors limit the diagnostic tests pursued. Therapy for the most likely treatable condition can be instituted and the response monitored. For example, dramatic improvement with doxycycline would support a presumption of rickettsial disease. Although corticosteroids play an important role in treating brain disease, the risks of side effects, including exacerbation of an infectious disease, need to be weighed carefully. Dramatic improvement with corticosteroids would be consistent with a neoplasia or infectious and inflammatory disease. Improvement with neoplasia is usually short-lived because it relieves the peritumoral edema but does nothing about the neoplasia. Some inflammatory disease may be kept in remission with prolonged treatment. Infectious diseases will also often respond dramatically to corticosteroids, only to worsen if appropriate antibiotics are not also instituted. Response to anticonvulsant drugs helps to confirm a seizure disorder but does not rule out an underlying cause to the seizures.

PRIMARY BRAIN DISEASES

The brain is the most metabolically demanding organ in the body. A large portion of the body's energy supply goes toward maintaining resting membrane potentials and neurotransmission. The nervous system has more limited energy metabolism pathways than other tissues; thus it is more sensitive to disturbances of glucose or oxygen supply. The brain is also quite sensitive to exogenous or endogenous toxins. The higher the level of function of a portion of the nervous system, the more sensitive it tends to be to metabolic insults. Thus forebrain signs are a common manifestation of systemic diseases. The brain can also be affected in disease processes such as infections, most of which are multifocal in nature (discussed in Chapter 192). This chapter will focus on diseases that primarily affect the brain and are not covered in other chapters. They are organized roughly by typical age of onset.

Congenital and Hereditary Diseases

Congenital refers to any disease or malformation present at birth. It encompasses both genetic conditions and the results of external influences during gestation such as toxins, malnutrition, birth trauma, or infections. If more than one individual in a family is affected, then the condition is familial. However, a familial disease does not necessarily have to be genetic, because families may share some things (e.g., diet, environment, infection exposure). Breed predilection for a disease suggests a genetic contribution, but again, could reflect other factors such as the typical use of a particular breed or supplements in vogue with those breeders. Multiple litters must be evaluated before any estimate of genetic contribution to a disease can be formulated. Many hereditary neurologic diseases will be congenital or at least apparent at an early age, but notable exceptions exist. Some lysosomal storage diseases require time for accumulation of byproducts. Animals with hereditary cerebellar ataxia (abiotrophy) may be normal clinically and histologically for a variable period of time and then develop clinical signs as the Purkinje cells undergo premature cell death. Finally some, like idiopathic epilepsy or ceroid lipofuscinosis (CL) will not show signs until early or even late adulthood.

Most hereditary disease will be due to autosomal recessive traits or have a complex inheritance, because dominant traits can be eliminated from a breed by simply not breeding affected dogs. The nervous system is especially sensitive to genetic disease. Many genes are expressed for brief periods to appropriately direct the complex development of the nervous system. Because few neurons are capable of reproducing after maturity, defective neurons cannot be replaced. Mutations that interfere with the ability of the cell to deal with insults such as oxidative stress can lead to accumulated damage and early onset of degeneration.

Congenital Malformations Congenital malformations of the brain would typically be present from birth and be nonprogressive. A few exceptions, such as congenital hydrocephalus, can manifest later in life with progressive signs. The nervous system originates from a plate on the dorsal surface of the embryo, which folds in to form the neural tube. This infolding begins in the thoracic area and extends rostrally and caudally. Genetic defects and in utero infection, toxins, or malnutrition may cause failure of normal closure of the neural tube, which is typically manifested at rostral or caudal end of the developing nervous system. These malformations can range in severity from complete failure of cerebral development (anencephaly) to clinically unapparent malformations such as agenesis of the corpus callosum. Typically the effects are most apparent in the midline structures. In some cases, concurrent malformation of overlying tissues allows protrusion of meningeal or brain tissue through the defect.[12] Severe malformations will be apparent on physical exam, whereas brain imaging or postmortem examination may be necessary to detect more subtle deficits. Brain anomalies may accompany other defects such as cleft palate or cardiac anomalies.

Once the neural tube has formed, differentiation of the various parts of the brain occurs and can be disrupted by similar genetic or environmental influences. Migration of neurons within the cerebral cortex leads to the characteristic sulci and gyri and the normal laminar arrangement of

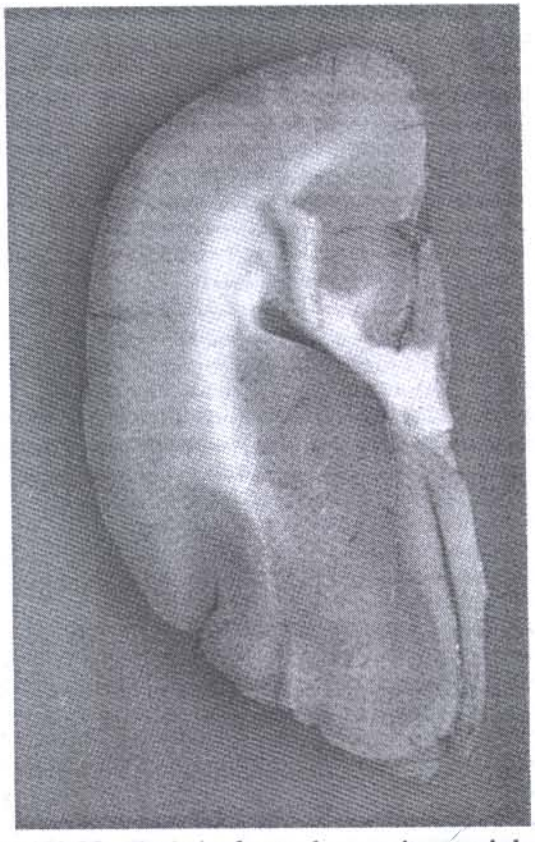


Figure 191-22 The lack of normal gyri in lissencephaly could be visualized with magnetic resonance imaging (MRI). Like most congenital anomalies, signs are present from birth and are static.

neurons within the cortex. In lissencephaly, this normal migration is disrupted (Figure 191-22). Some, or all, of the surface of the cortex is smooth and abnormally thickened (pachygyria), which can be visualized on MRI. In humans a variety of mutations have been associated with lissencephaly, and a genetic cause is suspected in dogs because it has been recognized primarily in Lhasa apsos.[12-14] Affected dogs showed behavioral changes, vision deficits, and seizures.[13,14] Excessive production of small gyri (polymicrogyria) has also been reported.[12] In other conditions the gross structure of the brain is normal, but the laminar arrangement of neurons and white matter within the cortex is disrupted, leading to abnormally placed nests or rows of neurons. Such dysplasia has been observed in the cerebellar cortex but was associated with severe motor problems, suggesting that more than cerebellar function was disrupted even though dysplasia was not apparent in other areas.[15]

Cerebellar hypoplasia is seen most commonly in cats after in utero or early neonatal infection with the feline panleukopenia virus. The rapidly multiplying granule cells of the cerebellum are sensitive to damage by the virus at this stage of development.[12] Although apparently much less common, evidence indicates that canine parvovirus infection can produce similar damage to the developing cerebellum of dogs.[16] Cerebellar hypoplasia can also occur as isolated malformation without evidence of infection or as part of a more generalized brain development abnormality. The Dandy-Walker syndrome of humans is characterized by agenesis of the cerebellar vermis. A similar malformation has been described in dogs and cats.[12]

For most congenital malformations, treatment is symptomatic and the prognosis will depend upon the severity of the neurologic deficits. History and serology can rule out toxic or infectious causes that may potentially be treatable. Genetic and nutritional counseling may help prevent future occurrences in breeding kennels.

Chiari-like Malformations Signs associated with abnormal conformation of the foramen magnum and cerebellar vermis were described as early as 1965 but were initially attributed to an enlargement of the dorsal aspect of the foramen (occipital dysplasia).[17,18] Subsequently it was demonstrated that a great deal of variation exists in the dorsal extent of the foramen magnum in normal dogs.[19] With the advent of MRI it became easier to image this area of the brain and spinal cord, and a malformation of the cerebellum similar to the Chiari type I malformation of humans was identified in the Cavalier King Charles spaniel, other dog breeds, and a cat.[20-22,22A] The Chiari type I malformation consists of an elongation of the caudal, ventral cerebellum through the foramen magnum, and in humans it is thought to be the result of small caudal fossa (the area caudal to the tentorium) crowding the enclosed structures. In addition to compressing the medulla, the herniated cerebellum obstructs normal outflow of CSF from the calvarium that can lead to secondary hydrocephalus. As the brain expands with each heart beat, the herniated cerebellum is forced caudally, generating pulsatile compression of the cervical spine. This leads to syringomyelia of the cervical spinal cord.[23] In addition to those referable to hydrocephalus and cerebellar compression, clinical signs include cervical myelopathy signs: ataxia, proprioception deficits, weakness, and cervical pain. The malformations appear to create paraesthesias, and excessive scratching of the ear, neck, or shoulder may be the major presenting complaint.[22]

The Chiari-like malformation also referred to as caudal occipital malformation syndrome,[22A] is readily diagnosed on a midsagittal MRI on which the herniation of the cerebellum and any concurrent hydrocephalus or syringomyelia can be visualized (Figure 191-23). Although some improvement can be achieved with antiinflammatory drugs and rest, definitive treatment consists of enlarging the foramen magnum via a suboccipital craniectomy and resecting any dural bands that are constricting the cerebellum. Sometimes the herniated portion of the cerebellum should be removed as well. With the improved CSF dynamics after such decompressive surgery, the hydrocephalus and syringomyelia may resolve.

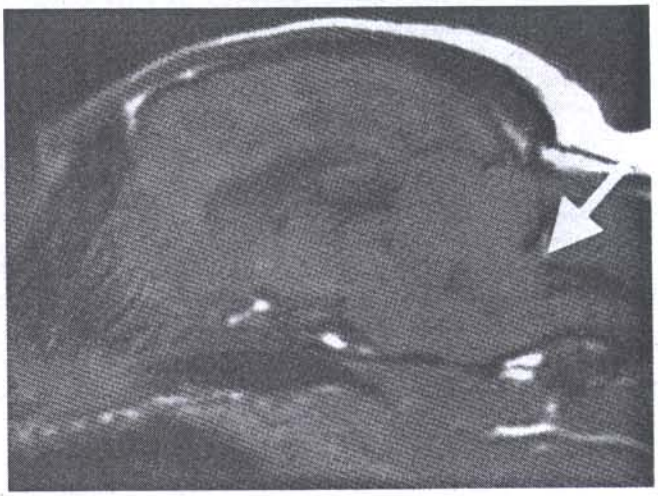


Figure 191-23 Midsagittal magnetic resonance image (MRI) of a Cavalier King Charles spaniel showing protrusion of the cerebellar vermis through the foramen magnum *(arrow)* similar to the Chiari type I malformation in humans.

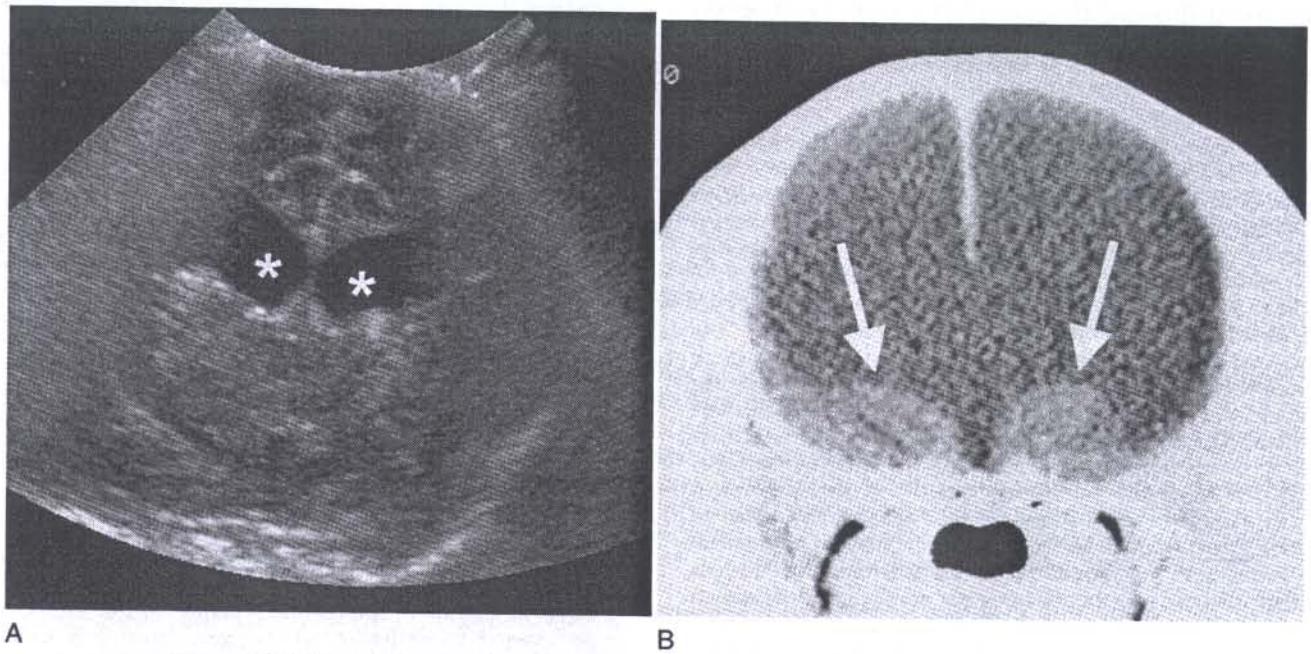
Hydrocephalus Hydrocephalus can be either congenital or acquired. It can also be categorized as either obstructive or communicating. Obstructive hydrocephalus occurs when a blockage occurs in the flow of CSF through the ventricular system. The obstruction typically occurs at the bottlenecks of CSF flow, the connection between the lateral ventricle and the third ventricle (the intraventricular foramen), or the connection between the third and fourth ventricle (the mesencephalic aqueduct). Obstruction of one intraventricular foramen will result in unilateral dilation of the lateral ventricle. With obstruction of the mesencephalic aqueduct, both lateral ventricles and the third ventricle will dilate. Obstructive hydrocephalus is acquired when a disease process such as neoplasia, hemorrhage, or inflammation occludes the pathway. In communicating hydrocephalus, no obstruction to flow is seen and all of the ventricular system dilates. Such diffuse dilation can be seen when absorption of CSF from the subarachnoid space into the venous drainage is impeded (e.g., by inflammation or neoplastic infiltrates in the meninges). The ventricles will also dilate in response to atrophy of surrounding brain tissue and is called *compensatory hydrocephalus* or *hydrocephalus ex vacuo*.

In spite of the fact that congenital hydrocephalus is common in some breeds, little published research exists on the condition in animals. It is occasionally seen in conjunction with other congenital problems such as Chiari-like malformations[22] or cerebellar ataxia in bull mastiffs,[24] but it most commonly occurs as an isolated finding. Toy and brachycephalic breeds appear to be at highest risk for the disease.[25] In some cases a congenital stenosis or aplasia of the mesencephalic aqueduct exists.[12] Neonatal infections, such as parainfluenza virus in dogs, can result in stenosis without leaving any indications of the cause once the initial ependymitis has resolved.[26] The strong breed predilection, however, suggests a hereditary basis in many of these dogs. Congenital hydrocephalus can lead to an enlarged calvarium and failure of normal closure of the suture lines of the skull. A small open fontanel is common in many toy breeds and does not necessarily indicate hydrocephalus.

Clinical signs of hydrocephalus include behavioral changes, ataxia, and seizures. A ventrolateral strabismus is common in congenital hydrocephalus, but it is not clear whether this is due to cranial nerve compromise or malformation of the skull. Lateralized signs such as circling will be evident with obstruction of the intraventricular foramen causing dilation of one lateral ventricle. Even in congenital cases, the disease may follow a waxing and waning course. Sometimes dramatic hydrocephalus may be present, and the owners report few clinical signs other than slowness to learn. Increased intracranial pressure can lead to tentorial herniation, particularly in acute, obstructive hydrocephalus.

The EEG may show a characteristic pattern of high-voltage synchronous activity, but imaging the dilated ventricles is necessary to confirm the diagnosis. If a large fontanel is present, the ventricles can often be adequately imaged with ultrasound. If not, then CT or MRI will be necessary to image the dilated ventricles and rule out obstructive disease (Figure 191-24). Normal ventricle size is 1.5 mm; anything exceeding 3.5 mm is considered to be characteristic of hydrocephalus.

The ideal treatment for hydrocephalus is to place a shunt into the dilated ventricle and drain the excess CSF into the peritoneal cavity. This may be indicated to relieve pressure even if a treatable condition is causing the hydrocephalus. A special valve is necessary to prevent excessive drainage of CSF (which could lead to collapse of the overlying cerebrum and subarachnoid hemorrhage) and to prevent pressure in the abdomen during coughing or exertion from being transmitted to the ventricles. Complications such as infection or occlusion of the shunt are common, and only a few centers perform this operation. Another mode of surgery is to enter the skull from above, open the third ventricle, and then fenestrate the floor of the third ventricle. This procedure allows drainage of



A B

Figure 191-24 A, Ultrasound can be used to image dilated ventricles *(asterisks)* if an open fontanel provides an acoustic window. B, Otherwise magnetic resonance imaging (MRI) or computed tomography (CT) scan is necessary. Some severe hydrocephalics may show minimal signs. The dog in B had minimal forebrain tissue left on CT scan *(arrows)*, yet the only complaint of the owners was irritability and polydipsia and polyuria. After a fall the dog developed adipsia and hypernatremia, which prompted referral.

CSF directly into the subarachnoid space and is less invasive. It is considered the treatment of choice for humans in most situations.

Medical management of hydrocephalus is largely symptomatic. Anticonvulsant drugs may be used to control seizures. Furosemide, corticosteroids, or both may help decrease intracranial pressure. Mannitol can be used in cases of acute decompensation, but the benefits are transient. Carbonic anhydrase inhibitors have been used to decrease CSF production but the side effect of acidosis limits their usefulness. Although medical therapy may ameliorate the signs, hydrocephalus tends to be a progressive disease.

Inborn Errors of Metabolism

Although some congenital diseases cause structural malformations of the nervous system, others interfere with function at a biochemical level or lead to premature death of neurons. Ultimately the hereditary disorders will be classified based on the gene or its product that is altered. Most such cases in veterinary medicine are classified according to the clinical presentation, pathologic changes, or both. For many, however, the clinical signs are relatively nonspecific. The clinician should have a high index of suspicion in young, purebred animals with diffuse, symmetrical signs of brain disease when toxic, routine metabolic and infectious causes have been ruled out. Breed tables can be consulted for specific diseases that have been reported.[6,7]

Some inborn errors of metabolism may be apparent on routine clinical pathology tests. Deficiencies in urea cycle enzymes will result in elevated blood ammonia, whereas ketonuria or acidosis, without a clear underlying cause like diabetes mellitus, may reflect errors in mitochondrial metabolism. If the error leads to the accumulation of an abnormal metabolite, that product can often be detected. Urine is the ideal sample to assay because the metabolite may be excreted into the urine in high concentrations, and sufficient volume of urine can be collected even in neonates. Simple urine screening tests are available for some inborn errors of metabolism, but most require testing at specialized labs. Serum or spinal fluid may need to be assayed for metabolites that are not excreted in the urine in detectable amounts. Others may require culturing fibroblasts and measuring specific enzyme activity.

Many inborn errors of metabolism will affect other organs that can be evaluated more readily than the brain. If peripheral nerve is involved, a nerve biopsy may yield clues such as the presence of vacuolated macrophages in globoid cell leukodystrophy (Figure 191-25). Occasionally such vacuolated cells may be visible on routine blood smears or CSF analysis. Because muscle also has a high metabolic demand, diseases affecting energy metabolism may show changes on muscle biopsy. If hepatomegaly or lymphadenopathy accompany neurologic signs, a biopsy of one of these more accessible organs may reveal storage products.[27,28]

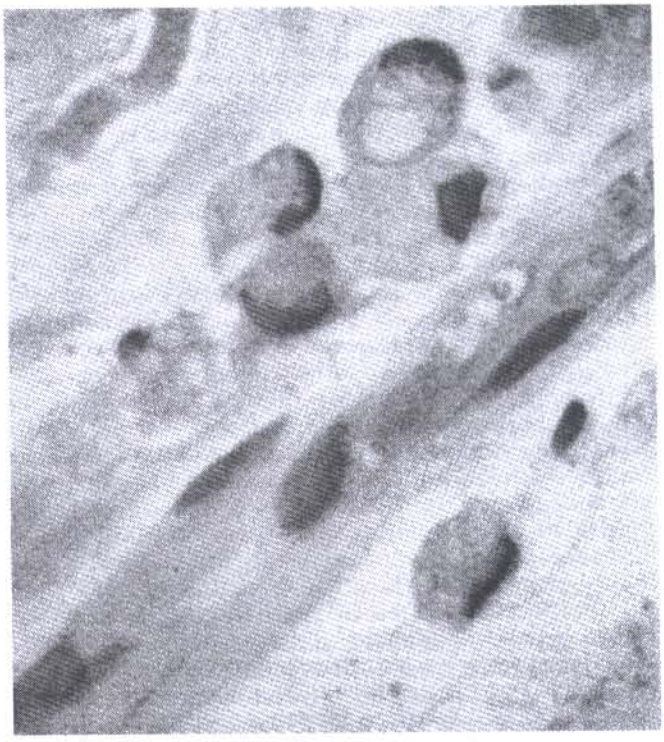


Figure 191-25 Evidence of inborn errors of metabolism can sometimes be found in more accessible tissues such as white blood cells (WBCs), liver, or peripheral nerve. Macrophages with lysosomal storage product in vacuoles (globoid cells) were found in this peripheral nerve of a Cairn terrier with globoid cell leukodystrophy.

Organic Acidurias These diseases are characterized by the presence of abnormal organic acids as the result of an error in the metabolic pathway. Although relatively few have been described in veterinary medicine, as a whole they are common diseases in humans and probably occur in purebred dogs with greater frequency than has been recognized. They can be diagnosed by urine organic acid screens and have the potential for therapeutic intervention if the deficient pathway can be bypassed.

Malonic acid levels in a cell regulate the switch between carbohydrates and fatty acids as an energy source in the fed versus fasted state respectively. A Maltese dog from a family with malonic aciduria developed seizures, stupor, hypoglycemia, acidosis, and ketonuria when it experienced a brief period of anorexia. Altering the diet to frequent feedings of a high-carbohydrate, low-fat diet eliminated the need to rely on fatty acids as an energy source and ameliorated the clinical signs.[29]

Cobalamin (vitamin B_{12}) is a necessary cofactor in the conversion of methylmalonyl-CoA to succinyl CoA, a significant step in gluconeogenesis. Cobalamin deficiency has been associated with elevated methylmalonic acid and ammonia, as well as hypoglycemia in a cat (presumably due to a deficiency of intrinsic factor necessary for absorption of B_{12}).[30] Dogs with congenital cobalamin deficiency present primarily with anemia and failure to thrive, although one case presented with seizures.[30A]

Abnormal increases of methylmalonic and malonic acid (and other intermediary metabolites) were found in the urine of a 12-week-old Labrador retriever pup with progressive neurologic signs. The pup was not ketoacidotic or hyperammonemic, and cobalamin levels were normal. Diffuse atrophy of the CNS was found at necropsy, but no specific metabolic defect was identified.[31]

Staffordshire terriers with L-2-hydroxyglutaric aciduria develop seizures, ataxia, and altered behavior between 6 months and 7 years of age. On T2-weighted MRI, dramatic hyperintensity was seen in the cerebral, cerebellar, thalamic, and brain stem gray matter.[32]

Spongiform Encephalopathies The spongiform encephalopathies compromise a heterogenous group of diseases that have in common spongiform change within the brain at necropsy.[33] Some lysosomal storage diseases (see following) may also be characterized by vacuolation of neurons, but in those cases the vacuoles are lysosomes distended with storage products. In the spongiform encephalopathies, vacuoles appear empty and, if intraneuronal, they are not membrane bound. They can be subdivided depending on whether the

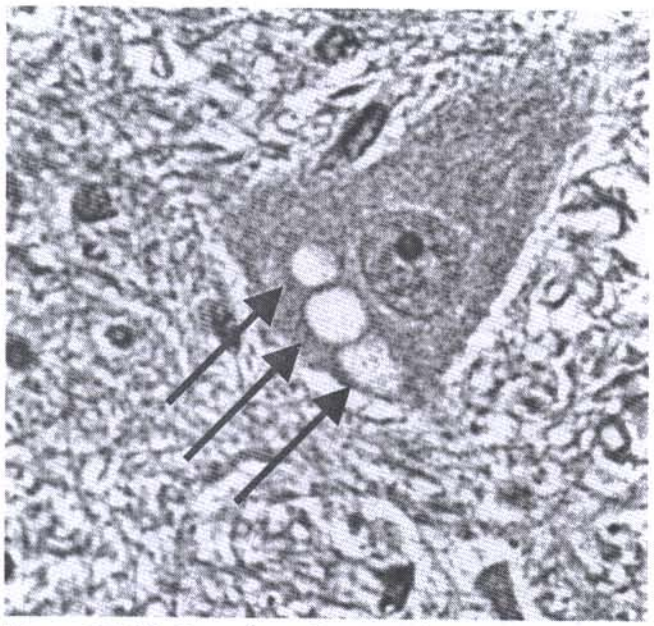


Figure 191-26 Spongiform change in the gray matter should arose suspicion of a transmissible spongiform encephalopathy (TSE), but such vacuolation *(arrows)* of neurons and their processes can be seen in hereditary diseases, such as hereditary spongiform encephalopathy in this rottweiler dog.

vacuolation occurs within the myelin sheaths in the white matter (discussed in Leukoencephalopathies) or in the gray matter within neurons or their process (Figure 191-26). The gray matter spongiform encephalopathies include both hereditary and acquired (transmissible) diseases.

Most researchers believe an enigmatic agent, the prion, causes transmissible spongiform encephalopathy (TSE). Scrapie was the first TSE to be described and, for a long time, these diseases were of little concern to small animal practitioners. The outbreak of the TSE bovine spongiform encephalopathy (BSE) in England, and the subsequent recognition that this disease may be spread to cats and humans by ingestion of meat products from affected cows, has made these diseases of more general interest.[34,35] The prion is unique in that it is not a nuclei acid-based organism but rather a rogue isoform of a protein (the prion protein). An alpha-helical isoform of the prion protein is found in normal neurons. The disease isoform (usually referred to as the *scrapie isoform*) of the protein forms a beta-sheetlike amyloid, which renders it resistant to degradation by proteases. These abnormal prions then accumulate in the neurons as scrapie-associated fibrils, interfere with cell function, and produce intraneuronal vacuolation. The scrapie isoform apparently propagates by inducing the normal cellular isoform to convert to the beta-sheet conformation. Exactly how this process occurs is still a matter of much research.[36] A long latency period characterizes the TSEs.

Cats affected with feline spongiform encephalopathy (FSE) show signs reminiscent of BSE: ataxia, behavioral changes, and hyperesthesia to touch or sound. At necropsy, the TSEs are characterized by vacuolation of nerve processes and to a lesser extent their cell bodies. In cats such lesions occur throughout the gray matter of the brain.[35] Although it is hoped that the control of BSE will mean that TSEs are no longer an issue for the small animal clinician, the potential exists for a similar outbreak in the future. Maintaining an index of suspicion will permit early recognition of the disease should it occur in dogs or cats.

Spongiform change in the gray matter also occurs in other diseases including rabies and hereditary disease. A hereditary spongiform encephalopathy has been recognized in rottweiler dogs. Beginning at 6 to 8 weeks of age, affected dogs develop progressive laryngeal paralysis, tetraparesis, and proprioception deficits most prominent in the pelvic limbs and cerebellar ataxia.[37] No abnormal prion proteins were detected in these dogs,[37] and no mutations were found in the gene for the prion protein.[37A]

A hereditary polioencephalomyelopathy of Australian cattle dogs appears to be an autosomal recessive trait. The first signs recognized in affected dogs were seizures beginning at less than 1 year of age. After a variable period of time, progressive ataxia, vestibular signs, and thoracic limb atrophy and muscle rigidity developed, ultimately resulting in recumbancy.[38,39] Symmetrical increased signal was apparent on T2-weighted MRI in the cerebellar, vestibular, and other brain stem nuclei.[39] At necropsy, degeneration of the ventral horn of the spinal cord and in the cerebellar and brain stem nuclei is seen. Within these areas, vacuolar degeneration occurs in the neuropil, astrocytes, and myelin. A mitochondrial defect in astrocytes is suspected.[38]

A litter of Malinois shepherd crosses with congenital generalized tremors has been reported with diffuse vacuolation of the gray matter,[40] and the bull mastiffs with hydrocephalus and cerebellar ataxia have spongiform change in the cerebellar nuclei.[24] Although such diseases are rare, it is important to differentiate them from the TSEs, which carry significant public health implications.

Polioencephalopathies Other conditions affect the gray matter without producing vacuolation. The selective involvement of gray matter suggests a metabolic deficit that creates a dysfunction in neurons or in some cases glia. The clinical signs of polioencephalopathies vary widely, but because neurons of the cerebral cortex are often affected, seizures and behavior changes are common, as are cerebellar ataxia and sensory or motor deficits. The hereditary movement disorders typically affect neurons of the cerebellum and motor nuclei but will be considered as a separate class of diseases because of the limited distribution of the lesions and hence clinical signs.

Because neurons have a high metabolic demand, they are particularly susceptible to disturbances of energy metabolism. Disorders of mitochondrial metabolism can thus produce polioencephalopathies. In human medicine, such encephalopathies can also be associated with pathology in the muscles, another cell with high-energy demands. Such an association has not been shown in any of the veterinary diseases to date. Two mitochondrial polioencephalopathies have been described in dogs. One English springer spaniel, at 16 months of age, had progressive ataxia, mild behavior changes, visual deficits, and vestibular signs. At necropsy, abnormal mitochondrial changes were associated with degeneration in the cerebellar and cerebral cortex, brain stem nuclei, and optic nerves (a nerve selectively affected in the human mitochondrial encephalopathy: Leber's optic neuropathy).[41] A suspected mitochondrial encephalopathy similar to Leigh's syndrome of humans was recognized in a family of Alaskan huskies that typically are less than 1 year of age when they exhibit an acute onset of ataxia, seizures, behavior changes, blindness, and facial sensation deficits. Dramatic cavitation was seen symmetrically in the gray matter of the thalamus that extended to a variable degree into the brain stem.[42] These lesions are clearly visible on MRI as high T2 signal.[43] The lesions are similar to those seen in acquired energy metabolism problems such as a deficiency of thiamine, a vital cofactor in the Krebs cycle.[44] The sudden onset of signs in huskies could reflect an incident where metabolic demand outpaced supply or susceptibility to an outside insult such as a low thiamine level. One severely affected dog improved dramatically with

supportive care that would support this hypothesis.[43] A similar condition has been reported in Yorkshire terriers.[45]

Chromatolysis refers to loss of Nissl bodies, the dense staining aggregates of ribosomes that give neurons their characteristic granular cytoplasm. Chromatolysis is most commonly seen in wallerian degeneration after destruction of an axon, but also occurs in hereditary diseases such as spinal muscular atrophy. A more diffuse multisystemic chromatolysis has been reported in Cairn terriers and Swedish Lapland pups. Affected pups develop progressive weakness, ataxia, head tremors, and cataleptic episodes.[12,46]

Neuroaxonal Dystrophy Swellings within the axons, called *spheroids*, characterize neuroaxonal dystrophies. They are thought to represent disorders of trafficking of cytoskeletal elements, which then accumulate in axons or synaptic terminals. Because longer axons have further to transport these elements, changes are often most prominent in the termination of the long proprioception tracts in brain stem nuclei. If peripheral nerve is involved, the disease can be diagnosed by nerve biopsy.

Neuroaxonal dystrophy has been reported in a variety of breeds including Chihuahua, collie, Jack Russell terrier, Papillon, and Siamese,[12,47-49] but it has been best characterized in a family of rottweilers. Affected dogs begin showing signs of hypermetria of the thoracic limbs at 1 year of age. Signs progressed over the next few years to include more pronounced dysmetria, truncal ataxia, intention tremors, menace deficits, nystagmus,[47,50] and laryngeal paralysis.[51] In a family of Scottish terriers, pups developed progressive tremors, ataxia, and paraparesis beginning at a much younger age (10 to 12 weeks). They differed from the neuroaxonal dystrophies previously described in that the axons were diffusely swollen rather than concentrated in spheroids.[52] Similar diffuse swelling of axons in the CNS is seen in giant axonal neuropathy where peripheral nerve signs predominate.

Leukoencephalopathies Leukoencephalopathies are diseases of myelin and thus affect predominantly the white matter. Such conditions typically produce cerebellar or long tract signs, although many variations exist. The spongiform encephalopathies that affect the white matter are often referred to as *spongy degenerations of the white matter* or *spongy leukodystrophies* to clearly differentiate them from the TSEs that affect primarily gray matter. In spongy degeneration of white matter, splitting of the myelin sheaths causes the vacuolation.[33] Other leukoencephalopathies disrupt myelin or axons without producing vacuolation and would be referred to as *leukodystrophies*. *Hypomyelinogenesis* refers to the conditions where myelin never forms normally. In dysmyelinogenesis, myelin formation is present but delayed or abnormal.[12] Many of the myelin diseases, such as the leukoencephalomyelopathy of rottweilers, are predominantly spinal cord diseases.[12]

Congenital disorders of myelin formation most commonly begin with generalized tremors and dysmetria noticeable from the first attempts at walking. In some breeds, such as the chow chow, improvement occurs with time, whereas others, such as the Springer spaniel, are permanently disabled. Typically, myelin throughout the CNS is affected; however, peripheral nerves are spared, so reflexes are normal or exaggerated. Both X-linked and autosomal recessive forms have been described, and mutations of one of the myelin proteins has been identified in the Springer spaniels.[12,53,54] Diagnosis is based on the typical clinical signs in a breed at risk and, if necessary, confirmed at necropsy.

Later age onset leukodystrophies have also been described in dogs. Alexander's disease (fibrinoid leukodystrophy)[12] has been reported as a sporadic occurrence in several breeds. They presented for progressive ataxia, weakness, and, in one case, seizures between 3 and 6 months of age. Perivascular accumulations of characteristic eosinophilic (Rosenthal's) fibers at necropsy permitted the definitive diagnosis.[12]

Spongy degeneration of the white matter similar to Canavan's disease of humans has been reported sporadically in a variety of breeds of dogs and cats.[12] Affected Labrador retrievers began showing signs at 4 to 6 months of age. Initial signs were episodes of extensor rigidity and dorsiflexion of the neck with retained consciousness. These were followed by progressive dysmetria, intention tremors, tetraparesis, hyperreflexia, and spasticity. Behavior, autonomic, and sensory functions remained normal. At necropsy, splitting of the myelin resulted in vacuolation of the whiter matter throughout the brain and to lesser extent the spinal cord (Figure 191-27).[55,56] In the familial

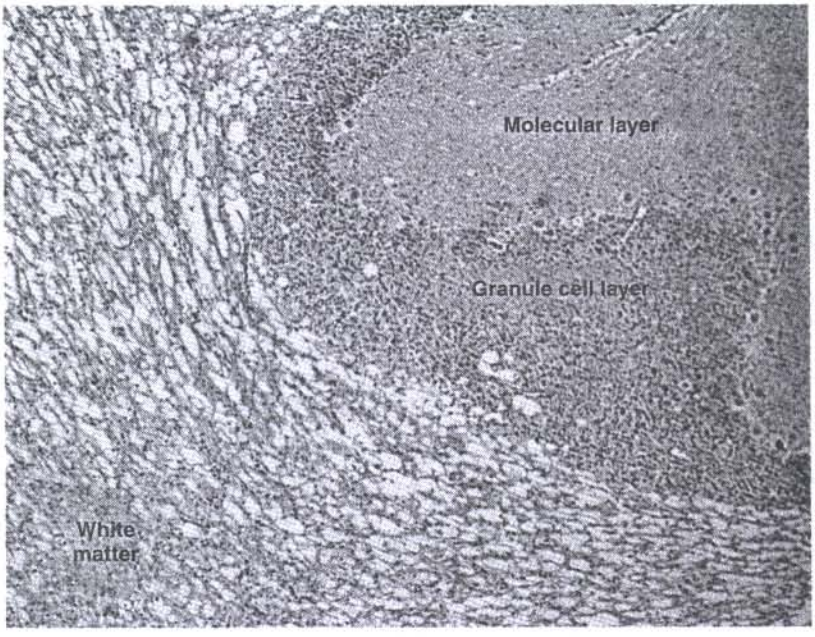


Figure 191-27 In spongy degeneration of white matter, the myelin lamellae are separated, producing vacuolation primarily within the white matter, such as in this section of the cerebellum.

spongiform leukodystrophy described in Shetland sheepdogs, the clinical signs began at less than 3 weeks of age and included progressive seizures, weakness, lethargy, and dysphagia. Spongiform degeneration was most prominent in the cerebellum and corona radiata. Biochemical screening tests in the sheepdogs failed to identify any of the abnormal organic acids or amino acids associated with spongy degeneration in people or cattle.[57]

Lysosomal Storage Disease Storage diseases are characterized by an accumulation of metabolic byproducts within lysosomes. Lysosomes are cellular organelles responsible for breaking down complex macromolecules. This compartmentalization allows for a more acidic pH within the lysosome and protects the rest of the cell from digestion. The substrates for catabolism within lysosomes include sphingolipids (a major component of myelin), oligosaccharides, mucopolysaccharides, glycoproteins, and proteins. The storage diseases are typically caused by a deficiency in a key enzyme in the breakdown of one of these molecules, and without the enzyme the substrate accumulates within the lysosome. The syndromes are usually named for the accumulated product. Proteases are less substrate specific, thus a deficiency in a single enzyme is less likely to produce problems. As a result, disorders of protein catabolism are uncommon, although CL may represent such a defect.[27,28,58] Alternatively the defect can interfere with cell's ability to use a normal enzyme. In I-cell disease (mucolipidosis) of cats, for example, the disorder appears to be one of trafficking of the enzymes into the lysosome. As a result, multiple enzymes are affected.[59] Recent reviews of the storage diseases in animals have been published and should be consulted for details on the individual syndromes in different breeds.[27,28,58] Some drugs and toxins, such as locoweed, can interfere with the activity of these enzymes, producing similar clinical signs and histologic lesions; however, this has not been documented in small animals.[27]

Accumulation of the storage product takes time; thus most storage diseases have a delayed onset of signs even though the enzyme has been deficient from birth. The age of onset and severity can depend upon how much residual function is left in the altered enzyme. Many of the storage diseases affect multiple organs, whereas others, such as those affecting degradation of myelin, only affect the nervous system. How the accumulated storage product produces neurologic disease is not always clear. In globoid cell leukodystrophy, one of the storage products is clearly toxic to oligodendroglia. In others, spheroid formation may be related to neuronal death.[27,28,60]

Cerebellar signs of dysmetria, truncal ataxia, and nystagmus are often the first signs of storage diseases.[28] The cerebellum is dependant on fast conduction to get sensory feedback during execution of a movement, and complex integration of sensory and motor information is necessary. Thus the cerebellum is sensitive to disorders affecting myelin or information processing. In addition, even subtle cerebellar deficits may be recognized, whereas more profound learning or mentation deficits may be necessary to reach a threshold of recognition. Signs often progress to weakness, behavior abnormalities, and seizures.[28] In some diseases, such as CL (see following), forebrain signs will be the earliest signs.[61] Peripheral nerves are involved in some conditions such as globoid cell leukodystrophy. Few imaging studies have been performed on the brains of animals with storage disease. In dogs with globoid cell leukodystrophy, increased signal intensity in white matter has been shown on T2-weighted MRI.[62] Cats with alpha-mannosidosis also show white matter changes on MRI.[63]

In some lysosomal storage diseases, signs of other organ involvement may be apparent. Ocular abnormalities can include visible changes in the retina or cataract formation. Skeletal or facial malformations are especially prominent in the mucopolysaccharidoses and may be apparent on radiographs. Cardiac, hepatic, splenic, or lymph node enlargement may accompany the neurologic signs.

Storage vacuoles may be apparent in white cells on a peripheral blood smear or, in the case of globoid cell leukodystrophy or fucosidosis, on CSF analysis. Alternatively, lymphoid tissue can be examined via biopsy of the spleen or lymph node. If the liver is enlarged, aspirate or biopsy may also reveal storage vacuoles. When peripheral nerve is involved, biopsy of the nerve may reveal vacuolated mononuclear cells. Muscle biopsy will be most useful when glycogen storage disease is suspected. Necropsy may be necessary to demonstrate storage product when only the nervous system is involved. Electron microscopy can demonstrate that the storage material is contained within lysosomes. Abnormal metabolites may be detectable in urine with some of the storage diseases. Definitive diagnosis depends upon demonstration of deficient enzyme activity in serum, leukocytes, or cultured fibroblasts.

Ceroid Lipofuscinosis Although a lysosomal storage disease, CL differs from the other diseases in that the storage products are proteins. These products have a characteristic autofluorescence similar to ceroid and lipofuscin, pigments that accumulate normally with aging. Although named for this similarity, ceroid and lipofuscin are not found in any appreciable amounts in these diseases. Among the known storage products in CL are subunit c of mitochondrial adenosine triphosphate (ATP) synthase and sphingolipid activator proteins (saposins) A and D.[64] The enzymes responsible (saposin A and D) have been identified in humans and sheep, respectively.[65] In addition to lysosomes, evidence exists that these enzymes may be involved in mitochondrial and synaptic functions, which may explain some of the neuropathology seen.[65,66]

The original classification of CL was based on age of onset and rapidity of progression. As discussed previously, this is probably more of a reflection of the degree of residual enzyme activity than differences in enzymes responsible. Nonetheless, because purebred dogs usually have a single mutation responsible for a genetic disease, there will be consistency between individuals within a breed, making such classifications useful. The earliest reported onset of signs in CL (<6 months of age) has been reported in a cat and in dalmatians, but affected dogs can live up to 7 to 8 years.[61,67] English setters, border collies, and other breeds have an early adult onset (about 1 year of age), acute disease, and die by 2 years of age.[61] The Tibetan terrier is the best characterized breed with adult onset, slowly progressive disease. Signs of visual impairment begin at 2 to 3 years of age, and behavior changes do not become apparent until 4 to 6 years of age.[61]

Diminished vision is usually the first sign of CL. This can be especially noticeable in dim-light situations. Behavior changes are prominent in the disease and include timidness, hyperesthesia, confusion, and unprovoked aggression. Seizures, jaw chomping, bruxism, and myoclonus are also reported. Ataxia and hypermetria are also reported but tend to be later manifestations in many breeds.[61] Brain atrophy and dilation of the ventricles can be seen on CT scan in later stages of the disease,[68,69] but definitive diagnosis relies upon identification of the characteristic autofluorescent material in the brain or other tissues.

Currently no effective therapy exists for any of the storage diseases. Gene therapy holds the promise of restoring function to affected individuals, but cost will limit its application to veterinary medicine. DNA testing is already available for some diseases and will become more readily available in the future. This will permit breeders to make informed decisions that are likely to decrease the incidence of some diseases in the future. Symptomatic therapy such as anticonvulsants and behavior-altering drugs can help ameliorate some of the symptoms.

Movement Disorders

Most of the movement disorders that are recognized in veterinary medicine are hereditary diseases, although acquired conditions are beginning to be characterized. The hereditary ataxias encompass a heterogeneous group of diseases. As with other hereditary diseases, these will ultimately be classified based on the gene responsible and its product. However, even then, signalment and clinical signs will be the initial clues that direct clinicians toward those answers. The most common movement disorders in animals are the cerebellar disorders, although in some breeds other motor systems are affected.[12,70]

Hereditary Cerebellar Ataxia The cerebellar ataxias can be divided into neonatal, early, and delayed onset.[70] Many neonatal conditions are associated with gross malformations of the cerebellum (discussed previously). In certain breeds with neonatal onset ataxia, such as beagles and Samoyeds, the loss of Purkinje cells is similar to that seen in later age onset conditions.[12] Others, such as neonatal ataxia in Coton de Tulear dogs, show minimal histologic changes and are presumably a biochemical dysfunction.[71]

Other hereditary ataxias are characterized by a variable period of normal development followed by progressive cerebellar ataxia as specific populations of neurons die prematurely. The age of onset of signs can vary from weaning age (e.g., English pointers, Kerry blue terriers)[72,73] to adulthood (e.g., Gordon setters, Old English sheepdogs)[74,75] to later life (e.g., Brittany spaniels).[76] This process is sometimes referred to as *abiotrophy*, based on the original hypothesis that lack of a trophic substance was responsible for the degeneration. The term is now used to emphasize the fact that these diseases have a delayed onset of degeneration and clinical signs.[12,70] The specific genetic deficit responsible has yet to be identified in any of these diseases in dogs or cats. Most are autosomal recessive, although the ataxia in English pointers is X linked.[73]

In most of these delayed onset ataxias of dogs and cats, the Purkinje cells of the cerebellum degenerate. Because the Purkinje cell is the sole efferent from the cerebellar cortex, degeneration results in a loss of cerebellar function. In addition to the period of normal function, clinicians can tell that the Purkinje cells formed and then degenerated by the presence of "empty baskets." Basket cells are interneurons that form a dense meshwork of dendrites around the Purkinje cell body. When the Purkinje cells degenerate, these empty baskets of dendrites remain, but they would not form if the Purkinje cell body had not been there initially.

Although Purkinje cell degeneration is the most common type of degeneration described, other parts of the cerebellum can be affected. In Jack Russell terriers, the granule cell layer is primarily affected.[76A] In beagles both cell types are affected.[77] In bull mastiffs, the cerebellar roof nuclei along with some brain stem nuclei undergo spongiform degeneration.[24]

Hereditary cerebellar ataxia should be suspected when a breed at risk or other young, purebred dog develops progressive cerebellar ataxia. Atrophy of the cerebellum may be apparent on MRI of the brain (Figure 191-28). CSF analysis may be helpful in ruling out infectious and inflammatory causes, but histologic examination may be necessary to determine the character of the lesion. The severity of signs varies a great deal. Some dogs and cats with pure cerebellar cortical degeneration have only mild to moderate ataxia and may be able to live with their disabilities. Ensuring against injury due to falls is the most pressing management concern. Feeding difficulties may require the use of a high-calorie food to maintain weight. In other cases the degree of ataxia may be severe enough to warrant euthanasia.

Multiple System Degeneration The basal ganglia, such as the caudate nucleus and substantia nigra, are also important in movement and are affected in Huntington's and Parkinson's disease in humans. When the cerebellum and basal ganglia are involved, these conditions are referred to as *multiple systems degenerations*. The best-characterized syndrome of this type in animals is the disease of Kerry blue terriers and Chinese crested dogs called *progressive neuronal abiotrophy* (PNA) by breeders. In these breeds, cerebellar ataxia begins at 8 to 12 weeks of age, but is followed at 6 to 12 months of age by degeneration of the basal ganglia.[72,78] As the basal ganglia degenerate, affected dogs have increasing difficulty initiating movements and maintaining balance. This results in a festinating locomotion in which the dog begins to lose balance and then runs in that direction to keep from falling (Figure 191-29). The degeneration of the basal ganglia is visible on MRI as an increased T2 signal. The severe motor difficulties associated with these conditions necessitate euthanasia by 1 to 2 years of age.

Dyskinesias and Dystonias *Dyskinesia* is a general term for a disorder of movement usually characterized by involuntary, stereotyped movements caused by disease affecting the basal ganglia (extrapyramidal) motor systems or their neurotransmitters. In human medicine, dyskinesias are classified based on the character of the movements. *Chorea* refers to arrhythmic, rapid, jerky movements, which are more sustained

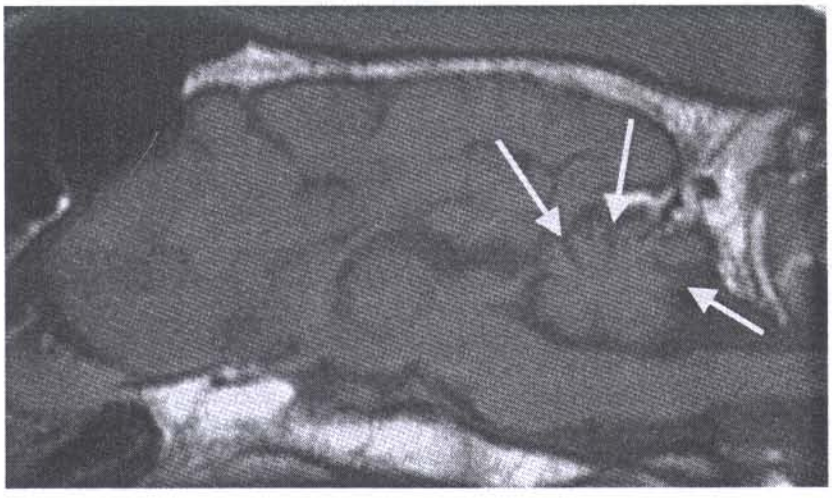


Figure 191-28 In the hereditary ataxias, atrophy of the cerebellar cortex *(arrows)* may be apparent as shrinkage and flattening of the cerebellum with an increased space between the folia.

Figure 191-29 As Chinese crested dogs with multiple system degeneration progress from cerebellar ataxia to basal ganglia degeneration, they develop difficulty initiating movements. They may shift weight forward until they begin to fall, and then they are able to move forward.

than the brief jerks of myoclonus. The rhythmic jerking associated with canine distemper has been called *chorea* in the past but is actually a myoclonus. When chorea affects proximal muscles producing flinging movements of the limbs, they are called *ballismus*. *Athetosis* describes slower, flowing movements. *Dyskinesias* can involve the entire body or be limited to one side or to the face. *Dystonia* refers to a sustained abnormal contraction often producing abnormal posturing or torticollis.

Such movement disorders have not been well documented in animals. In part, this may reflect a difference in the rolls of the cortical (pyramidal) and basal ganglia (extrapyramidal) motor systems in primates versus quadrupeds. More likely it is simply a failure to recognize movement disorders. Some idiopathic head tremors (see following discussion) may well represent basal ganglia disease. Oral-facial dyskinesias in animals have been observed that undoubtedly represent movement disorders. Increased availability of MRI will allow recognition of structural lesions of the basal ganglia. For example, infarcts of the basal ganglia have been identified in dogs with acute torticollis.[79]

Paroxysmal Dyskinesias Seizures are by far the most common neurologic disorder that occurs as discrete episodes of involuntary movement, and they are discussed in detail (see Chapter 48). Reports exist of paroxysmal abnormal movements in dogs that do not appear to be seizures. Episodic ataxia and paroxysmal dyskinesia are two examples of human diseases that occur in episodes but do not have the EEG changes that define seizure disorders. Generalized seizures are distinguished by a loss of consciousness, but in focal motor seizures, consciousness may not be impaired. Thus distinguishing between a focal seizure and a paroxysmal dyskinesia can be difficult without an EEG recording during an episode. The character of the movement in paroxysmal dyskinesias tends to be different from that observed with seizures. Focal motor seizures frequently produce an erratic twitching of one side of the face and may progress to affect the limbs on the same side. This reflects the origin of the seizure in the area with largest representation in the motor cortex of the dog followed by spread of seizure activity in that hemisphere. The movements in paroxysmal dyskinesias are more of the character of a dyskinesia or dystonia. In addition, the episodes may last much longer than the 2 minutes typical of most seizures and may be precipitated by excitement or exercise.

Scotty cramp is a condition of Scottish terriers characterized by episodes of rigidity with excitement or exercise. Affected dogs develop limb rigidity, which can result in recumbency in severely affected dogs.[80] The cause of the muscle hypertonicity is not clear, but a central motor problem is suspected. Serotonin antagonists will worsen the attacks, whereas alpha noradrenergic blocking drugs and benzodiazepines are reported to help alleviate the episodes. An autosomal recessive inheritance is suspected. Similar signs have been reported in dalmatians and a Shetland sheepdog.

A movement disorder characterized by episodes of flexion of the limbs has been described in adult Bichon frises. Affected dogs develop a kyphotic stance and alternately flex various limbs. This flexion is not limited to one side of the body and appears to affect pelvic limbs or thoracic limbs randomly rather than in set progression. These episodes resemble root signature seen with intervertebral disk disease. The dogs are not in pain, however, and herniated disks are not found on myelography. Facial grimacing also occurs.[81] Similar episodes have been described in two litters of young boxers.[82] Chinook dogs have a familial disorder characterized by prolonged episodes of inability to stand with dystonic posturing and sometimes rhythmic limb or tongue movements. Whether these episodes are focal seizures, a paroxysmal dyskinesia, or some other disorder is still not clear. Dancing Doberman disease is characterized by alternating flexion and extension of the pelvic limbs, resulting in the dog "dancing" from one foot to the other. It is thought to be a peripheral neuropathy, however, rather than a central movement disorder.[83]

Tremors Fine, fast tremors (enhanced physiologic tremors) are common with a wide variety of conditions such as weakness, fatigue, fear, pain, hypoglycemia, pheochromocytoma, hyperthyroidism, and certain drugs or toxins such as pyrethrins or caffeine. Benign tremors are common in older animals, particularly in the hind limbs. Beta-blocking drugs can ameliorate physiologic tremor, but usually the tremor does not interfere with the animal's function. The major concern is ruling out treatable underlying causes of the tremor.

An idiopathic tremor syndrome was first reported in Maltese and West Highland white terriers and called *little white shakers* syndrome.[84-86] Although these breeds appear to have a predilection of the disease, a wide variety of breeds have been reported with the disease[84,87]; *idiopathic tremors* is a more appropriate name for the condition. Most affected dogs are young adults (6 months to 5 years of age) with an acute onset of tremors. The tremors affect the entire body, including the eye, and vary from mild to severe enough to interfere with the dog's ability to stand or walk. They are exacerbated by excitement or movement and disappear at rest (intention tremors). Other signs such as absent menace response, ataxia, head tilt, or paresis may accompany the tremors. CSF analysis typically includes mild lymphocytic and monocytic pleocytosis, and a few dogs that have been necropsied have shown mild inflammatory changes on histopathology.[12,86,87] Most dogs respond very well to immunosuppressive doses of corticosteroids for 1 to 3 weeks, though relapses can occur. Benzodiazepines or propranolol may help relieve the tremors.[85-87]

A syndrome of head tremors is seen in some breeds. Doberman pinschers sometimes develop a head tremor after administration of droperidol when that drug was used in an injectable neuroleptic and analgesic combination that is no longer marketed. Because droperidol is a dopamine antagonist, the assumption was that the head tremor was akin to the tremors

in human patients with Parkinson's disease. Occasionally, isolated head tremors are seen without any history of intoxication in Doberman pinschers, boxers, bulldogs, and Shetland sheepdogs. The exact cause of the tremors is not known. Often they are discrete episodes, which could represent a focal motor seizure, but response to the anticonvulsant drugs has been variable. Generally they appear to be benign.

Encephalitis

Encephalitis refers to an inflammation of the brain. Most infectious or inflammatory diseases of the nervous system involve the spinal cord and the brain, producing multifocal disease (discussed in Chapter 192). Potential causes include viral, bacterial, rickettsial, protozoal, fungal, and parasitic. A few diseases affect the brain almost exclusively. Encephalitis is typically an acute disease, but in some cases, such as canine distemper or FIV, can be chronic and insidious. Some infections can be quite focal, and signs will reflect the area of the brain affected; however, others will produce more diffuse signs. Altered mentation with focal facial muscle twitching, seizures, or both is a typical presentation. If the meninges are involved, pain may be a prominent feature. Signs of systemic illness may or may not be present. CSF analysis can confirm inflammation, but prior treatment with corticosteroids may mask any CSF changes. With a few exceptions such as cryptococcosis, organisms are rarely seen or cultured in CSF and titers or PCR testing is necessary to identify the cause.

Because results of culture or titers may be delayed, symptomatic therapy is usually instituted when encephalitis is suspected based on signs or CSF results. Corticosteroids are usually indicated in acute encephalitis to decrease inflammation and the attendant morbidity. Immunosuppression can lead to subsequent worsening of the condition, however, if the underlying cause is not identified and treated appropriately. CSF analysis should be completed before corticosteroids are administered, but the pet should not be sacrificed for the sake of a definitive diagnosis.

Appropriate antibiotics are instituted based on the most probable organism. The choice of antibiotics is influenced by disease prevalence in an area, evidence from physical exam or clinical pathology, and ability to penetrate the blood brain barrier in significant concentrations. During tick season in endemic areas, doxycycline can be administered to treat rickettsial disease, especially if other signs, such as thrombocytopenia or polyarthritis, are present. Clindamycin or potentiated sulfonamides can be used if protozoal infection is suspected. Trimethoprim-sulfonamide and enrofloxacin are bactericidal, broad-spectrum antibiotics that have good to fair blood-brain barrier penetration respectively. They can be used if bacterial infection, such as spread from an otitis media or septicemia, is suspected. If better activity against anaerobes were needed, metronidazole and clindamycin would be logical choices. In areas where coccidiomycosis is endemic or if cryptococcosis is suspected, antifungals may be necessary.

Viral Encephalitis Though rabies is uncommon in dogs and cats, the public health risk requires that it always be considered in the differentials for unvaccinated animals with brain disease. If the virus gains entry through a wound on the limbs, rabies may affect the spinal cord, producing an ascending LMN paralysis prior to brain signs. Commonly, however, the bite occurs on the face, and the signs will reflect cranial nerve and forebrain involvement. For the first few days after infection there may be a fever, pruritus of the bite site, and anxious or irritable behavior. Progression and signs of the disease are quite variable, with considerable overlap between the two general forms of the disease. In the paralytic or dumb form of rabies, LMN paralysis of cranial nerves can produce a dropped jaw, dysphagia, laryngeal paralysis, and voice change. Signs progress over days to coma and respiratory arrest. The furious form consists of the classic behavior changes of rabies. Animals become hyperesthetic, irritable, and restless. They may be photophobic and hide or avoid contact with people. They may attack inanimate objects such as their cage and pica is common. As signs progress, ataxia, disorientation, and generalized seizures develop. The animal may develop a brief paralytic stage before death.[88]

A herpes virus causes pseudorabies (Aujeszky's disease). Dogs and cats typically acquire the infection from eating tissue from infected pigs. It produces a fulminate encephalitis characterized by dementia, seizures, and intense pruritus, often to the point of self-mutilation. No effective treatment is available; affected animals typically die within 48 hours, although cats may be more resistant to the infection.[88]

Increasing evidence suggests that feline immunodeficiency virus (FIV) infection can cause an encephalopathy not related to secondary infection. Affected cats develop progressive, symmetrical forebrain signs including depression, restlessness, learning and memory deficits, and mild coordination difficulties.[89] Diagnosis is based on serology and compatible clinical signs. Encephalitis due to a secondary infection such as toxoplasmosis needs to be ruled out or treated appropriately. Drugs used in treating acquired immunodeficiency syndrome (AIDS) in humans may prove useful in FIV infected cats, but currently the prognosis is poor.

Encephalitis of Unknown Cause Pug encephalitis is a necrotizing meningoencephalitis that affects young adult pug dogs.[90] Affected dogs typically develop an acute onset of seizures and other forebrain signs. Maltese and Yorkshire terriers develop a similar encephalitis, although brain stem involvement is more common in the Yorkshires. CSF analysis shows a lymphocytic pleocytosis. Histologically, asymmetrical necrosis and inflammation exists that affects both gray and white matter.[12] The cause is unknown. Immunosuppressive therapy may slow the course of the disease. Many affected dogs die within days of the onset of signs, though some may survive for months.

Granulomatous meningoencephalomyelitis (GME) can affect the spinal cord, but primarily causes encephalitis. Affected dogs tend to be young adults but any age may be affected. Onset of signs is typically acute. CSF typically shows a marked elevation in white cells (lymphocytes and monocytes) and protein, but may be unremarkable, especially after corticosteroid therapy. Imaging may reveal multifocal areas of contrast enhancement or a single mass. Histologically, GME shows perivascular cuffs of inflammatory cells often with epithelioid differentiation. Lesions are most prominent in the white matter.[12,91,92] Unless confirmed by brain biopsy, GME is a diagnosis of elimination once other causes of meningoencephalitis are ruled out. Immunosuppressive doses of corticosteroids will often achieve remission of signs for a variable period of time. When the disease becomes refractory to corticosteroids, radiation therapy or chemotherapeutic agents such as lomustine or cytosine arabinoside have been used with some success, but the prognosis is poor.

Vascular Disease

Stroke is uncommon in animals compared with humans because of the lower incidence of atherosclerosis and primary hypertension. With advanced imaging, however, vascular disease is being recognized with increasing frequency in veterinary medicine. Cerebrovascular disease can be subdivided into infarction and hemorrhage, although the two categories overlap in the case of hemorrhagic infarcts.

Infarction can occur due to thrombosis or embolism of the arterial supply or due to thrombosis of venous drainage. Thrombosis typically occurs when a clot forms in vessels

compromised by atherosclerosis. In dogs, atherosclerosis is seen in hypothyroidism and idiopathic hyperlipidemia, and stroke can occur in these patients. Embolism will be secondary to some systemic disease such as sepsis, cardiac disease, neoplasia, or coagulopathy. Venous occlusion can occur secondarily to thrombosis or compression of the vein. Although a rich collateral drainage usually prevents signs with venous thrombosis, a severe occlusion may result in impaired blood flow to the tissues drained.

Intracranial hemorrhage occurs most commonly secondary to head trauma. When venous thrombosis occurs, the arterial supply is still intact and hemorrhage into the area of infarction may occur. Primary intraparenchymal hemorrhage can occur with hypertension. Hypertension in animals is most commonly secondary to hyperthyroidism, renal disease, pheochromocytoma, or hyperadrenocorticism.

Feline ischemic encephalopathy is a cerebral infarction syndrome in cats. Some cases have been associated with aberrant migration of *Cuterebra* larvae into the brain. Not all cases have obvious vascular lesions, leading to the hypothesis that the larvae induce vasospasm.[12]

Vascular disease is characterized by a peracute onset of signs. Unilateral forebrain signs of circling, hemiparesis, seizures, and personality changes would be most common, though any part of the brain could be affected. Some progression of signs could be expected from increased intracranial pressure. CT is good at detecting acute hemorrhage, whereas MRI is more sensitive for infarction. The signal changes with time, allowing estimation of the chronicity of the lesion (Figure 191-30).[93] Because infarction is rarely due to thrombosis in animals and the therapeutic window is a matter of hours, the thrombolytic drugs used in human stroke patients hold little promise in veterinary medicine. Thus treatment will be largely symptomatic, controlling seizures and intracranial pressure and treating any underlying cause such as vasculitis or hypertension.

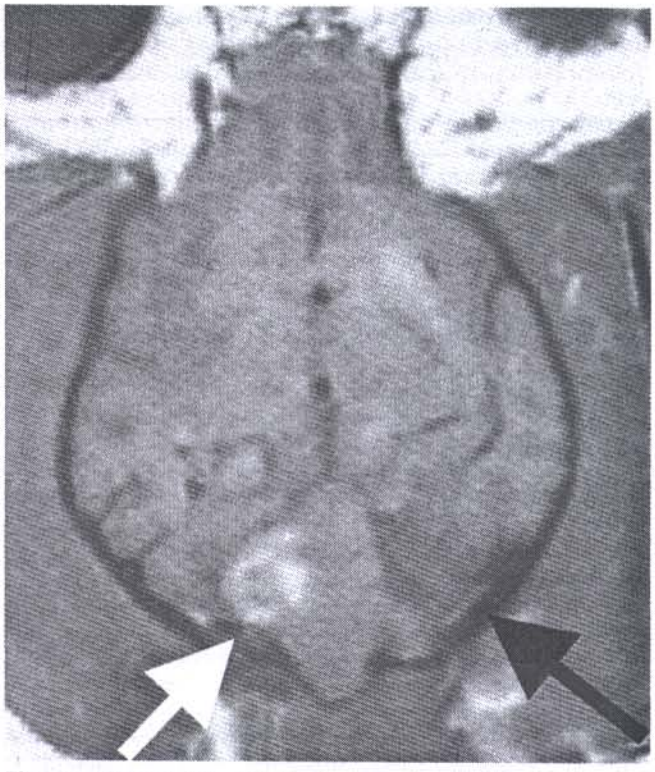


Figure 191-30 T1-weighted magnetic resonance imaging (MRI) with contrast enhancement from a dog with two suspected strokes of the cerebellum 1 year apart. The older infarct on the right *(black arrow)* shows the atrophy of a wedge-shaped portion of the cerebellum replaced with cerebrospinal fluid (CSF). The left side shows an area contrast enhancement *(white arrow)* 4 days after an acute recurrence of cerebellar signs.

Brain Tumors

Brain tumors in dogs are more properly classified as intracranial neoplasms, because not all tumors that arise inside the cranium originate from brain tissue (Table 191-1). Regardless of the tissue origin, intracranial neoplasms result in a characteristic milieu of clinical signs in dogs. Signs typically develop as a result of a focal tumor and can be due to the disturbance of surrounding normal brain tissue from expansive growth of the tumor or the result of the peritumoral effects, such as edema and compromised blood flow. As the disease progresses the clinical signs may change to reflect further damage within the cranial vault. This is especially true when intracranial pressure rises and causes a shift in the intracranial contents. Additional damage and clinical signs can result from expansion of the tumor into non-neural tissues, such as the nasal cavity, periorbita, or the surrounding cranial bones. Rarely, primary intracranial neoplasms can disseminate throughout the CNS either by hematogenous or CSF routes. Intracranial neoplasms rarely spread systemically, although metastasis is not unprecedented. When this occurs it generally spreads to the lungs, most likely through venous drainage from the venous sinus plexuses in the cranial vault.

Although intracranial tumors in the dog and cat have been well described, the prevalence is largely unknown due to the lack of a comprehensive screening system. The incidence for primary CNS tumors in the dog have been reported as 14.5 in 100,000 dogs and 3.5 in 100,000 cats.[94,95] The tumor incidence in dogs is virtually identical to that in humans (11.8 per 100,000).[96] Interestingly, primary CNS tumors in humans, specifically malignant gliomas and CNS lymphomas, are becoming recognized at a higher rate in some studies.[97] However, as is probably the case in small animals, this data may only be reflecting an increased availability of imaging modalities that are necessary to identify the tumors.

Clear risk factors for the development of intracranial neoplasms in the dog have not been identified. In humans, much press has been devoted to the role of cellular phones, exposure to high-tension wires, the use of hair dyes, head trauma, and exposure to N-nitrosourea compounds and other nutritional factors. To date, none of these have been definitively linked to the development of a brain tumor. Ionizing radiation, however, has been identified as an unequivocal risk factor for the development of glial and meningeal neoplasms. Exposure of the cranium to even low doses of radiation can increase the incidence of glial tumors in humans by a factor of 3 to 7, with a latency period of 10 years or more after exposure.[98] It is unknown whether small animals respond similarly to ionization radiation.

This section will focus on the diagnosis of the most common intracranial neoplasms and general treatment guidelines. It is important to note that an in-depth analysis of tumor behavior and of specific treatment regimes for intracranial neoplasms is difficult to perform in companion animals, because this information has not been comprehensively gathered and disseminated. To compensate for the relative paucity of information, data derived from the diagnosis and treatment of human tumors will be provided when appropriate.

Diagnostic Procedures An intracranial mass can be confirmed on brain imaging with MRI or a CT scan. A CT scan, though adequate for identifying tumors in the majority of the cerebral cortex, is more prone to artifact production when imaging the caudal fossa because of interference from the surrounding

Table • 191-1

World Health Organization Classification System for Intracranial Neoplasia[93A]

TYPE	EXAMPLES
Astrocytic tumors	Astrocytoma
	Anaplastic (malignant) astrocytoma
	Glioblastoma multiforme
	Pilocytic astrocytoma
	Subependymal giant cell astrocytoma
	Pleomorphic xanthoastrocytoma
Oligodendroglial tumors	Oligodendroglioma
	Anaplastic (malignant) oligodendroglioma
Ependymal cell tumors	Ependymoma
	Anaplastic ependymoma
	Myxopapillary ependymoma
	Subependymoma
Mixed gliomas	Mixed oligoastrocytoma
	Anaplastic (malignant) oligoastrocytoma
	Others (e.g., ependymoastrocytomas)
Neuroepithelial tumors of uncertain origin	Polar spongioblastoma
	Astroblastoma
	Gliomatosis cerebri
Tumors of the choroid plexus	Choroid plexus papilloma
	Choroid plexus carcinoma (anaplastic choroid plexus papilloma)
Neuronal and mixed neuronal-glial tumors	Gangliocytoma
	Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)
	Ganglioglioma
	Anaplastic (malignant) ganglioglioma
	Desmoplastic infantile ganglioglioma
	Central neurocytoma
	Dysembryoplastic neuroepithelial tumor
	Olfactory neuroblastoma (esthesioneuroblastoma)
Pineal parenchyma tumors	Pineocytoma
	Pineoblastoma
	Mixed pineocytoma/pineoblastoma
Tumors with neuroblastic or glioblastic elements (embryonal tumors)	Medulloepithelioma
	Primitive neuroectodermal tumors with multipotent differentiation
	Medulloblastoma
	Cerebral primitive neuroectodermal tumor
	Neuroblastoma
	Variant: ganglioneuroblastoma
	Retinoblastoma
	Ependymoblastoma
Tumors of the sellar region	Pituitary adenoma
	Pituitary carcinoma
	Craniopharyngioma
Hematopoietic tumors	Primary malignant lymphomas
	Plasmacytoma
	Granulocytic sarcoma
Germ cell tumors	Germinoma
	Embryonal carcinoma
	Yolk sac tumor (endodermal sinus tumor)
	Choriocarcinoma
	Teratoma
	Mixed germ cell tumors
Tumors of the meninges	Meningioma: variants include meningothelial, fibrous (fibroblastic), transitional (mixed), psammomatous, angiomatous, microcystic, secretory, clear-cell, chordoid, lymphoplasmacyte-rich, and metaplastic subtypes
	Atypical meningioma
	Anaplastic (malignant) meningioma

petrous temporal bone. An MRI is the preferred diagnostic modality, because it provides images with superb soft tissue detail and is not interfered by the surrounding bony structures. It is important to remember that any ferrous substance locating in the magnetic field will dramatically alter the image, resulting in poor tissue detail. As such, it is a good practice to perform a radiograph of the target area prior to performing an MRI to ensure a clean field. An MRI should be performed both with and without the addition of gadolinium, an intravenous contrast agent. Although it is not a definitive test, the degree of contrast enhancement and specific tumor location will aid the clinician in making a presumptive tumor diagnoses. This will be discussed in more detail with each individual tumor. The quality of images with an MRI has reached the point that a normal gadolinium-enhanced MRI of the brain essentially rules out the possibility of a brain tumor in both small animals and humans.

Other diagnostic modalities, including CSF analysis, EEG, and brain stem–evoked responses may provide evidence of an intracranial neoplasm or other CNS disease process. In a recent clinical study of 115 dogs with seizures, 36 of 37 dogs (97%) with an abnormal neurologic examination and abnormal CSF analysis (protein >25 mg/dL or nucleated cell count >5 cells/μL) were found to have MRI abnormalities.[99] Statistical analysis of the data indicated that a CSF protein concentration greater than 25 mg/dL was associated with a 76% sensitivity and 70% specificity for prediction of MRI abnormalities, whereas a CSF protein greater than 35 mg/dL resulted in 52% sensitivity and 96% specificity. Although this does show some value to CSF analysis as a screening test, disadvantages still exist. Prediction of MRI abnormalities is not the same as diagnosis of a brain neoplasm (non-neoplastic diseases may also result in MRI abnormalities). Even if a neoplasm is suspected based upon the CSF, the cytology is usually nonspecific for tumor type and tumor location.[100] Although CSF collection generally carries a low-level of risk for the patient, if a brain neoplasm is suspected, it is recommended to perform MRI before CSF tap (due to the risk of tentorial herniation with CSF tap under conditions of increased intracranial pressure).

EEG has been used in humans as a useful aid to imaging studies in the localization of structural and functional brain lesions. An EEG is not as useful for lesion localization in companion animals as it is in humans because dogs and cats have a relatively small brain that is extremely well protected by a thick calvarium and masticatory muscle mass. In addition, EEG abnormalities are not specific for different types of intracranial neoplasia, so the value in the diagnosis of neoplasia is limited to screening at best.

The BAER test reflects audiologic and neurologic function at the level of the brain stem, and is used in human beings to aid in the diagnosis and localization of lesions of the cochlea, the vestibulocochlear nerve, and brain stem auditory pathways. In a prospective study of 26 dogs with naturally occurring brain tumors, BAER was abnormal in 13 of 15 dogs with tumors of the brain stem but only in 1 of 11 dogs with forebrain lesions.[101] Although this type of information may be useful in localizing a lesion, it is nonspecific as to lesion type, and like an EEG, is useful only as a screening tool.

Functional brain imaging, combined with structural data gleaned from either MRI or CT, is becoming more integrated in the identification and management of intracranial neoplasms and other CNS diseases. Specifically, flourodeoxyglucose (FDG) positron emission tomography (PET) and functional MRI are gaining widespread use in the human field for diagnosing and staging neurologic diseases. These imaging modalities are limited to few veterinary institutions, but they may be used more frequently in the future as the technology becomes widely accepted.

Once an intracranial structural lesion (tumor suspect) is identified, it is necessary to specifically identify the type of tumor present to tailor a specific treatment regime. The primary method of obtaining tissue for histopathologic diagnosis is by surgical exploration and excisional biopsy. This is most often accomplished when the lesion is located in the superficial aspect of the cerebral or cerebellar cortex. The surgeon is often able to remove or debulk these tumors at the time of surgery, thereby affecting not only a diagnosis but also substantial cytoreduction and potential cure. Disadvantages include cost, morbidity, and mortality associated with the surgery itself; tumor seeding of the surgical site; and the potential of enhancing the biologic activity of the tumor itself. Additionally, the possibility exists of the tumor being responsive to chemotherapy, in which case the risks of surgery would not be warranted.

Less invasive biopsy techniques are available. Fine needle aspiration and needle core biopsy using stereotaxic CT or ultrasonographic guidance are routinely available at some institutions and have proved invaluable in diagnosing tumors that are located in surgically inaccessible areas of the brain. The inherent advantages and disadvantages of fine needle and needle core biopsies relate to the small sample that is obtained. Small needle diameter limits the amount of damage to nontarget tissues, but also limits the amount of tissue available for examination. Fine needle aspiration limits the method of examination to cytology. This offers the advantages of superior assessment of individual cell morphology and rapid turnaround for intraoperative use. The disadvantages of cytology are poor ability to assess histologic architecture and limited ability to apply special staining techniques. The accuracy of fine needle aspiration for diagnosis of intracranial neoplasia has been compared with histopathology in a number of studies, both human and veterinary. In a recent study of 10 clinical cases with necropsy confirmation of the diagnosis, fine needle aspiration had an exact agreement with the histopathologic diagnosis in 60% of the cases and made the correct diagnosis with regard to neoplasia and degree of malignancy in 100% of the cases.[102] In these cases, fine needle aspiration was performed after the brains had been removed en bloc from the cranium and the lesions were located with MRI. Whether similar results can be obtained antemortem in clinical cases remains to be evaluated.

Meningioma Meningiomas are the most common intracranial neoplasm in dogs and cats. They are mesenchymal tumors that arise from the cells of the three layers of the meninges: (1) the dura mater, (2) the arachnoid, and (3) the pia mater.[93,103,104] However, most commonly from the meningiocytes of the arachnoid layer. These neoplasms are in most cases benign, solitary tumors that grow slowly, often adhering to the dura mater or leptomeninges. Intracranial and extracranial metastases have been reported but are extremely rare. Meningiomas can also occur within spinal cord and intraorbital locations, although greater than 80% are reported to be intracranial.[105]

There does not appear to be a particular breed or sex of dog predisposed to meningiomas; however, it has been suggested that dolichocephalic breeds may be at increased risk.[106] Meningiomas are characteristically a neoplasm of older dogs, with 95% occurring in dogs over 7 years of age.[107]

Clinical signs in dogs with meningioma depend on the location of the tumor.[108] The majority of canine meningiomas are located in the cerebrum and often arise from over the convexities of the cerebral cortex or the falx cerebri.[104,106,109] The most common clinical signs in these dogs are seizures and changes in behavior or attitude. Cerebellar meningiomas may cause dysmetria, circling, ataxia, or intention tremors, and meningiomas that arise from the brain stem can potentially result in cranial nerve deficits or paresis.[108]

Although definitive diagnosis of an intracranial meningioma can only be made by histopathologic tissue examination,

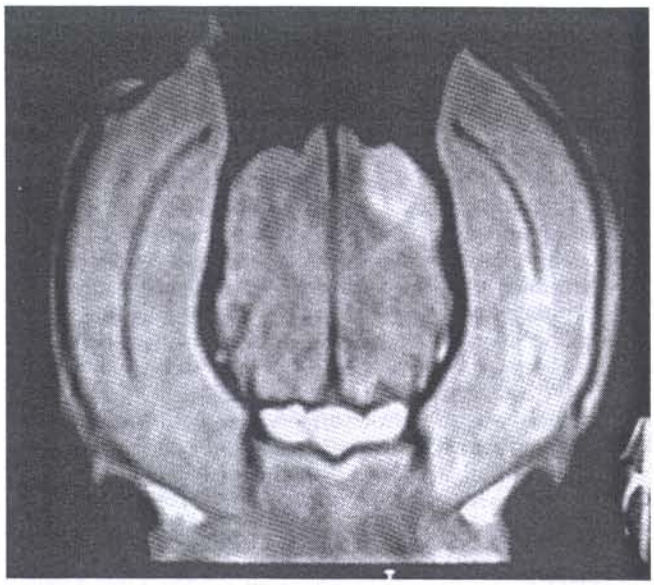


Figure 191-31 Meningiomas appear as a solitary, contrast-enhancing mass with a broad base on the dural surface. They are found most commonly over the convexity of the cerebrum.

CT images and MRI are often highly suggestive of this tumor type. Meningiomas are usually visualized as a solitary, contrast-enhancing, broad-based mass (Figure 191-31).[110] Typically, the tumor is homogenous in appearance with a low-intensity capsule separating the mass from adjacent brain parenchyma. In some cases, meningiomas are cystic in appearance.[111]

The three major treatments that are used in veterinary medicine today for treatment of canine meningiomas are (1) surgery, (2) radiation therapy, or (3) a combination of the two.[112] Gene therapy has also been attempted in a limited number of studies, and some reduction in tumor size has been achieved; however, this practice has not yet gained wide acceptance.[112,113] Efficacy of chemotherapeutic compounds for the treatment of meningioma has not been demonstrated.[114] In humans the role of chemotherapy for the treatment of meningiomas is unclear and is usually reserved as a rescue protocol in nonresponders.[115] Studies in the past have reported extended survival times in dogs with brain tumors that received radiation therapy with or without surgery.[116-118] Cobalt-60 has been the most common source of radiation therapy used for treatment of canine brain tumors in the past and has been used successfully for several years to treat intracranial meningiomas.[103,119] Orthovoltage radiation has also been used successfully, although it is not considered ideal due to poor beam penetration, profile, and limited field configuration. Linear accelerators are becoming increasingly available for animal treatment at large referral institutions, and external beam megavoltage irradiation is the current recommendation for brain tumors in dogs and cats.[120]

Past radiation treatment protocols have varied from total doses of 30 to 36 Gy in 5 to 6 fractions over 14 to 19 days to the more recent total doses of 45 to 48 Gy in 12 fractions over 26 days.[116] Acute effects have been minimal and usually remain limited to the temporary disruption of normal epithelial tissue within the radiation field. Early delayed effects due to transient demyelination can cause recurrence of presenting signs or mental depression and usually occur within a few weeks to a few months after treatment. These changes are typically steroid responsive and transient. Late delayed effects can occur more than 6 months after treatment, are not responsive to therapy, and are usually associated with brain necrosis.[121] In the human literature, daily fractions of 3 Gy or less given over 4 weeks with a total normal tissue dose of 50 to 55 Gy appears to induce fewer late effects, and this approach has been advocated by some in veterinary medicine.[122] The use of stereotaxic delivery of radiation may be of benefit because it decreases the dose of ionizing radiation to the surrounding healthy tissue. This method has been used recently to treat canine meningiomas with encouraging results.[123]

The prognosis for dogs with intracranial meningiomas that receive no treatment is poor. One study found that untreated dogs had a median survival time (MST) of 75 days after CT diagnosis.[124] Dogs receiving only palliative therapy (corticosteroids and anticonvulsants) after diagnosis by CT or MRI have shown average survival times ranging from 59 to 81 days.[118,121] However, extended survival times of greater than 16 months have been noted when surgical resection of the meningiomas is followed by radiation treatment.[117,125]

Neuroepithelial Tumors Neuroepithelial tumors or gliomas are comprised of both astrocytic and oligodendroglial cell lines, as well as other neuroepithelial tissues (see Table 191-1). Although the true incidence in dogs is unknown, these tumors are second only to meningiomas when an intracranial neoplasm is histopathologically diagnosed. Astrocytomas are the most common human intracranial neoplasm; much effort has been devoted to the identification of imaging and histopathologic findings associated with rapidly growing, aggressive tumors. The World Health Organization (WHO) classification scheme characterizes astrocytomas based upon aggressiveness and allows for treatment planning and prognostication. High-grade (malignant) astrocytomas may arise alone or from a preexisting low-grade tumor. Low-grade astrocytomas (secondary) are much less invasive and carry an improved prognosis. Regardless, astrocytomas are usually fatal in both dogs and humans, although the survival time is unpredictable. In humans, the MST of patients with low-grade astrocytomas is 5 years. Interestingly, death usually results from malignant transformation into a high-grade tumor.

The characteristic appearance of an astrocytoma or oligodendroglioma on an MRI is that of a diffuse, nonenhancing or variably enhancing mass (Figure 191-32) that is hypointense on T1-weighted images and best seen on T2-weighted images. Typically the lesion exhibits a local mass effect. The borders of the tumor often appear distinct on MRI but histologically these tumors are usually invasive. Occasional evidence of invasion can be imaged if a powerful MRI is used.

Treatment of gliomas, whether an undifferentiated tumor, oligodendroglioma, or astrocytoma, is similar to that of a meningiomas: surgery and radiation therapy. These tumors, depending on the classification, tend to be invasive. As such, surgery would be expected to be less curative than it would for meningiomas. Chemotherapy may play a larger role in the adjunctive treatment of malignant gliomas compared with meningiomas. Although still controversial, sole-drug and multidrug chemotherapy has been shown to increase the proportion of long-term survivors in humans from less than 5% to approximately 15% to 20%.[126] The most commonly used drugs are procarbazine, lomustine, and vincristine. The role of these drugs and others has yet to be defined in dogs.

Choroid plexus tumors typically display homogenous contrast enhancement with discrete borders and appear hyperintense on (postcontrast) T1-weighted images. They can occur in the lateral, third, or fourth ventricle, because these locations are where the choroids plexus resides (Figure 191-33). The most common location, however, is in the lateral aspect of the fourth ventricle.[127] Choroid plexus tumors are well vascularized, leading to good contrast enhancement and increased bleeding if the tumors are excised. These tumors often cause obstructive hydrocephalus due to their location in the ventricular system. This will be evident on imaging studies

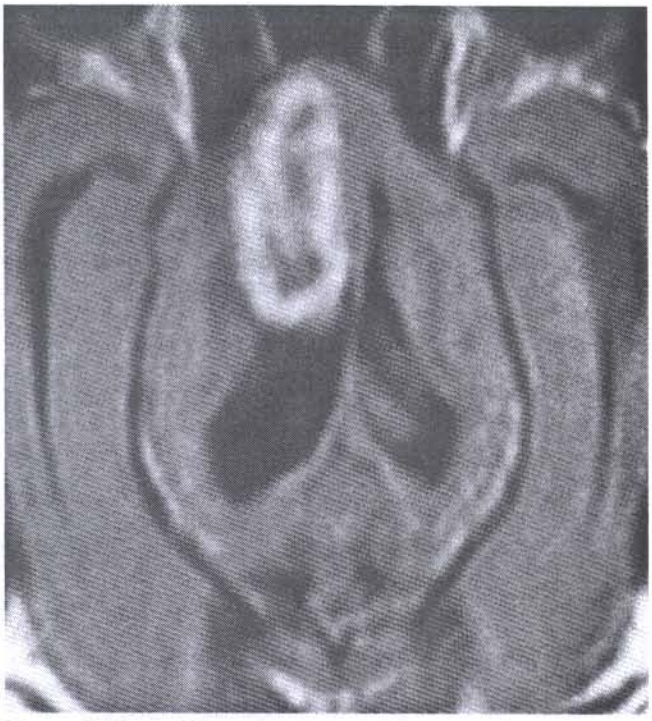


Figure 191-32 Gliomas appear as intraparenchymal masses with variable enhancement.

and may contribute to the overall morbidity of the animal. Embryologically the choroid plexus and ependymal cells are derived from similar tissues. As such, the MRI appearance and tumor distribution for choroid plexus papillomas and ependymomas are similar. However, ependymomas appear to be more uncommon and have a predilection for brachycephalic breeds of dogs.[128] Treatment for choroids plexus and ependymal tumors is largely conjectural, because no study has clearly defined the role of surgery, radiation therapy, or chemotherapy. When accessible, surgery is probably the treatment of choice. However, the high vascularity of these tumors, combined with the relative inaccessibility, indicate that chemotherapy or radiation therapy may play a vital role in effective management.

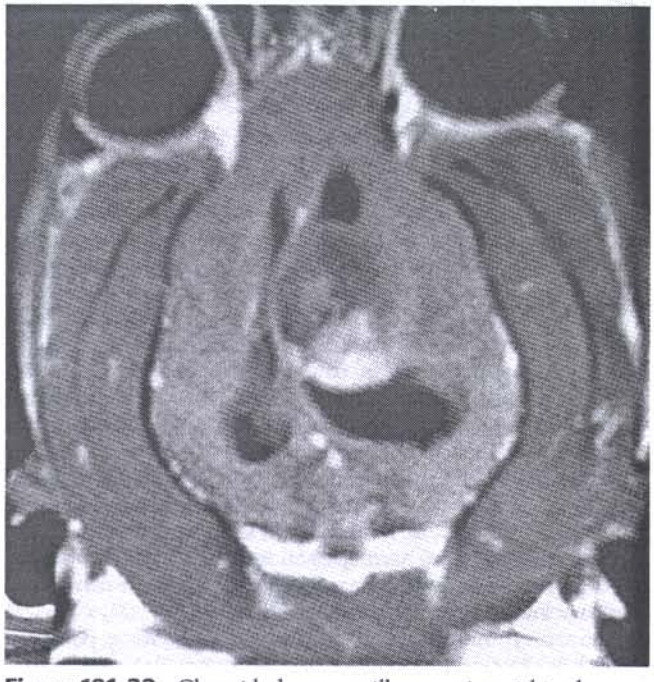


Figure 191-33 Choroid plexus papillomas arise within the ventricular system and have discrete borders. They usually are more uniformly enhancing than this example.

Central Nervous System Lymphoma Primary CNS lymphoma is a result of neoplastic transformation of native lymphocytes within the CNS, whereas secondary CNS lymphoma results from spread of systemic disease. Regardless, involvement of the CNS provides the clinician with a challenge in both disease diagnosis and treatment. The blood-brain barrier effectively excludes many common drugs that are used to treat systemic disease and can hide involvement of the brain, making it difficult to confirm the presence of a neoplastic process within the brain. Diagnosis of CNS lymphoma is made by CSF analysis and, in cases of systemic disease, the presence of atypical lymphocytes in other body systems. In one study, 7 out of 7 dogs with CNS lymphoma had atypical lymphocytes noted in the CSF.[129] The clonal expansion of lymphocytes in lymphoma will all express identical unique DNA sequence in the variable region of the antigen receptor gene. A PCR assay that detects clonal rearrangement of these genes has been developed for dogs and hold promise as a means of diagnosing CNS lymphoma from CSF.[129a] Localized radiation therapy of the brain may be effective in cases of primary CNS lymphoma. Intrathecal administration of cytosine arabinoside at 20 mg/m^2, diluted in 2 to 4 mL of lactated Ringer's solution, given twice weekly for a total of 6 treatments, has been advocated by one author.[129] Another treatment method uses 100 mg/m^2 of cytosine arabinoside (intrathecal) given weekly 1 week beyond the point at which the CSF is devoid of all atypical lymphocytes. Lomustine (CCNU), an alkylating nitrosourea chemotherapeutic, is effective at crossing the blood-brain barrier and has gained support for the treatment of resistant systemic lymphoma in dogs.[130] CCNU and other chemotherapeutics that cross the blood-brain barrier (e.g., hydroxyurea, methotrexate) may also be considered a good choice for systemic treatment of lymphoma when the CNS is involved.

Intravascular lymphoma, a type of systemic lymphoma that is limited to the lumen and walls of blood vessels, has also been reported in the dog. This disease has a propensity for the brain and lungs in both dogs and humans and ultimately results in the occlusion of blood vessels.[131] Diagnosis is difficult, because both the CSF and peripheral blood analysis are not diagnostic for this disease. Imaging of the brain with MRI could yield evidence of multifocal abnormalities. In one case report, an MRI revealed diffuse postcontrast enhancement of the brain parenchyma and multifocal areas of hyperintensity.[132] Definitive diagnosis is made by histopathologic examination of a biopsy specimen. Treatment for intravascular lymphoma is similar to that for systemic disease: chemotherapy. However, specific treatment regimes and survival data for a large case series is not available.

Metastatic Neoplasms of the Central Nervous System Metastatic neoplasms of the CNS are common in both humans and dogs. Generally, systemic tumors spread to the brain; spread to other parts of the CNS occurs with less frequency. Although the exact incidence of CNS metastasis in veterinary patients is unknown, it is known that in humans metastasis occurs in 20% to 30% of cases of systemic neoplasia. It has been noted in some studies that the rate of CNS metastasis has increased over the last 2 to 3 decades.[133] However, this finding may only reflect an increased ability to detect antemortem evidence of metastasis with advanced imaging

procedures or increased longevity of animals with systemic neoplasia as a result of better treatment regimes. Regardless, CNS metastasis has become a real concern for veterinarians and, like treatment of CNS lymphoma, presents a unique challenge in both the diagnosis and treatment of these tumors.

Although it is true that any form of neoplasia has an inherent ability to spread, certain tumor types have been found to metastasize to the CNS with some regularity. Involvement of the CNS can be accomplished by direct invasion from the surrounding structures or systemic spread through the vascular system. Nasal adenocarcinomas tend to be locally invasive, and systemic tumors such as melanomas, hemangiosarcomas, and lymphosarcomas tend to spread hematogenously.

Recognizing CNS metastasis in an animal with systemic disease requires paying careful attention to the neurologic examination and questioning of the animal's caregiver. Because neurodiagnostic procedures are expensive and require anesthesia, reasonable suspicion is necessary to justify the search for CNS metastasis. CSF analysis may be beneficial as a screening test. Although CSF cytology rarely yields abnormal cells, it can provide other clues to CNS involvement. Albuminocyotologic disassociation, or increased protein without an increased cell count, is a common finding in cases of tumors within the CNS. In other cases the CSF may have increased white cells. To confirm a diagnosis, however, advance imaging with MRI or CT should be performed. Metastatic tumors will lack a defined blood-brain barrier; therefore they commonly exhibit well-defined contrast enhancement (Figure 191-34) and are best visualized on MRI that is T1-weighted. Biopsy would be necessary to confirm a diagnosis.

In some instances an animal with systemic neoplasia may have signs limited to the CNS. In these cases a tumor may be diagnosed on MRI and treatment begun prior to diagnosis of a systemic tumor. Therefore it is good practice to perform a thorough systemic workup, including thoracic and abdominal radiographs and, potentially, abdominal ultrasonography on every animal that is diagnosed with a brain tumor.

Pituitary Tumors Pituitary tumors can be considered one of the most common intracranial neoplasms in dogs. Cushing's disease, or pituitary-dependent hyperadrenocorticism (PDH), comprises 80% to 85% of dogs with naturally occurring Cushing's syndrome. Virtually 100% of dogs with PDH have a functional tumor of either the pars distalis (80%) or pars intermedia (20%) of the anterior pituitary. These tumors are generally less than 1 cm in diameter and cause little damage to surrounding neural tissue. However, these tumors may continue to grow throughout the animal's life, ultimately resulting in both neurologic deterioration and death. Pituitary macrotumors—tumors greater than 1 cm in diameter—are also fairly common in dogs. These tumors are generally nonfunctional and cause clinical signs related to a space-occupying mass in the cranium. Most animals with expansive pituitary tumors exhibit signs related to hypothalamic disturbance (diencephalic syndrome), such as propulsive and constant pacing, behavior changes, endocrine disturbances, loss of vision, and potentially proprioceptive deficits.

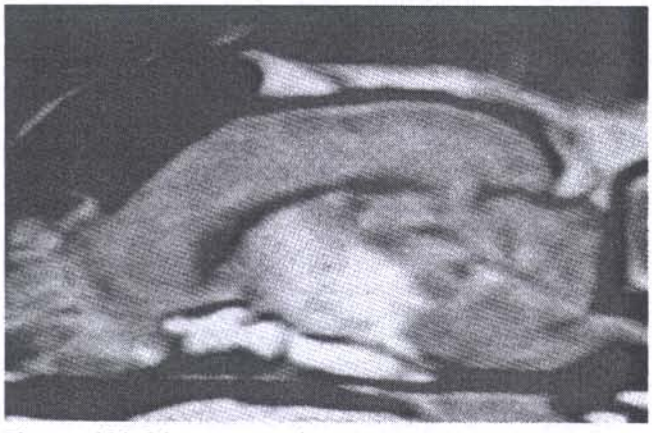


Figure 191-34 Because they lack a blood-brain barrier, metastatic tumors such as this hemangiosarcoma of the diencephalon show well-defined contrast enhancement.

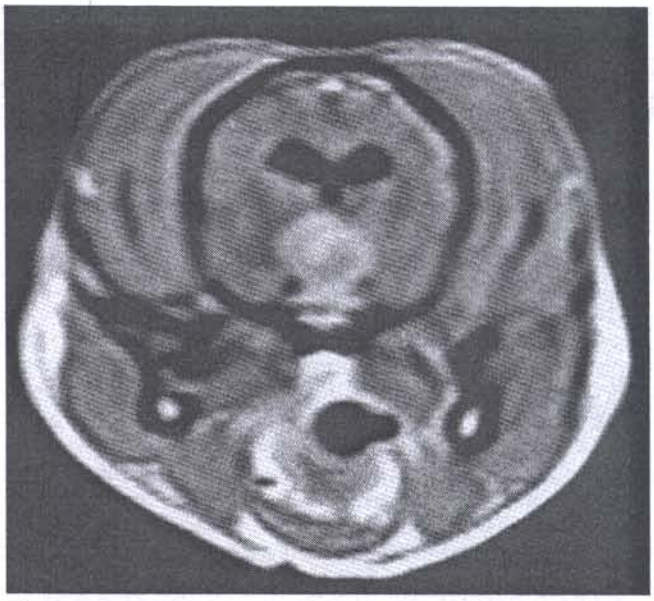


Figure 191-35 Pituitary macrotumors arise from the sella and invade the hypothalamus. They typically show marked contrast enhancement.

Diagnosis of a pituitary tumor is made with an MRI or CT (Figure 191-35). These tumors exhibit bright homogenous contrast enhancement with distinct borders. Peritumoral edema can be extensive in animals with large pituitary tumors. It is important to note that the anterior pituitary lacks a functional blood-brain barrier, because this tissue embryologically is derived from Rathke's pouch of the oral ectoderm. As such the tissue will normally enhance with the addition of a contrast agent. However, a pituitary microtumor can generally be visualized as an asymmetrical enhancement of the anterior pituitary.

Some pituitary tumors in humans are responsive to chemotherapy, but the treatment of choice is surgical excision. The cure rate is high, and perioperative morbidity and mortality is low. In dogs, pituitary surgery is rarely performed. Where it is performed in dogs with pituitary microtumors and PDH, a remission time of up to 39.4 months has been noted. The 1-year estimated survival rate was 84%, the 2-year survival was 80%, and the overall success rates of hypophysectomy around 73.1%.[134] The growth rate of pituitary tumors in dogs with PDH is unknown, but in one study 36% of dogs that had a tumor greater than or equal to 4 mm exhibited continued tumor growth and developed CNS signs within 1 year.[135] This finding may indicate that surgical removal of the tumor should be performed early in the disease process, prior to expansive tumor growth and CNS dysfunction.

Surgery for pituitary macrotumors is rarely performed, because the size of the tumor and location make complete excision improbable. In these cases, radiation therapy is generally recommended.

CHAPTER • 192

Multifocal Neurologic Disease

Rodney S. Bagley

Many diseases occur primarily or exclusively in specific areas within the nervous system. These conditions cause clinical signs that allow clinicians to localize lesions to discrete areas within the nervous system. Some diseases, however, affect the nervous system in a number of anatomically and functionally distinct areas (Box 192-1). In these instances, a constellation of clinical signs result from dysfunction of these differing neuroanatomic areas. It is also possible that, when clinical signs reflect more than a single level of neuroanatomic involvement, more than one disease is present within the nervous system in the same animal (e.g., a brain tumor and a cervical disk extrusion). Therefore it is reasonable to expect that signs of neurologic dysfunction will be found in multiple areas within the nervous system in animals with more than a single disease process. Diseases that primarily affect specific areas of the nervous system, such as the spinal cord or brain, are discussed in those chapters pertaining to those discrete neurologic regions. In this chapter the more clinically important

Box • 192-1

Diseases That Commonly Result in Multifocal Nervous System Signs

Degenerative
- Storage disease
- Multineuronal degeneration

Anomalous
- Hydrocephalus/syringomyelia/hydromyelia complex

Metabolic
- Hepatic
- Renal
- Hypoglycemia
- Thyroid (hypo and hyper)
- Hyperadrenocorticism
- Hyperosmolar syndromes
  - Adipsia

Neoplastic
- Lymphoma
- Leukemias
- Metastatic tumors

Nutritional
- Thiamine

Inflammatory
- Infectious
  - Viral
    - Distemper
    - Herpes
    - Parvo
    - Parainfluenza
    - FIP (Feline infectious peritonitis virus)
    - FIV (Feline immunodeficiency virus)
  - Bacterial
    - Bacterial encephalitis
    - Tetanus
  - Fungal
    - Cryptococcosis
    - Blastomycosis
    - Coccidiomycosis
    - Candidiasis
    - Aspergillosis
  - Protozoal
    - Toxoplasmosis
    - Neosporosis
  - Parasitic
    - *Toxocara*
    - *Cuterebra*
  - Rickettsial
    - Rocky Mountain spotted fever (RMSF)
    - *Ehrlichia*
  - Unclassified
    - Protothecosis
- Noninfectious
  - Granulomatous meningoencephalitis (GME)
  - Breed-associated CNS inflammation
    - Pug encephalitis
    - Maltese encephalitis
    - Yorkshire terrier encephalitis
  - Spinal cord vasculitis
  - Nonclassified
    - Steroid-responsive meningitis
- Idiopathic
  - Dysautonomia
- Toxins
- Vascular disease
  - Intracranial hemorrhage
  - Thromboembolism
  - Hypertension
  - Spinal hemorrhage

diseases that often result in multifocal or diffuse clinical signs are reviewed. If the neurologic signs present in an animal cannot be localized to one functional area within the nervous system, consideration should be given to these diseases.

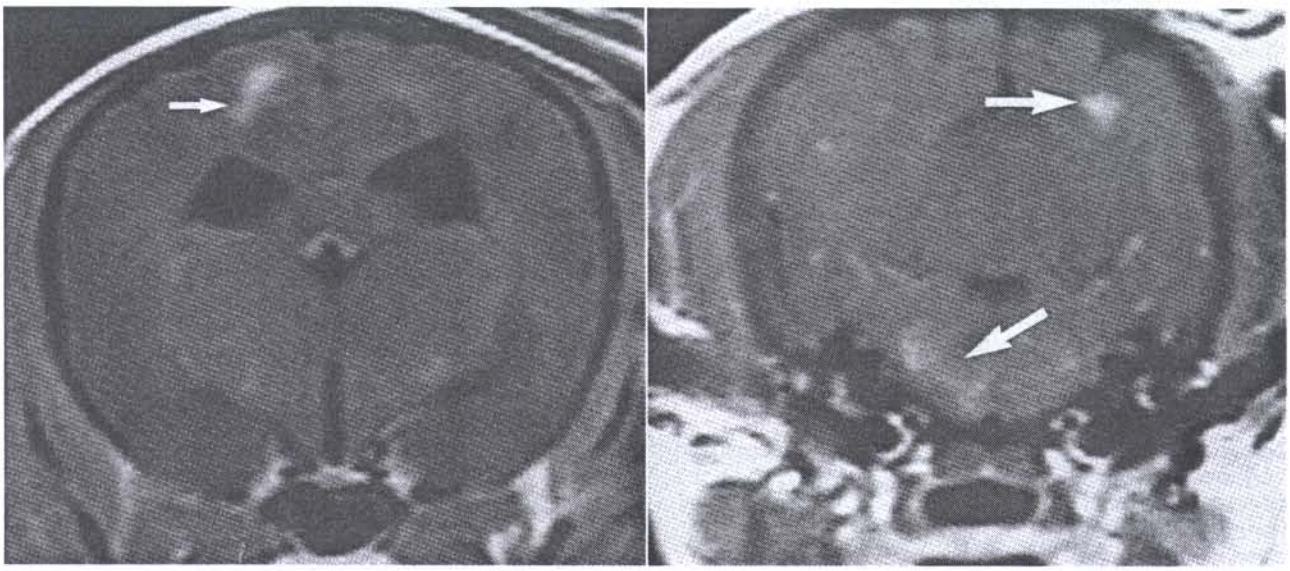
INFLAMMATORY DISEASES

Encephalitis and meningitis often exist concurrently in dogs and cats and are the most common group of diseases that result in multifocal nervous system signs.[1-3] Causes include both infectious and noninfectious causes. Infectious agents associated with encephalitis and meningitis include viral (distemper, parvovirus, parainfluenza, herpes, feline infectious peritonitis [FIP], pseudorabies, rabies), bacterial, rickettsial (Rocky Mountain spotted fever [RMSF], *Ehrlichia*), spirochete (Lyme disease, leptospirosis), fungal (blastomycosis, histoplasmosis, cryptococcosis, coccidiomycosis, aspergillosis), protozoal (toxoplasmosis, neosporosis), parasitic, and unclassified organisms (protothecosis). Incidence of infectious agents causing meningitis varies with geographic location. Additionally, infectious causes of encephalitis and meningitis exist that have not been identified or well-clarified as causes of inflammatory central nervous system (CNS) disease in small animals.

Encephalitis and meningitis may affect the nervous system at multiple levels. Intracranial signs (behavior changes, mental status abnormalities, visual deficits) including cranial nerve dysfunction and spinal cord signs (paresis, ataxia) are commonly seen. Neck pain is a prominent clinical feature of meningitis but may be less obvious with pure parenchymal involvement (e.g., myelitis). Pain may be assessed by vocalization during direct palpation or by reluctance to move the head and neck freely or with manipulation (decreased range of motion). Diffuse spinal pain is also possible. Because these diseases are often polysystemic, diffuse pain may also result from an associated articular facet polyarthritis or myositis. Some animals will react as if painful to minimal palpation (hyperesthestic) anywhere on the body, especially of the limbs and face. Many animals become irritable and uncharacteristically aggressive. Because chorioretinitis is often concurrent, fundic examination may yield important clues to the polysystemic nature of the problem.

In many animals with encephalitis and meningitis, the cardinal signs of systemic inflammatory processes, such as the presence of a fever and increases in white blood cells (WBCs) in the leukograms, may not be found as localized inflammatory disease in the CNS and may not elicit a systemic inflammatory response. For ultimate diagnosis, imaging studies such as magnetic resonance imaging (MRI) and computed tomography (CT) are helpful in defining structural lesions (Figure 192-1).[4] Multifocal, discrete, anatomic lesions are often present within the nervous system and may be especially conspicuous after intravenous contrast medium administration, suggesting alterations in the blood-brain barrier to the cerebral vasculature. Cerebrospinal fluid (CSF) analysis is often important in diagnosis of an inflammatory CNS disease. CSF results alone, however, rarely yield a definitive causative diagnosis and are most helpful when evaluated concurrently with CNS anatomic imaging. Increased numbers of nucleated cells and increased protein concentrations commonly present in CSF from animals with inflammatory CNS disease may also be present with a variety of CNS diseases that result in secondary inflammation (i.e., tumors, trauma, vascular disease) (Figure 192-2). Nucleated cell numbers and types are variable depending upon the cause. In most primary inflammatory CNS conditions, however, mononuclear cells and neutrophils are the predominant cell types present. Eosinophils may indicate a parasitic or allergic response but have also been seen with certain infection conditions, such as *Cryptococcus* in cats and protothecosis in dogs. If prior CNS hemorrhage has occurred, erythrophagocytosis may be noted (see Figure 192-2). Primary CNS hemorrhage may also secondarily result in inflammation.

Unfortunately, evidence of inflammation on CSF evaluation alone is not specific for primary encephalitis because other CNS diseases (e.g., neoplasia, trauma, infarction) may result in a CSF pleocytosis and protein elevations. Therefore evaluation of serum or CSF titers for the aforementioned infectious diseases is often necessary to establish associated infectious diseases. It is recommended to assess several titers in animals with inflammatory CNS disease in an effort to



A B

Figure 192-1 Transaxial, T1-weighted, contrast-enhanced (Magnevist [gadolinium DTPA], Berlex Laboratories, Inc., Cedar Knolls, NJ) magnetic resonance image (MRI) at the level of the thalamus (A) and brain stem (B) from a dog with multifocal clinical signs. Multifocal lesions are present in the cortex and brain stem *(arrows)*. Diagnosis was granulomatous meningoencephalitis (GME).

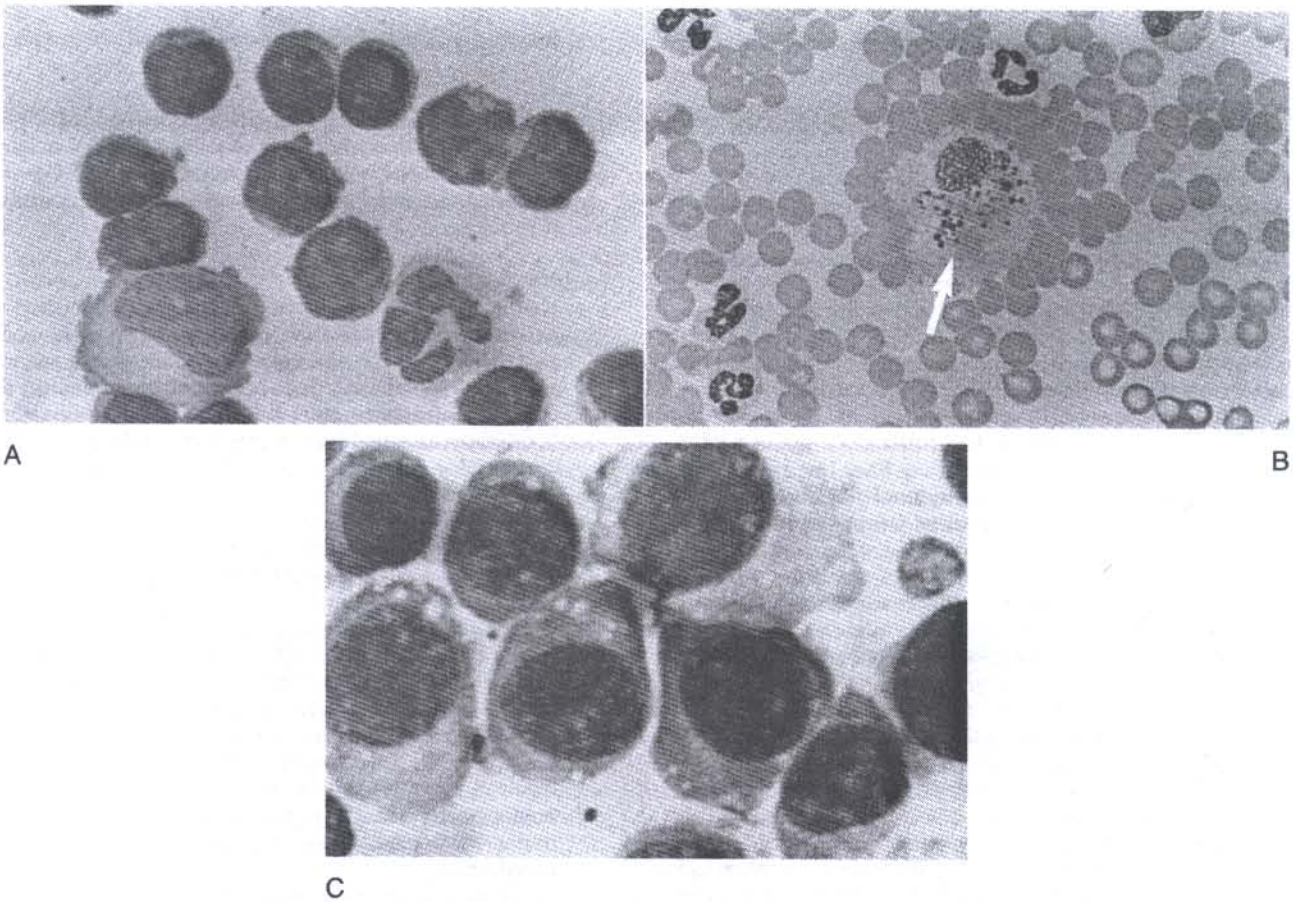


Figure 192-2 Cerebrospinal fluid (CSF) cytology from various dogs with multifocal clinical signs. **A,** Predominantly small mononuclear cells with some neutrophils and monocytes are seen, consistent with a lymphoid pleocytosis (×100). **B,** Numerous red blood cells (RBCs), some neutrophils, and erythrophagocytosis *(arrow)* are seen (×50). **C,** The predominant cell is a large blast-type cell, consistent with lymphosarcoma (×100).

establish an infectious cause. Common infectious causes for dogs include toxoplasmosis, neospora, distemper, and some fungi. Common infectious causes in cats include toxoplasmosis, FIP, *Cryptococcus*, and other as yet unclassified but suspected viral agents. In up to 60% or more of cases of encephalitis, however, an infectious cause is not identified.

Occasionally, CSF from an animal with inflammatory CNS disease will be normal at a single sampling. This is especially true when the disease is primarily intraparenchymal and sometimes after previous corticosteroid administration.

Treatment of meningitis is ideally directed at a specific causative organism. However, treatment often needs to be initiated prior to establishing the exact cause of inflammation because results of serologic testing may delay diagnosis. More aggressive treatment is warranted in animals with severe to rapidly deteriorating clinical signs prior to a definitive diagnosis being rendered.

In this situation, multiple drug therapies are recommended and treatment should begin earlier rather than later in the disease course. Trimethoprim-sulfadiazine (30 mg/kg every 12 hours), clindamycin (20 to 25 mg/kg every 12 hours), doxycycline (10 mg/kg orally every 24 hours), and corticosteroids (prednisone 1 to 4 mg/kg every 12 hours) can be used in combination. Although corticosteroids may seem to be contraindicated with infectious diseases, they are often beneficial in the acute treatment of brain inflammation and edema and have proven beneficial even with bacterial meningitis in children. It is often the associated inflammatory reaction in the CNS that is more detrimental to CNS function than the primary pathophysiologic effects of the organism itself. If rickettsial diseases are suspected, chloramphenicol (15 to 25 mg/kg orally every 8 hours) can be substituted or added to the regime; however, this drug is becoming infrequently used in veterinary medicine in general. If the animal is receiving phenobarbital, the clinician should not use chloramphenicol, because this drug will decrease the metabolism of the barbiturate and the animal could become comatose and die. Therefore in animals with encephalitis and seizures, it is probably wise to avoid chloramphenicol in case barbiturates are needed for seizure control.

SPECIFIC INFLAMMATORY DISEASES

Bacterial Diseases

Bacterial meningitis is rare in dogs and cats.[1] Often, a concurrent disease that results in persistent bacteremia is present. Notable examples in dogs are endocarditis and pyometra. Extension of a local bacterial disease process, most commonly from the nasal passages or middle ear, is also possible (Figure 192-3). Dogs and cats with bacterial meningitis usually have rapidly progressing clinical signs, and the disease is often fatal. Abscesses may form, resulting in focal clinical signs.[5] A variety of causative bacteria may be present.

Diagnosis is aided by CSF analysis. CSF collection should be performed with caution, however, because the associated intracranial alterations associated with fulminant bacterial

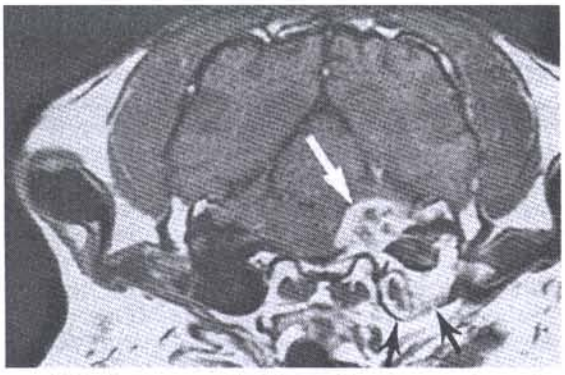


Figure 192-3 Transaxial, T1-weighted, contrast enhanced (Magnevist [gadolinium DTPA], Berlex Laboratories, Inc., Cedar Knolls, NJ) magnetic resonance image (MRI) at the level of the vestibular area from a snow leopard with seizures and a head tilt. A brain abscess is present, extending from the middle and inner ear to the brain stem *(arrows)*. A surgical biopsy and culture found both fungal and bacterial organisms were present.

encephalitis may result in an increased intracranial pressure and resultant brain herniation. Although attempts have been made to classify CSF changes commonly associated with septic inflammatory CNS diseases, the degree of crossover in CSF nucleated cell counts and types makes it difficult to presumptively diagnose a specific inflammatory disease from the CSF results alone. One clue to the presence of bacterial component is a decreased glucose concentration in CSF as compared with plasma, presumably due to consumption of glucose by the organisms. If bacterial encephalitis is suspected, additional CSF should be collected in a sterile container without fixative or other chemicals for culture and sensitivity. Glass tubes containing ethylenediamine tetra-acetic acid (EDTA), commonly used for submission of CSF for cytologic analysis, are not appropriate for culture because the EDTA is bacteriostatic and may hinder organism growth. Because the number of organisms in CSF can be small, the greater amount of CSF cultured the more likely an organism will be isolated.

Because identification of the organism may take a few days and the clinical signs are often rapidly progressive, treatment is often initiated prior to culture analysis. As stated previously, prior to a specific cause being identified, trimethoprim-sulfadiazine, clindamycin, doxycycline, and corticosteroids can be used in combination for treatment of CNS inflammation and infection. Methylprednisolone sodium succinate (30 mg/kg) can be administered intravenously initially if the animal is severely impaired, rapidly deteriorating, or unable to swallow. If the animal is more mildly affected and can swallow effectively, prednisone or prednisolone can then be initiated at anti-inflammatory doses. In some instances, the infection will form a discrete abscess. Because this abscess and its associated inflammation can rapidly increase intracranial pressure, surgical decompression of a focal abscess should take place as soon as possible. Similarly, penetrating intracranial wounds may require débridement to avoid infectious complications.

Although not associated with meningitis per se, tetanus can result in both confusing and diffuse clinical signs. Tetanus is due to a neurotoxin secreted by the organism *Clostridium tetani*. This toxin binds to interneurons and inhibits the release of inhibitory neurotransmitter (glycine) in inhibitory interneurons (Renshaw cells). The organism gains access to the body through a wound, which often cannot be seen in dogs. Cats, which are more resistant to the disease than dogs, usually have a visible wound.

Clinical signs include extensor rigidity, inability to open the mouth, salivation, prolapsed nictitating membrane, inability to urinate, and seizures. Bradycardia, megaesophagus, and hiatal hernia may be seen.[6,7] Tetanus localized to one part of the body is occasionally found. Diagnosis is based upon clinical signs. Anaerobic culturing of a wound may reveal the organism. A serum test for antibodies has occasionally been useful but is not readily available. Treatment includes wound débridement, antitoxin (administered once intravenously), penicillin, muscle relaxants, enteral or parenteral nutrition support, a quiet environment, and good supportive care. Anticonvulsants are given if seizures occur.

Viral Diseases

Canine distemper remains a surprisingly common cause of neurologic dysfunction in dogs. This disease is caused by a paramyxovirus. Clinical signs can occur at any age, regardless of vaccination status. Most commonly, young dogs with inadequate vaccinations are affected with the polysystemic signs (i.e., gastrointestinal [GI], respiratory) and the neurologic signs of infection. However, in the modern era of prophylactic vaccination for distemper, distemper infection may only result in nervous system signs. Nervous system disease associated with distemper is characterized pathologically by two main forms: (1) neuronal and glial cell death (polioencephalopathy) and (2) demyelination (leukoencephalopathy).[3,8-10] It has been suggested that those animals with a poorer antibody response to the virus tend to have the former form and those with an adequate immune response to the virus tend to have the latter—immune-mediated demyelination. Any region of the nervous system can be involved. Myoclonus, a rhythmic, shock-like contraction of a muscle or group of muscles, is usually the result of previous or concurrent distemper infection and lends a clue to the virus' presence. Muscles of the limbs are commonly involved, but other muscles, including the tongue, may be affected.[11]

Clinical signs of a prior or concurrent systemic illness (respiratory, GI) are not always found in dogs with distemper. Diagnosis is suggested by finding inclusion bodies in pathologic specimens. Elevated CSF antibody titer (immunoglobulin G [IgG] and immunoglobulin M [IgM]) against distemper virus is supportive of a diagnosis, especially if concurrent serum distemper titers are not elevated or if a CSF electrophoresis suggests intrathecal antibody production. Occasionally, dogs with CNS distemper do not have positive CSF distemper titers.[12] No specific treatment is effective against the distemper virus. Corticosteroids, although seemingly contraindicated, may decrease inflammation and improve clinical signs in some dogs.

Other viruses of dogs that result in encephalitis and meningitis do so primarily in very young animals. Examples include herpes virus, parvovirus, and parainfluenza virus. Occasionally, these viruses will cause encephalitis and meningitis in adult dogs. Parainfluenza virus has a propensity for causing hydrocephalus.

FIP results from a coronavirus-induced vasculitis. This disease can involve various areas of the nervous system, primarily the intracranial structures and spinal cord. Very young and, conversely, very old cats seem predisposed.[13] Of the two forms of FIP that exist in cats, the "dry" form commonly affects the nervous system. This viral infection results in an immune complex vasculitis that is responsible for most of the pathologic effects. CSF analysis may show a pleocytosis, with either mononuclear cells or neutrophils as the predominant cell type and elevated protein concentration, often greater than 1 g/L (0.1 g/dL). No specific treatment is effective. Immunosuppressive therapy may result in short-term improvement of clinical signs.

Feline immunodeficiency virus has been associated with nervous system signs including behavior changes, seizures, anisocoria, and muscle twitching.[3] As the clinical spectrum of this disease evolves, it may represent an important CNS pathogen of cats. Feline leukemia virus (FeLV) has also been

associated with a myelopathy independent of the presence of lymphoma.[14]

Toxoplasma gondii and *Neospora caninum* are protozoal organisms that can affect any area of the nervous system resulting in encephalitis, myelitis, peripheral neuropathy, or myositis in dogs.[15] These organisms are the most common cause of infectious encephalitis and myelitis in the Pacific Northwest. A classic sign of the infection in young animals is a hyperextended pelvic limb or limbs. Other systemic signs such as chorioretinitis may also be present. Cats also commonly have toxoplasmosis within the nervous system; however, neosporosis has only been established experimentally in this species. CSF analysis often contains a pleocytosis and increased protein concentration. In some instances, discrete granulomas may be found within the CNS and peripheral nerves. Diagnosis of toxoplasmosis is based on the presence of IgM or rising IgG titers to the organism (toxoplasmosis), on visualization of the protozoan in biopsy specimens, or on both.[16] Clinical distinction between the two organisms is not always possible but is increased by awareness of the later protozoal organism and special staining and electron microscopic characteristics. Although sometimes helpful in the diagnosis, CSF titers to toxoplasmosis antibodies may be negative in the presence of CNS toxoplasmosis infection. Serum titers may be more often positive compared with CSF titers with CNS toxoplasmosis. Serologic titers to the presence of Neospora are also available to support the diagnosis of this infection. As with most systemic titer results, the presence of antibodies against these organisms does not ensure the presence of active CNS infection.

Treatment for toxoplasmosis currently is clindamycin[17]; however, this drug is often used in combination with a potentiated sulfa drug in immunosuppressed humans with toxoplasmosis.[18] Trimethoprim sulfa antibiotics have also been used successfully to treat CNS toxoplasmosis. Treatment courses of antibiotics are usually administered for as long as 4 weeks. In some animals, constant treatment with antibiotics is necessary to control clinical signs. A similar treatment is used for neosporosis; however, few cases with definitive treatment success have been reported.[19]

Rickettsial Diseases

Infection with rickettsial organisms associated with RMSF and *Ehrlichia* commonly involve the brain stem, particularly the vestibular system.[20] With RMSF a history of systemic illness (usually with a thrombocytopenia) often exists 5 to 10 days prior to development of neurologic signs. As the animal's fever is decreasing, neurologic signs commonly appear. Diagnosis is based on lack of mass lesion with intracranial imaging studies and a pleocytosis on CSF evaluation. Occasionally, increased contrast enhancement is noted in the choroid plexus area in affected dogs. This must be differentiated from the degree of contrast enhancement normally seen in these structures. CSF usually contains mild increases in nucleated cells (< 50 nucleated cells/μl; normal < 5 nucleated cells/μl) and mild increases in protein concentration (< 50 mg/dL; normal < 25 mg/dL). Increasing serum titers to the organism supports diagnosis, but results are often available after the disease has progressed. Prognosis is dependent primarily on the severity of clinical signs prior to treatment. Dogs that are severely obtunded prior to treatment are less likely to recover. Dogs with clinical features of vestibular disease after a systemic febrile illness associated with thrombocytopenia should be treated with tetracycline or doxycycline prior to establishing a definitive diagnosis with titers.

Fungal Diseases

Of the fungal diseases that can affect the nervous system, *Cryptococcus*, blastomycosis, coccidiomycosis, candidiasis, and aspergillosis are most common.[2,3] Immunodeficiency may play a role in these uncommon nervous system infections. Definitive diagnosis is made through viewing the organism in CSF or biopsy samples and fungal culture of infected nervous tissues. Treatment can be attempted with antifungal agents; however, the presence of an intact blood-brain barrier may interfere with drugs reaching therapeutic concentration in CNS tissue. Fluconazole and itraconazole hold the most promise for treating fungal encephalitis and meningitis. These drugs have historically been rather expensive and owner financial constrains often limit effective long-term therapy.

With cryptococcosis, identification of the organism from cytologic evaluation of samples such as CSF, nasal discharge, and skin lesions supports the diagnosis. A neutrophilic pleocytosis, and occasionally an eosinophilic pleocytosis, may be found on CSF analysis. Detection of the cryptoccal capsular antigen in serum is usually diagnostic. Tissue biopsy and fungal culture or fungal culture of CSF may be more definitive in establishing a diagnosis.

Parasites

Involvement of the intracranial nervous system can occur with parasites such as *Cuterebra* larvae, *Toxocara*, and aberrant heartworm migration. These parasitic conditions may result in inflammation with eosinophils.

NONINFECTIOUS DISEASES

Most meningitis syndromes (~60%) in dogs do not have a definable infectious cause. Noninfectious disease of the supratentorial structures includes some specific diseases such as granulomatous meningoencephalitis (GME), breed-specific encephalitis and meningitis, and many nonspecific entities. GME can occur as a disseminated disease, a focal mass-lesion, or as a primary ocular disease. Unfortunately, many nonspecific encephalities are inappropriately diagnosed as GME. The cause of true GME is not known.[1] Some animals initially thought to have this disease have been shown to have lymphoma. CSF usually shows a mononuclear pleocytosis but is rarely pathognomonic for the disease. Occasionally the CSF will be normal or contain only increases in protein. CT or MRI may show diffuse inflammatory changes or a mass lesion.[4] Biopsy is needed for definitive diagnosis. Treatment options include immunosuppression (corticosteroids, azathioprine), surgery (if a focal mass), or radiation therapy. The latter has shown the most promise recently for definitive treatment of this disease.[21] Most dogs with GME die within 6 months to 1 year after diagnosis unless radiation therapy is used. Newer medical treatments under investigation that show promise in treatment of GME include cytosine arabinoside and procarbazine.[22]

Breed-Associated Encephalitis, Meningitis, and Vasculitis

Multiple primary CNS inflammatory and CNS vasculitis diseases are inherent in specific breeds of dogs. Pug encephalitis is an example of a breed-associated inflammatory brain disease[23]; it usually occurs in young pugs but has been reported in dogs up to 7 years of age. The disease is characterized histologically by forebrain inflammation and necrosis, primarily of the cerebral hemispheres.[23] It is not unusual, however, that initial clinical signs include neck pain, and that the disease is misinterpreted as a primary spinal cord disease such as intervertebral disk disease. Usually this disease has been fatal, and therapy (corticosteroids) has not altered the course of the disease; however, the prognosis with this disease is debatable. A similar disease has been described in Maltese terriers, Yorkshire terriers, and some other breeds.[24-26]

Other inflammatory diseases that do not have a definitive cause are also often grouped together under the heading of

"steroid-responsive meningitis."[2,3] Almost assuredly, multiple diseases exist within this group. Younger, large breed dogs such as retrievers are often affected. Clinical signs often include cervical pain as a prominent feature. Additionally, there exists a syndrome of spinal cord vasculitis that occurs in beagles and Bernese mountain dogs. Other dogs such as German shorthaired pointers and Nova Scotia duck trolling retrievers have an apparent breed-associated meningitis syndrome.[2,3] Clinical signs are similar to other meningitis syndromes. CSF from affected dogs often contains a preponderance of neutrophils. In some cases associated hemorrhage will make the CSF bloody upon collection. This is often misinterpreted as iatrogenic at time of collection; however, the presence of erythrophagocytosis is helpful in establishing previous CNS hemorrhage. Some of these animals will have positive LE (Lupus erythematous) cell tests, suggesting a possible immune-mediated component to the disease, although LE is quite nonspecific in dogs. Corticosteroid therapy often is rapidly beneficial in these dogs.

Generalized Tremors

Adult animals that have generalized tremors often have associated encephalitis. Many of these dogs also have additional clinical signs that reflect dysfunction of multiple regions with the nervous system. Generalized tremor syndrome occurs in numerous dog breeds.[27-29] Diffuse, low-amplitude tremors are the norm. Many dogs are initially thought to be hypothermic or apprehensive. Historically, dogs with white haircoats were more often affected, thus the term *white shakers*. However, dogs with a variety of haircoat colors, like the miniature pinscher, can be affected.[29] Clinical signs usually occur in young (1 to 4 years of age) dogs and include generalized tremor, ocular muscle tremor, vestibular signs (head tilt, ataxia), cerebellar signs, and seizures. The disease is often associated with a mild encephalitis. CSF from affected animals usually contains mild increases in nucleated cell counts and mild to normal protein content. No obvious cause of the encephalitis has been found. Clinical signs usually respond to immunosuppressive doses of corticosteroids. After the clinical signs have initially resolved, the corticosteroid dose can be slowly decreased (over weeks to months) to prevent recurrence. The disease, in some dogs, will only remain in remission with continual corticosteroid administration.

Dysautonomia

Dysautonomia is a disease that seems to have regional prevalence in the United States with primary concentration in the Midwest (Kansas, Missouri).[30-35] Animals with this disease can have numerous clinical signs reflective of both a diffuse neurologic and systemic process. Clinical signs may include vomiting, diarrhea, ileus, decreased GI motility, dry mucous membranes, dry eyes (keratoconjunctivitis sicca [KCS]), dramatic loss of body mass, pupillary changes with decreased pupillary light reflex (PLR) (mydriasis), dilated anal sphincter, dysuria, and bradycardia. In some instances, decreased to absent spinal reflexes suggest lower motor neuron (LMN) involvement. A regional infectious or toxin cause is suspected. Diagnosis is suspected based on the presence of the aforementioned constellation of clinical signs. Some pharmacologic manipulations may also be helpful, such as assessment of response to 0.1% pilocarpine instillation in the eyes and assessment of wheal and flare reaction subsequent to intradermal histamine administration. Radiographic assessments may show evidence of ileus, distended intra-abdominal organs, decreased intestinal motility after barium administration, megaesophagus (with or without aspiration pneumonia), and distention of the bladder. Treatment is directed at supporting body functions; however, the overall prognosis is poor because clinical signs are persistent.

Central Nervous System Hemorrhage

Hemorrhage in or around the CNS may also result in a multifocal clinical picture.[36,37] Hemorrhage may be associated with systemic bleeding disorders, thrombosis and other vascular occlusive disease, vasculitis, and hypertension. Vascular and other hemorrhagic diseases involving the nervous system are uncommonly reported in animals, as compared with human beings. With the advent of the increased use of advanced imaging studies such as MRI, vascular disease and CNS hemorrhagic phenomenon are increasingly recognized. Thrombosis, infarction, and hemorrhage can occur spontaneously—secondary to drug therapy (L-asparaginase, anticoagulants)—with thrombocytopenia and other bleeding disorders, anticoagulant rodenticide toxicity, trauma, hypertension (hyperthyroidism, hyperadrenocorticism), atherosclerosis from hypothyroidism, infection (septic emboli), and diseases that result in hypercoagulability such as glomerulonephritis. Of special note, many dogs with idiopathic thrombocytopenia have CNS bleeding complications. Greyhounds appear predisposed to cerebrovascular problems. Clinical signs are usually acute in onset and may be initially progressive because the vascular event results in secondary ischemia, inflammation, and edema. Hemorrhage and infarction may be seen with CT and MRI. Acutely, the associated mass effect and edema can mimic other intracranial structural diseases such as tumor. Diagnosis is supported by cerebral angiography; however, this is uncommonly performed in dogs and cats. Treatment is directed at any underlying cause of thrombosis or hemorrhage. If the hemorrhage results in mass effect, acute surgical decompression may be necessary to avoid severe brain or spinal cord dysfunction. Blood product support, procoagulant, or anticoagulant drugs (as necessary) may be needed during the perioperative and postoperative time.

METABOLIC DISEASES

Many metabolic diseases may affect the nervous system at multiple levels and result in diffuse or multifocal clinical signs.[38] Hypoglycemia secondary to insulinoma can result in clinical signs of CNS (depression, seizures, tremors) and peripheral (weakness, decreased spinal reflexes, muscle atrophy) dysfunction.[39-44] The dichotomy of seizures (a supratentorial sign) and decreased to absent reflexes (an LMN sign) may initially result in confusion during neuroanatomic localization. Clinical signs of weakness with insulinomas are often attributed to the hypoglycemia, and the concurrent neuropathy is often overlooked.

Hyperthyroidism of cats has been associated with both central and peripheral nervous system abnormalities.[45] CNS signs include restlessness, hyperexcitability, irritability, aggression, wandering, pacing, circling, insomnia, and seizures. Apathy, lethargy, and depression occur infrequently. Focal neurologic deficits may result from associated cerebrovascular accidents, most likely secondary to hypertension. Clinical signs of peripheral nervous system involvement include generalized weakness, neck ventroflexion, muscle tremors, gait abnormalities, and muscle atrophy. Muscle weakness often manifests as a decrease or inability to jump. Neck ventroflexion may occur with other diseases, including myasthenia gravis (MG), polymyopathy (including hyperkalemic polymyopathy), and organophosphate toxicity.

Conversely, hypothyroidism has been associated with various nervous system abnormalities in dogs.[46] Whether these signs reflect a primary metabolic disturbance or secondary structural abnormalities associated with underlying vascular disease is not always determined. Cranial (vestibular, facial, trigeminal) and appendicular peripheral nerves may be abnormal. Morphologic changes in nerves included demyelination, remyelination, and axonal necrosis. These changes, however, are not specific for hypothyroid neuropathy.

Hyperadrenocorticism may result in abnormalities of the muscle and peripheral nervous system.[47] Affected dogs usually are weak, but an extremely small percentage of dogs (<1%) have a stiff gait, most obvious in the pelvic limbs. An associated pseudomyotonic state has been described. In some instances, myotonia may predominate. Whether this secondary consequence of hyperadrenocorticism is primarily a myopathy or neuropathy has not been determined. If hyperadrenocorticism is the result of a pituitary tumor, clinical signs of intracranial disease are also possible. Macroadenomas may enlarge dorsally from the sella and compress the diencephalon. The most common abnormalities are listlessness, decreased appetite, and, less commonly, disorientation. Seizures and blindness are extremely rare.

Neoplasia

Tumors of the nervous system include primary and secondary (metastasis) neoplasms.[48] Often tumors of the nervous system result in focal clinical signs. Some tumors, however, are diffuse and therefore result in diffuse clinical signs. Prominent examples include lymphosarcoma and carcinomatosis. Multiple cranial nerves (III, IV, V, VI, VII) may be involved with hematogenous neoplasia (leukemias) due to direct involvement with the tumor cells.[49] Choroid plexus tumors, which often arise within the ventricles of the brain, may metastasize within the neural axis by metastasis through the CSF.[48] If the spinal cord is affected, clinical signs of spinal dysfunction may occur concurrent with intracranial signs from the primary tumor. Diagnosis is aided by advanced imaging and CSF analysis.

Neoplasia secondarily involves the brain via metastasis or via direct extension from extraneural sites.[50-52] Clinical signs may be localized or multifocal depending upon the number and location of metastasis and associated pathophysiologic sequelae such as hemorrhage and edema.[51]

OTHER DISEASES

Many degenerative neurologic diseases of dogs and cats are inherited or congenital; therefore they are seen primarily in young animals.[1] Storage diseases are prominent examples. Diseases that involve the neuronal cell body are more likely to have cerebral, cranial nerve, or peripheral nerve signs, whereas diseases that primarily involve myelin are more likely to result in ataxia and paresis of the limbs.[1] The storage diseases and other degenerative diseases of dogs and cats have been reviewed previously.[1]

Numerous toxins can affect the nervous system, often at multiple sites.[53,54] Examples of primary toxins include organophosphates, metaldehyde, lead, and bromethalin. Diagnosis can be difficult if exposure has not been documented historically. Treatment is directed toward the specific toxin.

CHAPTER 193

Diseases of the Spinal Cord

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MECHANISMS OF DISEASE

Spinal cord diseases can be divided into two groups.[1] The first group comprises diseases that affect both the nervous system and other organ systems. The second group includes diseases that are unique to the nervous system, such as disorders of myelin, neurons, or supporting cells (glial cells and the like). Categories of disease that may be included in either of these two groups are congenital and familial disorders, toxicities, nutritional disorders, degenerative diseases, neoplasia, and idiopathic disorders.

The localization of specific functions in the nervous system has important effects on the clinical presentation and progression of spinal cord diseases. Localization of function in the spinal cord causes a pathologic process to result in many different clinical presentations, depending on the part or parts of the spinal cord it affects. For example, a spinal cord neoplasm at the level of the C3 vertebra may result in tetraparesis, whereas the identical neoplasm at the level of the T13 vertebra may result in paraparesis, leaving the thoracic limbs unaffected. Furthermore, localization of function in the spinal cord renders the cord inherently vulnerable to focal lesions that in other organs, where function is more uniformly distributed, might not result in detectable clinical signs. For example, a small infarction of the cervical spinal cord may result in tetraplegia, whereas a similar lesion in the hepatic parenchyma probably would not compromise liver function.[1]

The unique susceptibility of the nervous system to a localized lesion is compounded by its strictly limited capacity to restore function in damaged tissue. Because the pathologic reactions of the spinal cord to disease are to a degree nonspecific, various disorders may induce a somewhat similar histologic appearance.[2,3]

Clinical syndromes that affect the spinal cord may be characterized by a single focal lesion (transverse myelopathy) or by several focal lesions (multifocal disorders). Myelopathies may be *extrinsic*, meaning that spinal cord dysfunction occurs secondary to diseases of the vertebrae, meninges, or epidural space, or it may be *intrinsic*, which means the disease begins as an intramedullary lesion. Extrinsic myelopathies are almost always transverse myelopathies.

Because the nervous system can respond in only a limited number of ways to the numerous causes of myelopathies, a systematic diagnostic approach must be taken for an animal with a spinal cord disorder.

APPROACH TO A SPINAL CORD PROBLEM

Diagnosis

Signalment

Accurate diagnosis of a spinal cord disorder must include consideration of the animal's age, breed, and gender. Diseases may be specific to certain species and breeds.[4-8]

History

An accurate and complete history constitutes the initial step in the diagnosis of all neurologic problems. Important aspects of the history include the rapidity of onset of the problem and the nature of its progression. This information may be helpful for determining the cause of a problem. For example, neoplastic diseases that affect the spinal cord often result in focal signs that have an insidious onset and a gradual progression. In contrast, vascular disorders, such as infarction or hemorrhage, may manifest an acute onset of focal signs without evidence of progression. Inflammatory, degenerative, or metabolic disorders generally cause a diffuse distribution of signs with an insidious onset and gradual progression. Traumatic and congenital diseases may result in either a focal or multifocal distribution of signs, most often with an acute onset and without progression, although such diseases may have a progressive course.

Although careful consideration of these factors is helpful in determining the cause of a spinal cord problem, so many exceptions to general statements exist that such information must be used with caution. For example, an acute onset of signs does not rule out neoplasia as a possible cause of myelopathy, because a neoplasm may be associated with rapid decompensation of neural tissue, particularly if vascular factors, such as infarction or hemorrhage, are involved.

Physical Examination

The physical examination consists of a series of observations that provide information about the general health of all body systems. The results of this examination supplement the information collected in the history and may implicate involvement of body systems other than the nervous system. For example, an animal suspected of having spinal pain may in fact have abdominal pain. A thorough orthopedic examination should be performed for any dog or cat suspected of having a spinal cord disorder. Particular attention should be paid to examination of the joints. Rupture of anterior cruciate ligaments bilaterally or bilateral patellar luxations may mimic paraparesis caused by a neural disorder.

Neurologic Examination

The neurologic examination is an extension of the physical examination. When spinal cord disease is suspected, it is essential to complete a thorough, comprehensive, and unbiased examination of the nervous system. Errors in diagnosis commonly occur when the examiner focuses on only the region of an obvious neurologic deficit and overlooks more subtle alterations in other parts of the nervous system. The objectives of the neurologic examination are to detect any disorder of the nervous system and to determine its location and extent.[4-8]

Problem List and Differential Diagnosis

A comprehensive list of problems should be compiled after the physical and neurologic examinations have been completed. All identified problems should be included, even though some may not appear to be directly related to the presenting complaint. A list of the possible causes of each problem should be compiled, with the most probable causes listed first. Ranking of the differential diagnoses is based on the information collected in the history (e.g., signalment, nature of onset and progression of signs) and on the results of the physical and neurologic examinations.

Minimum Database

Initial clinicopathologic tests include a complete blood count, blood chemistry profile, and urinalysis. The results of the initial blood and urine tests may support a diagnosis of an infectious or a metabolic or toxic disorder that is either producing or complicating signs of spinal cord dysfunction. Additional diagnostic tests may be required for investigation of disorders suspected on the basis of the results of the initial screening tests. For example, hyperglobulinemia detected in a cat with signs of myelopathy may support completion of a serum feline infectious peritonitis (FIP) virus titer.

Thoracic radiographs should be obtained as part of the minimum database in dogs or cats with a spinal cord disorder. This is especially necessary in older animals, in animals in which abnormalities of cardiovascular or respiratory function are suspected, and in animals in which neoplasia is included on a list of differential diagnoses. Abdominal radiography or ultrasonography should also be performed.

Ancillary Diagnostic Investigations

The recommended essential procedures for diagnosis of a myelopathy, in advised order of completion, are noncontrast vertebral radiography, cerebrospinal fluid (CSF) analysis, and myelography. Other procedures, such as electrophysiologic testing or advanced imaging (computed tomography [CT] or magnetic resonance imaging [MRI]), may be added to this list, depending on the nature of the problem investigated.

Noncontrast vertebral radiography Noncontrast vertebral radiography is essential to the accurate diagnosis of a disorder affecting the spinal cord.[4-8] Owing to the limitations of a neurologic examination in outlining multiple lesions of the spinal cord and for the purpose of comparison if problems related to other regions of the vertebral column occur in the future, the entire vertebral column must be radiographed. Correct technique, exact positioning, and use of appropriate projections are essential.[9-12] Further diagnostic investigations may be indicated based on the initial interpretation of the noncontrast vertebral radiographs. For example, a finding of discospondylitis may be followed by culture and sensitivity testing of the blood, urine, or an aspirate from an infected disk or by serologic testing for *Brucella canis*. Differentiation of an infectious lesion from a vertebral neoplasm may be difficult on the basis of noncontrast vertebral radiography alone. In such cases, a biopsy, by means of needle aspiration or surgical excision, may be indicated.

Cerebrospinal fluid analysis Collection and analysis of the CSF are essential when noncontrast vertebral radiographs do not completely define the location, nature, and extent of a spinal cord disorder.[13] CSF may be collected by means of a cisternal or a lumbar subarachnoid puncture. It has been recommended that CSF be collected from a cisternal site if cervical spinal cord disease is suspected and from a lumbar location if a thoracolumbar disorder is involved. However, a lumbar collection site (most often between the L4 and L5 or L5 and L6 vertebrae) may be used for most dogs or cats with a spinal cord disorder regardless of the suspected location of the problem. Precautions must be taken in the collection of CSF from animals suspected of having increased intracranial pressure.

Analysis of CSF collected from a dog or cat suspected of having a spinal cord disorder should always include a total red blood cell count, total and differential white blood cell (WBC) count, and quantitative estimation of protein content. The results for CSF from normal dogs and cats have been published.[14-17] It should be noted that normal values for CSF collected from lumbar sites differ from those for CSF collected from cisternal sites.[17,18]

The results of CSF analysis may support further examination of the cerebrospinal fluid, such as bacterial or fungal culture and sensitivity testing, completion of titers, or CSF protein electrophoresis and determination of the immunoglobulin G (IgG) index.[19-21]

Myelography Myelography is the radiographic examination of the spinal cord and emerging nerve roots after injection of contrast material into the subarachnoid space. Myelography should be done when the results of noncontrast vertebral radiography and CSF analysis do not fully define a disorder affecting the spinal cord or when spinal surgery is contemplated.[11,12] Patterns of myelographic alteration may be used to differentiate intramedullary, intradural-extramedullary, and extradural space-occupying lesions.[11,12]

Myelography should be considered only if positive findings are essential for diagnosis and prognosis, or to determine a precise site for surgery, because it is a difficult procedure to complete and may have undesirable consequences.[22-24] A lumbar injection site is preferred for dogs or cats with spinal cord disease at any level of the vertebral column. Dynamic radiographic techniques and oblique projections may augment the diagnostic information gained from a myelographic study.

Electrophysiology The role of electrophysiologic testing in the diagnosis of spinal cord disease is limited. Abnormal findings on electromyographic (EMG) examination are seen only when the lower motor neurons in the ventral horn of the spinal cord, or their axons in the ventral root are affected by a pathologic process. EMG examination may be performed to define the extent of a lesion affecting the brachial or lumbar enlargement of the spinal cord; the examination maps the distribution of EMG abnormalities caused by denervation and correlates this information with the spinal nerve root origins of the nerves supplying the affected muscles.[1] Electrophysiologic findings may be valuable for defining precisely the location and extent of a spinal cord lesion, because EMG may help distinguish between disuse atrophy and atrophy secondary to denervation.[25,26]

Determination of the sensory or motor nerve conduction velocities of the thoracic or pelvic limbs may aid in the identification of the nerve roots affected by a spinal cord disorder. Spinal cord potentials (cord dorsum potentials) evoked by stimulation of a peripheral sensory nerve may be used, along with the sensory nerve conduction velocities, to determine involvement of sensory nerve roots proximal to the dorsal root ganglia. However, in animals with spinal cord disorders, evoked spinal cord potentials are of limited usefulness for localizing lesions, determining the disease's severity and prognosis, or evaluating the response to therapy.[25,26]

A variety of pressure, flow, and electrophysiologic techniques have been developed to assess the function of the lower urinary tract.[5] Cystometry, profile recording of the urethral closure pressure, electromyography of the urethral sphincter, uroflowmetry, and evoked spinal cord potential measurements after pudendal nerve stimulation have all been investigated in dogs or cats.[5] Combinations of these electrophysiologic tests may provide the information needed about the functional status of spinal cord segments involved in micturition.

CLINICAL SIGNS OF SPINAL CORD DISEASES

Assessment of an animal's gait and posture, postural reactions, spinal reflexes, cranial nerve function, and state of consciousness is essential in determining whether a spinal cord disease exists, the most likely location or locations of a spinal cord lesion, and whether a focal, multifocal, or disseminated disease process is present that involves the spinal cord and/or other parts of the nervous system.[1]

Five groups of clinical signs are seen to a varying degree in all animals with disease that affects the spinal cord: depression or loss of voluntary movement, alteration of spinal reflexes, changes in muscle tone, muscle atrophy, and sensory dysfunction. Careful assessment of these groups of clinical signs in an animal suspected of having a disease affecting the spinal cord facilitates localization of the lesion and diagnosis. Neurologic disorders that result in either loss of voluntary movement alone or sensory dysfunction alone are unlikely to be spinal cord disorders, because most spinal cord diseases do not affect selected tracts while sparing anatomically adjacent pathways.

Diseases of the spinal cord may also result in dysfunction of the bladder, urethral sphincter, and anal sphincter and in loss of voluntary control of urination and defecation. This may be due to interruption of spinal cord pathways connecting the brain stem and cerebrum to the bladder and rectum that are important in normal detrusor reflex function and voluntary control of micturition and defecation, or it may be due to interruption of the parasympathetic nerve supply to the bladder and urinary and anal sphincters (L7 to S3 spinal cord segments and spinal nerves). Spinal cord diseases also indirectly interferes with excretory functions by impairing the animal's ability to assume the posture necessary for normal defecation or urination.

Voluntary Movement

Loss of voluntary movement as a result of interruption of motor pathways at any point from the cerebrum to the muscle fibers is referred to as *paralysis (plegia)*. Lesser degrees of motor loss are referred to as *paresis*. The terms *tetraplegia* (or *quadriplegia*) and *tetraparesis* (or *quadriparesis*) refer to an absence of voluntary movement in the thoracic and pelvic limbs and to depression of movement in the thoracic and pelvic limbs, respectively. The terms *paraplegia* and *paraparesis* describe the absence of voluntary movement and depression of voluntary movement in only the pelvic limbs. *Hemiplegia* and *hemiparesis* refer to paralysis or motor dysfunction, respectively, of a pelvic limb and a thoracic limb on the same side.

Voluntary movement must be differentiated from reflex movement by means of neurologic examination findings and general observation.

Ataxia (incoordination) is seen in association with paresis and probably occurs as a result of interference with both the ascending and descending spinal cord pathways. Many ascending spinal cord tracts contribute to the transmission of sensory information to the cerebrum for coordination of voluntary movements; however, interference with the spinocerebellar tracts probably causes a large part of the ataxia seen in association with spinal cord disease in animals. Observation of gait is the only clinical testing technique for assessing these pathways.

Spinal Reflexes

Spinal reflexes are stereotyped involuntary actions that occur independent of brain input and that may be elicited consistently by specific stimuli. The central nervous system (CNS) components of spinal reflex arcs are located entirely in the spinal cord. Disturbance of spinal reflexes occurs in almost all animals with spinal cord disease. A spinal reflex may be normal, depressed *(hyporeflexia)*, absent *(areflexia)*, or exaggerated *(hyper-reflexia)*. Classification of spinal reflexes into one of these categories is helpful for localizing a spinal cord lesion.

Depression of a spinal reflex in association with spinal cord disease most frequently occurs as a result of involvement by a pathologic process of spinal cord segments that mediate

the reflex. It must be remembered that involvement of motor nerves arising from or of sensory nerves traveling to such spinal cord segments, or abnormalities of the effector organ (muscle), may also result in depression of spinal reflexes.

Exaggeration of a spinal reflex in association with spinal cord disease occurs when a lesion affects the spinal cord cranial to segments that mediate a reflex. The neural mechanisms that result in spinal reflex exaggeration are not completely understood. The concept that reflex exaggeration simply results from interruption of descending inhibitory pathways is useful for lesion localization; however, other factors are likely to be involved, such as collateral axonal sprouting or the development of denervation supersensitivity. Exaggeration of a reflex may result from a brain lesion, as well as from a spinal cord lesion.

Spinal cord lesions that affect both gray and white matter may result in depression of spinal reflexes mediated by spinal cord segments involved in a pathologic process and in exaggeration of spinal cord reflexes mediated by spinal cord segments caudal to a lesion. This is useful for lesion localization, particularly lesions that affect the cervical enlargement (C6 to T2 spinal cord segments), where thoracic limb hyporeflexia and pelvic limb hyper-reflexia may be present.

Interpretation of reflex abnormalities must be approached with the knowledge that two (or more) lesions in the same anatomic division of the spinal cord may produce reflex changes identical to those seen with a single lesion. For example, two lesions between the T3 and L3 spinal cord segments cause hyper-reflexia in the pelvic limbs indistinguishable from that resulting from a solitary lesion in this location. Furthermore, hyporeflexia produced by one spinal cord lesion may mask hyper-reflexia that would otherwise result from a second lesion in a more cranial location. For example, a lesion in the lumbar enlargement (L4 to S3 spinal cord segments) causes hyporeflexia in the pelvic limbs that masks the hyper-reflexia that otherwise would result from a second lesion cranial to the L4 spinal cord segment.

Depression of spinal reflexes caudal to a lesion may be seen for several days after spinal cord injury in humans or primates and is called *spinal shock*. Spinal shock may occur in quadrupeds; however, it is too brief to be of clinical significance. Hyporeflexia observed immediately after spinal cord injury should be attributed to damage to spinal cord segments that mediate the reflexes or to other systemic complications (e.g., hypovolemic shock) that frequently accompany spinal cord trauma.

Muscle Tone

Maintenance of normal muscle tone is a function of spinal reflexes (tonic muscle stretch reflexes). Alterations in muscle tone therefore are interpreted in a fashion similar to that for alterations in spinal reflexes described above. Abnormal muscle tone may be depressed *(hypotonia)*, absent *(atonia)*, or exaggerated *(hypertonia)*, depending on the location of the spinal cord lesion.

Muscle Atrophy

Two types of muscle atrophy may occur in association with a spinal cord disease. *Denervation atrophy* is seen when the lower motor neurons (LMNs) innervating a muscle are damaged by a lesion that affects their spinal cord segment or segments of origin. Denervation atrophy is evident within a week of injury, usually is severe, and is associated with EMG abnormalities. *Disuse atrophy* may be seen in muscles innervated by LMNs caudal to a spinal cord lesion. Disuse atrophy commonly is slower in onset and progression than denervation atrophy, most often is less severe, and usually is not associated with EMG alterations.

Sensory Dysfunction

Abnormalities of sensory (ascending) pathways of the spinal cord contribute to the ataxia of spinal cord disease; however, specific clinical tests of their function do not exist. Perception in animals must be inferred from certain behavioral responses that indicate that ascending sensory signals have reached the cerebral cortex (e.g., aversive response to a noxious stimulus). Interruption of sensory signals at any point between (and including) sensory receptors in the periphery and cerebral cortex may depress or obliterate normal sensory function. Therefore the results of a clinical examination for signs of sensory dysfunction alone may not be of value in localizing a lesion to the spinal cord. However, combined with the results of other parts of a neurologic examination, signs of sensory dysfunction may provide important diagnostic and prognostic information.

Proprioceptive positioning (perception of body position or movement) and pain perception are tested during a neurologic examination. Proprioceptive positioning is a sensitive indicator of spinal cord function, and depression or loss of proprioceptive positioning frequently is the sign first caused by a myelopathy.

Pain perception may be normal, depressed *(hypesthesia)*, absent *(anesthesia)*, or exaggerated *(hyperesthesia)*. Two types of pain perception may be distinguished in animals. *Cutaneous ("superficial") pain perception* is manifested by a response to pricking or pinching of the skin; *deep pain perception* is manifested by reaction to pinching of the toes or tail across bone with hemostatic forceps. Areas of decreased or absent cutaneous pain perception may aid the identification of specific nerves, nerve roots, and spinal cord segments involved in a pathologic process. This technique of cutaneous mapping is especially useful with lesions that affect the cervical or lumbar enlargements.

Deep pain perception appears to be the sensory function most resistant to a spinal cord disease, and it is the last spinal cord function to disappear in myelopathies of any type. An animal with complete bilateral loss of deep pain perception due to a transverse myelopathy is necessarily paralyzed caudal to the lesion. Loss of deep pain perception, therefore, is a grave prognostic sign.

Hyperesthesia in association with a spinal cord disease may indicate nerve root or spinal nerve involvement, or it may be consistent with meningeal irritation. A focal area of hyperesthesia over the vertebral column may indicate the location of a spinal cord lesion.

LOCALIZATION OF SPINAL CORD DISEASES

Motor, sensory, reflex, and sphincter abnormalities may help determine the location of a lesion in one of four major longitudinal divisions of the spinal cord: the cervical region (C1 to C5 spinal cord segments), the cervical enlargement (C6 to T2), the thoracolumbar region (T3 to L3), and the lumbar enlargement (L4 to Cd5). It is essential to remember that these divisions refer to spinal cord segments, not vertebrae, and that spinal cord segments do not correspond exactly with vertebrae of the same number. Some variations may be encountered because of slight differences among animals in segments that form the cervical and lumbar enlargements. The diseases most commonly associated with neurologic signs referable to each of these four regions are listed in Boxes 193-1 to 193-4.

A disorder of any of the four regions of the spinal cord results in a combination of neurologic signs specific for that region.[6] Recognition of these clinical signs allows accurate localization of a spinal cord lesion. The presence of neurologic deficits indicative of involvement of more than one region of

Box • 193-1

*Diseases Affecting the Cervical Region (Spinal Cord Segments C1 to C5)**

Hereditary/Congenital Causes
Atlantoaxial subluxation
Congenital vertebral anomalies
Spina bifida
Myelodysplasia
Syringomyelia/hydromyelia
Globoid cell leukodystrophy
Hereditary ataxia
Pilonidal sinus/epidermoid cyst/dermoid cyst
Spinal stenosis

Degenerative Causes
Intervertebral disk disease
Cervical spondylomyelopathy
Leukoencephalomyelopathy of rottweilers
Neuroaxonal dystrophy of rottweilers
Spondylosis deformans
Dural ossification
Synovial cyst

Inflammatory/Infectious Causes
Discospondylitis
Corticosteroid responsive meningitis-arteritis
Granulomatous meningoencephalomyelitis
Distemper myelitis
Feline infectious peritonitis meningitis/myelitis
Bacterial/fungal/rickettsial/protothecal meningitis/myelitis
Protozoal myelitis
Feline polioencephalomyelitis
Spinal nematodiasis

Neoplastic Causes
Neoplasia

Traumatic Causes
Spinal cord trauma

Vascular Causes
Ischemic myelopathy
Progressive hemorrhagic myelomalacia
Hemorrhage
Vascular malformations and benign vascular tumors

Nutritional Causes
Hypervitaminosis A (cats)

Idiopathic Causes
Spinal intra-arachnoid cysts
Osteochondromatosis
Calcinosis circumscripta

*Common causes are in italics.

Box • 193-2

*Diseases Affecting the Cervical Enlargement (Spinal Cord Segments C6 to T2)**

Hereditary/Congenital Causes
Congenital vertebral anomalies
Spina bifida
Myelodysplasia
Syringomyelia/hydromyelia
Globoid cell leukodystrophy
Hereditary ataxia
Pilonidal sinus/epidermoid cyst/dermoid cyst
Spinal stenosis

Degenerative Causes
Intervertebral disk disease
Cervical spondylomyelopathy
Spondylosis deformans
Dural ossification
Synovial cyst

Inflammatory/Infectious Causes
Discospondylitis
Distemper myelitis
FIP meningitis/myelitis
Bacterial/fungal/rickettsial/protothecal meningitis/myelitis
Protozoal myelitis
Feline polioencephalomyelitis
Granulomatous meningoencephalomyelitis
Spinal nematodiasis

Neoplastic Causes
Neoplasia

Traumatic Causes
Spinal cord trauma

Vascular Causes
Ischemic myelopathy
Progressive hemorrhagic myelomalacia
Hemorrhage
Vascular malformations and benign vascular tumors

Nutritional Causes
Hypervitaminosis A (cats)

Idiopathic Causes
Spinal intra-arachnoid cysts
Osteochondromatosis

*Common causes are in italics.

Box • 193-3

Diseases Affecting the Thoracolumbar Region (Spinal Cord Segments T3 to L3)*

Hereditary/Congenital Causes
Congenital vertebral anomalies
Spina bifida
Myelodysplasia
Syringomyelia/hydromyelia
Mucopolysaccharidosis
Globoid cell leukodystrophy
Pilonidal sinus/epidermoid cyst/dermoid cyst
Spinal stenosis

Degenerative Causes
Intervertebral disk disease
Degenerative myelopathy
Spondylosis deformans
Dural ossification
Synovial cyst
Diffuse idiopathic skeletal hyperostosis

Inflammatory/Infectious Causes
Discospondylitis
Distemper myelitis
Feline infectious peritonitis (FIP) meningitis/myelitis
Bacterial/fungal/rickettsial/protothecal meningitis/myelitis
Protozoal myelitis
Feline polioencephalomyelitis
Spinal nematodiasis
Granulomatous meningoencephalomyelitis

Neoplastic Causes
Neoplasia

Traumatic Causes
Spinal cord trauma

Vascular Causes
Ischemic myelopathy
Progressive hemorrhagic myelomalacia
Hemorrhage
Vascular malformations and benign vascular tumors

Idiopathic Causes
Osteochondromatosis
Spinal intra-arachnoid cyst
Calcinosis circumscripta

*Common causes are in italics.

Box • 193-4

Diseases Affecting the Lumbar Enlargement (Spinal Cord Segments L4 to Cd5) and Cauda Equina*

Hereditary/Congenital Causes
Spina bifida
Sacrocaudal dysgenesis
Congenital vertebral anomalies
Myelodysplasia
Syringomyelia/hydromyelia
Globoid cell leukodystrophy
Pilonidal sinus/epidermoid cyst/dermoid cyst
Spinal stenosis

Degenerative Causes
Intervertebral disk disease
Lumbosacral vertebral canal stenosis
Spondylosis deformans
Dural ossification
Diffuse idiopathic skeletal hyperostosis
Synovial cyst

Inflammatory/Infectious Causes
Discospondylitis
Protozoal myelitis
Distemper myelitis
FIP meningitis/myelitis
Bacterial/fungal/rickettsial/protothecal meningitis/myelitis
Feline polioencephalomyelitis
Spinal nematodiasis
Granulomatous meningoencephalomyelitis

Neoplastic Causes
Neoplasia

Traumatic Causes
Spinal cord trauma

Vascular Causes
Ischemic myelopathy
Progressive hemorrhagic myelomalacia
Hemorrhage
Vascular malformations and benign vascular tumors

Idiopathic Causes
Osteochondromatosis
Spinal intra-arachnoid cyst

*Common causes are in italics.

the spinal cord is highly suggestive of multifocal or disseminated spinal cord disease.

The functional differences between upper motor neurons (UMNs) and LMNs may be used to localize lesions to one of the longitudinal regions of the spinal cord. Cell bodies of spinal cord LMNs are located in the spinal cord gray matter. Their axons leave the spinal cord via the ventral nerve roots to become part of a peripheral nerve and terminate in a muscle. The cell bodies of the LMNs of the thoracic limb are in the C6 to T2 spinal cord segments, which form the cervical enlargement, whereas the LMNs of the pelvic limb arise from the L4 through S1 spinal cord segments of the lumbar enlargement. Anal and urethral sphincter LMNs originate from the S1 through S3 spinal cord segments. Signs of LMN dysfunction,

which in diseases affecting the spinal cord reflect damage to the spinal cord segment or segments from which the LMNs originate, include decreased or absent voluntary motor activity; decreased or absent muscle tone; normal, decreased, or absent segmental spinal reflexes; and rapid, severe atrophy of an affected muscle as a result of denervation.

UMNs arise from cell bodies in the brain. Their axons form the descending pathways of the spinal cord and terminate on interneurons, which in turn synapse with LMNs. Lesions that affect UMNs result in UMN signs, which are the result of an increase in the excitatory state of LMNs. UMN signs include depression or loss of voluntary motor activity, normal or exaggerated segmental spinal reflexes, appearance of abnormal spinal reflexes (e.g., crossed extensor reflex), increased muscle tone, and muscle atrophy as a result of disuse.

Unilateral signs caused by spinal cord disease are unusual; however, signs frequently are asymmetric. In most cases a lesion that results in asymmetric signs is located on the side of the greater motor and sensory deficit.

Cervical Region (C1 to C5 Spinal Cord Segments)

Fatal respiratory paralysis resulting from interruption of descending respiratory motor pathways or damage to motor neurons of the phrenic nerve (C5 to C7 spinal cord segments) occurs in a complete transverse myelopathy. Lesions that are less than complete may not affect respiration, but other signs may be detectable.

Ataxia and paresis of all four limbs usually are seen. Tetraplegia rarely is seen, because lesions severe enough to cause tetraplegia also cause respiratory paralysis. Hemiparesis occasionally may be present in association with a cervical lesion. Lesions of the cervical spinal cord may result in paraparesis with minimal neurologic deficits in the thoracic limbs. The reasons for this are poorly understood.

Spinal reflexes and muscle tone are intact in all limbs and may be normal or exaggerated. Muscle atrophy generally is not present; however, disuse atrophy may develop in disease that has a chronic course. Anal reflexes are intact, and anal tone usually is normal. Bladder dysfunction may occur as a result of detrusor muscle areflexia, with normal or increased urinary sphincter tone and loss of voluntary control of micturition. Reflex dyssynergia may also be seen. Although voluntary control of defecation may be lost, reflex defecation occurs when feces are present in the rectum. Horner's syndrome (ptosis, miosis, and enophthalmos) rarely may be present in an animal with a severe destructive cervical lesion. Proprioceptive positioning and other postural reactions usually are depressed or absent in all limbs. Complete loss of proprioceptive positioning may occur without detectable loss of pain perception.

Cervical hyperesthesia ("spasms," apparent pain on palpation, cervical rigidity, and abnormal neck posture) may be seen in some animals with cervical myelopathy. It should be noted that apparent cervical pain may also be seen in association with lesions affecting the brain stem and cerebrum. Occasionally an animal may hold a thoracic limb in a partly flexed position, a posture that may be consistent with C1 to C5 nerve root or spinal nerve entrapment *(root signature)*, although this posture is seen more commonly with a disorder affecting the cervical enlargement.

Disorders that affect the cervical region of the spinal cord must be differentiated from brain lesions that result in tetraparesis. This may be accomplished with a complete neurologic examination; however, occasionally the distinction may be difficult to make. In most circumstances, a cervical lesion does not result in neurologic deficits attributable to involvement of the medulla oblongata; however, there are several notable exceptions to this rule. Positional strabismus, resulting from loss of the vertebral joint proprioceptive input to the attitudinal reflexes, may be seen in association with a cranial cervical lesion (C1 to C3 spinal cord segments). A cranial cervical lesion may also cause facial hypesthesia as a result of involvement of the spinal nucleus and tract of the trigeminal nerve. Cranial cervical trauma often results in clinical signs referable to injury of the caudal brain stem (head tilt, pharyngeal paresis, facial paresis) or cerebellum.

The Schiff-Sherrington sign (syndrome or phenomenon), which consists of hypertonicity of thoracic limb muscles and hyperextension of the neck, is seen in association with spinal cord lesions caudal to the cervical enlargement. It is essential to differentiate this sign from thoracic limb hypertonicity caused by a cervical lesion.

Cervical Enlargement (C6 to T2 Spinal Cord Segments)

Ataxia and paresis of all four limbs usually are present with lesions of the cervical enlargement. Occasionally paresis of the thoracic limbs and paralysis of the pelvic limbs may be seen.

Spinal reflexes and muscle tone may be normal or decreased in the thoracic limbs and normal or exaggerated in the pelvic limbs. The nature of thoracic limb reflex alterations depends on the exact craniocaudal location of a lesion in this region. Muscle atrophy often is severe in the thoracic limbs. The panniculus reflex may be depressed or absent unilaterally or bilaterally as a result of interruption of the LMNs involved in this reflex (C8 and T1 spinal cord segments). If bladder dysfunction occurs, it is similar to that observed with a lesion in the cervical region, with loss of voluntary control of urination. Anal reflexes and anal tone most often are normal, although voluntary control of defecation may be absent. Unilateral Horner's syndrome is commonly observed with a spinal cord lesion of the cervical enlargement, particularly a lesion involving the T1 to T3 spinal cord segments or nerve roots.

Proprioceptive positioning and other postural reactions usually are depressed in all four limbs. Alterations in these functions may be more pronounced in the pelvic limbs than the thoracic limbs. Occasionally, proprioceptive positioning is absent only in a thoracic and pelvic limb on the same side. Severe depression or loss of pain perception rarely is seen in association with a lesion of the cervical enlargement, except in intrinsic myelopathies (e.g., ischemic myelopathy). Hyperesthesia at the level of a lesion of the cervical enlargement, thoracic limb lameness, or apparent neck pain may be seen.

Thoracolumbar Region (T3 to L3 Spinal Cord Segments)

Most spinal cord lesions of dogs or cats occur in the thoracolumbar region. Typically the thoracic limb gait is normal, and paresis and ataxia, or paralysis, is seen in the pelvic limbs. The thoracic limb spinal reflexes are normal. Pelvic limb spinal reflexes and muscle tone are normal to exaggerated, depending on the severity of the lesion. Muscle atrophy is not seen in the thoracic limbs. Pelvic limb muscle atrophy, if present, is the result of disuse and is seen in animals with a severe, chronic lesion.

Anal reflexes and anal tone usually are normal or exaggerated. Voluntary control of defecation may be lost. Reflex defecation occurs when the rectum is filled with feces; however, it may not be at an appropriate time or place. The degree of bladder dysfunction varies, depending on the severity of the spinal cord lesion. There may be loss of voluntary control of urination, detrusor muscle areflexia with normal or increased urinary sphincter tone, or reflex dyssynergia, in which initiation of voiding occurs and is stopped by involuntary contraction of the urethral sphincter. The bladder can be manually expressed in some animals, but not others, as a result of increased tone of the urinary bladder sphincter; this is often referred to as a *UMN bladder.* Although "overflow" incontinence may occur with lesions of the spinal cord in this region, secondary to overfilling of the bladder, detrusor muscle tone and urinary sphincter tone are present, which distinguishes

this type of incontinence from that due to lesions of the lumbar enlargement and cauda equina (LMN bladder).

Proprioceptive positioning and other postural reactions are normal in the thoracic limbs and depressed or absent in the pelvic limbs. Pain perception is normal in the thoracic limbs and may be normal, depressed, or absent in the pelvic limbs. The panniculus reflex may be reduced or absent caudal to a lesion. In the lumbar region, the panniculus reflex may be present in lesions caudal to L3 as a result of the pattern of cutaneous innervation of lumbar spinal nerves.[1] There may be an area of hyperesthesia at the level of a lesion. The Schiff-Sherrington sign may be seen with a lesion in the thoracolumbar region. It usually is an indication of an acute, severe spinal cord lesion, although such a lesion may be reversible.

Lumbar Enlargement (L4 to Cd5 Spinal Cord Segments) and Cauda Equina

Involvement of the lumbar enlargement and cauda equina by a pathologic process results in varying degrees of pelvic limb paresis and ataxia, or paralysis, and is often accompanied by dysfunction of the bladder and by paresis or paralysis of the anal sphincter and tail. Thoracic limb function is normal. Pelvic limb reflexes and muscle tone are reduced or absent. Muscle atrophy often is present in the pelvic limbs. Conscious proprioception and other postural reactions may be reduced or absent in the pelvic limbs.

Anal tone and anal reflexes are reduced or absent. The rectum and colon may become distended with feces, and fecal incontinence, with continual leakage of feces, is often seen. Constipation may result from the inability to void feces. Paresis or paralysis of the urethral sphincters and detrusor muscle result in overfilling of the bladder and "overflow" incontinence. Affected animals have a large residual volume of urine in the bladder, and the bladder is easily expressed manually (LMN bladder). The Schiff-Sherrington sign occasionally may be seen with an acute lesion that affects this region of the spinal cord.

The term *cauda equina* is used to describe the lumbar, sacral, and caudal nerve roots and spinal nerves as they extend caudally from the caudal tip (conus medullaris) of the spinal cord in the vertebral canal. Lesions that affect the cauda equina result in clinical signs that are indistinguishable from those produced by lesions affecting the spinal cord segments from which the nerves of the cauda equina arise (L6 to Cd5).

ALPHABETIC LISTING OF DISEASES

Atlantoaxial Subluxation (Atlantoaxial Instability) and Malformations of the Odontoid Process

Etiology and Pathogenesis

Subluxation, instability, or malformation of the atlantoaxial joint that permits excessive flexion of the joint may result in compression of the spinal cord as a result of dorsal displacement of the cranial portion of the body of the axis into the vertebral canal. Such conditions may result from congenital or developmental abnormalities, trauma, or a combination of these factors.[9,10,27,28]

Agenesis or hypoplasia of the dens, nonunion of the dens with the axis, absence of the transverse ligament of the atlas, and dorsal angulation of the odontoid process with compression of the spinal cord have been associated with atlantoaxial instability in dogs.[29,30] Traumatic atlantoaxial luxation may occur in any breed of dog or cat and usually results from rupture of the atlantoaxial ligaments or fracture of the dens at its junction with the axis. The onset of signs usually is acute and coincides with the trauma, but occasionally it is delayed.

Clinical Findings

Congenital or developmental malformations occur most frequently in small dog breeds.[31] Animals with congenital atlantoaxial joint abnormalities usually develop clinical signs during the first year of life. Occasionally a dog with a congenital atlantoaxial abnormality appears normal until trauma occurs at an older age, at which time clinical signs may occur.

Clinical signs associated with congenital atlantoaxial instability may have an acute onset, may be slowly progressive, or may be intermittent. Signs are indicative of a transverse myelopathy between C1 and C5 and vary from mild cervical pain to tetraparesis or tetraplegia and possibly death as a result of respiratory paralysis. Occasionally, signs of brain stem dysfunction may follow an atlantoaxial luxation (e.g., dysphagia, facial paralysis, or vestibular deficits).

Atlanto-occipital luxation results in trauma to the medulla oblongata and clinical signs indicative of a caudal brain stem or cranial cervical spinal cord injury. Severe injuries may result in respiratory paralysis and death.

Diagnosis

Atlantoaxial instability is best demonstrated by radiography. Radiographically, the body of the axis is displaced dorsally and cranially into the vertebral canal, and the distance between the dorsal arch of the atlas and the spinous process of the axis is increased. If lateral views are not diagnostic, slight flexion of the head may be necessary. Extreme care must be taken when manipulating an animal suspected of having atlantoaxial instability while it is under anesthesia or during radiography, because flexion of the animal's neck may result in further spinal cord compression. Splinting the animal's neck and head in extension beforehand may help prevent excessive flexion of the head during induction of anesthesia, intubation, and positioning for radiography. Abnormalities of the dens may be seen on ventrodorsal views or slightly oblique lateral views such that the wings of the atlas are not superimposed on the dens (Figure 193-1). An open mouth view may show agenesis, nonunion, or fracture of the dens; however, the degree of cervical flexion required for completion of this view may result in further spinal cord compression. Therefore obtaining an open mouth view usually is not recommended.

Animals with congenital or developmental abnormalities of C2 may have additional vertebral abnormalities, such as shortening of C1 or abnormal atlanto-occipital articulation. Agenesis or malformation of the dens may be an incidental finding and is probably not of clinical significance unless associated with radiographic findings of atlantoaxial instability. However, spinal cord compression associated with hypoplasia of the dens without radiographic evidence of atlantoaxial instability has been reported in a dog. Similarly, abnormal angulation of the dens may cause spinal cord compression. In these cases, myelography or advanced imaging (especially CT) may be necessary to demonstrate spinal cord compression (Figure 193-2).

Treatment

Animals with an acute onset of neurologic deficits resulting from atlantoaxial instability or traumatic atlanto-occipital luxation should be treated medically, as described for other forms of spinal cord trauma. In addition, the head and neck should be splinted in extension. Animals with mild luxations and cervical pain only or with minimal neurologic deficits, or animals with multiple vertebral abnormalities, such as atlantoaxial instability and shortening of the body of C1, may respond to splinting of the head and neck in extension and strict cage rest for at least 6 weeks. Casting material or a metal metacarpal splint may be used for this purpose. Care must be taken to ensure that respiration is not compromised. Splinting the head and neck may permit the formation of fibrous tissue

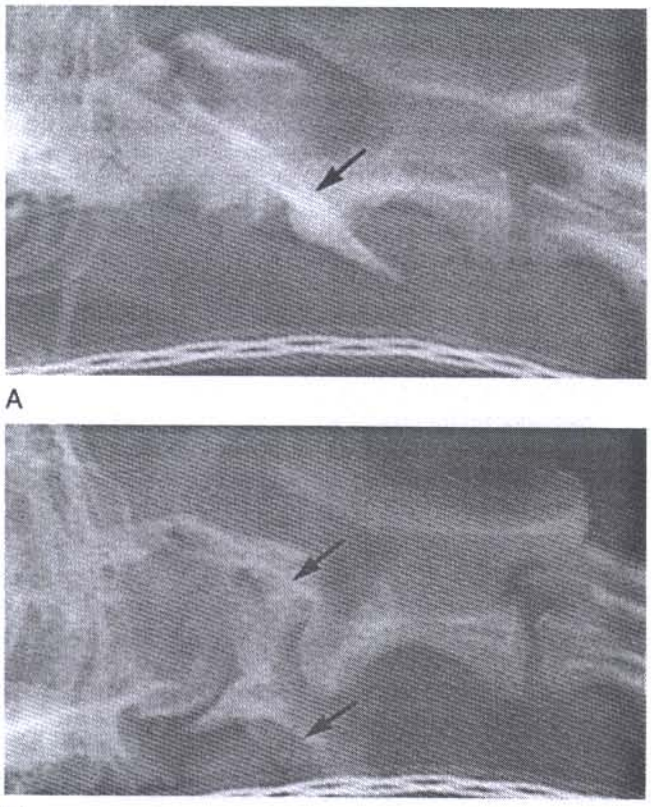


Figure 193-1 Atlantoaxial subluxation and agenesis of the dens. Lateral **(A)** and oblique **(B)** radiographs of the cranial cervical vertebrae of a 10-month-old female miniature dachshund that was tetraparetic after a minor trauma. In the lateral projection **(A)**, the wings of the atlas are superimposed *(arrow)*, obscuring the cranial aspect of the axis. In the oblique projection **(B)**, the cranial aspect of the axis is visible because the wings of the atlas *(arrows)* are rotated out of the primary area of interest, and absence of the dens is confirmed.

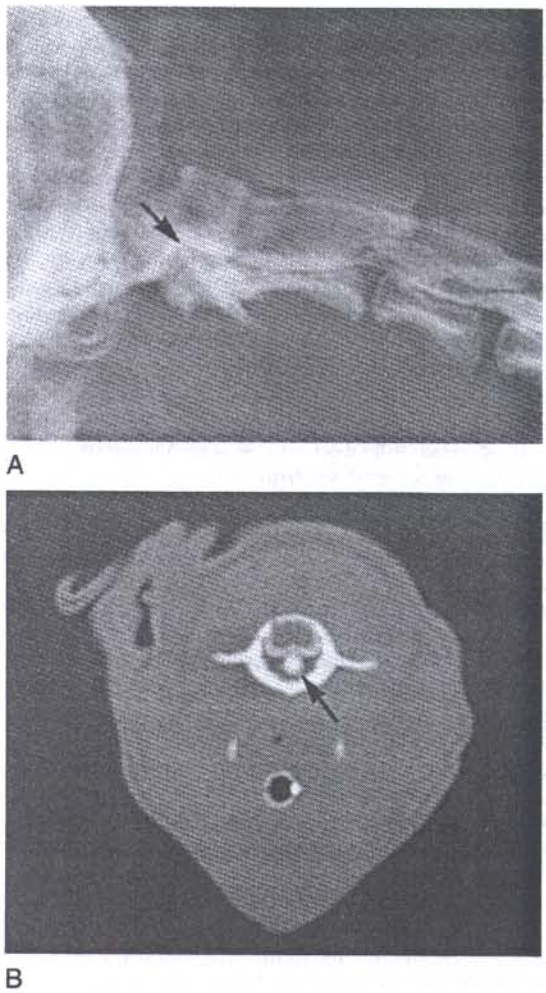


Figure 193-2 Dorsal angulation of the dens. Lateral myelogram **(A)** and transverse computed tomography (CT) image **(B)** taken after myelography of the cranial cervical vertebrae of a 3-year-old male Chihuahua that had an acute onset of tetraparesis and generalized ataxia. The myelogram **(A)** confirms ventral compression of the spinal cord *(arrow)* in the region of the dens. The CT image **(B)** confirms that the dens *(arrow)* is causing compression of the overlying spinal cord.

to stabilize the atlantoaxial joint and is most successful in small dogs. However, clinical signs may recur.

Surgical stabilization or decompression (or both) is indicated in animals with moderate to severe neurologic deficits or recurrent episodes of neck pain unresponsive to medical therapy or splinting and in animals in which angulation of the dens results in spinal cord compression. Various surgical techniques that use either a dorsal or a ventral approach have been described.[32-34]

The prognosis for animals with atlantoaxial instability varies, depending on the severity of the spinal cord injury that occurs. The prognosis is fair to good for those with mild to moderate neurologic deficits and guarded for those with an acute onset of tetraplegia.

Bacterial, Fungal, Rickettsial, or Protothecal Meningomyelitis

Etiology and Pathogenesis

Dogs and cats are affected infrequently by bacterial or fungal meningitis and/or myelitis.[3-6,35,36] Several routes of infection exist. Direct implantation of organisms may occur with a bite wound, spinal puncture, or surgery or may accompany migration of a foreign body, such as a grass awn. Extension may occur from a focus of infection, such as a paravertebral infection, discospondylitis, or dermoid sinus, or from infection following tail docking. Infection may also result from hematogenous spread of systemic infection (e.g., endocarditis). Because clinical signs produced by bacterial or fungal agents depend more on the neural structures affected than on the agent responsible, these agents are discussed together.

Meningitis may be accompanied by infection of the underlying parenchyma of the spinal cord (myelitis). Meningitis and/or myelitis may be focal, multifocal, or disseminated in distribution and is frequently accompanied by meningoencephalitis. Pathologically, meningitis is characterized by infiltration of inflammatory cells into the leptomeninges. Inflammation may occur throughout the entire subarachnoid space of the brain and spinal cord. Myelitis is characterized by necrosis and infiltration of inflammatory cells into the spinal cord parenchyma.

Bacteria that have been isolated from cats or dogs with meningitis and myelitis include *Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus albus,* and *Pasteurella, Actinomyces,* and *Nocardia* spp. Fungal infections have been caused by *Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum,* and *Coccidioides immitis. C. neoformans*

is found ubiquitously and frequently causes infection in immunosuppressed animals. Cryptococcosis is more common in cats than in dogs, and infection may result from extension of nasal infection through the cribriform plate. *Blastomyces, Histoplasma,* and *Coccidioides* infections are found in certain geographic areas in the United States, and in such cases the CNS is infected by hematogenous spread.[1]

Focal epidural infections have been reported to occur, generally as a result of migrating grass awns or penetrating wounds.[37] Proliferation of inflammatory tissue may result in an extradural space-occupying lesion that causes spinal cord compression and clinical signs of a transverse myelopathy.[38] Abscessation may occur within the spinal cord and may have the radiographic appearance of an intramedullary mass.[39]

Rickettsial or protothecal infections may cause meningomyelitis similar in clinical presentation to that resulting from bacterial or fungal infection of the CNS. Ehrlichiosis (*Ehrlichia canis* infection) and Rocky Mountain spotted fever ([RMSF] caused by *Rickettsia rickettsii*) may cause meningoencephalitis or meningomyelitis in dogs. Rocky Mountain spotted fever is transmitted primarily by two outdoor ticks (*Dermacentor variabilis* and *Dermacentor andersoni*), whereas ehrlichiosis is transmitted by a tick that is frequently found inside houses *(Rhipicephalus sanguineus)*. Acutely, both diseases may induce immune-mediated vasculitis in a variety of tissues, including the CNS. Borreliosis, caused by *Borrelia burgdorferi*, has been reported to occur in dogs and may be expected to cause meningomyelitis, as it does in humans.[40] *Prototheca wickerhamii* and *Prototheca zopfii*, species of ubiquitous, colorless, unicellular algae, have been isolated from pyogranulomatous lesions of the spinal cord and other organs. Protothecosis rarely occurs, and infection may depend on inadequate host immune response.[40]

Clinical Findings

Bacterial or fungal infections Clinical signs of meningitis include apparent spinal pain, hyperesthesia, and cervical or thoracolumbar rigidity, occasionally manifested as a "sawhorse" posture.[40] Irritation of the numerous nerve endings in the meninges results in reflex muscle spasms when affected animals are stimulated. Fever is intermittent and is more likely to occur in association with concurrent bacteremia or disseminated fungal infection. Fever may occur in association with primary CNS infections as a result of leukocytic pyrogens in the CSF or hypothalamic circulation.

Neurologic deficits are indicative of associated myelitis or radiculitis, and abnormalities depend on the location and extent of infection. Focal myelitis may result in signs of transverse myelopathy. Disseminated bacterial meningomyelitis often is associated with meningoencephalitis, and clinical signs usually are acute and rapidly progressive. Focal bacterial meningitis and/or myelitis and fungal meningomyelitis may be associated with the development of more slowly progressive clinical signs.

Paraparesis and pelvic limb ataxia are common in animals with cryptococcal meningitis and/or myelitis. Progressive paralysis of a single pelvic limb has been reported in two cats with cryptococcal infection of the lumbar spinal cord. Cats with CNS cryptococcal infections may show an acute onset of clinical signs despite chronic destruction of nervous tissue.

The clinical signs of bacterial or fungal meningitis and myelitis in animals are indistinguishable from those of other causes of meningitis and myelitis, such as granulomatous meningoencephalitis and corticosteroid-responsive meningitis; necrotizing vasculitis of the meningeal arteries and distemper virus myelitis in dogs; and CNS toxoplasmosis and FIP meningomyelitis in cats. The differential diagnosis of meningitis also includes intervertebral disk protrusion (especially in the cervical spine), spinal fracture, discospondylitis, polymyositis, and polyarthritis.

Rickettsial infections Central depression is the most consistent clinical finding in dogs with rickettsial infection. Other abnormalities indicative of spinal cord and/or meningeal involvement include paraparesis, tetraparesis, ataxia, and generalized or localized hyperesthesia.[41,42] Cervical rigidity and apparent pain may occur in animals with RMSF.[1] Neurologic abnormalities indicative of cerebral involvement include vestibular disturbances, seizures, cerebellar abnormalities, and coma. Other clinical signs that occur in dogs with rickettsial infections include listlessness, depression, fever, anorexia, lymphadenopathy, dyspnea, diarrhea, vomiting, hemorrhagic diathesis, and joint pain. Dogs of all ages may be infected, and the clinical signs are often indistinguishable from those of systemic viral infections (especially canine distemper), septicemia, and immune-mediated disorders.

Protothecal infections Clinical signs reported in dogs with CNS protothecosis have included ataxia, circling, and paresis or paralysis. Only the cutaneous form of this disease has been reported in cats.[40]

Diagnosis

Bacterial or fungal infections A diagnosis of bacterial or fungal meningitis and/or myelitis is made on the basis of the results of CSF analysis and isolation of a causative organism by culture of CSF. Clinical signs may reflect meningeal irritation or myelopathy that may be indistinguishable from signs caused by other, noninfectious myelopathies, such as intervertebral disk disease. The presence of fever or an abnormal hemogram cannot be relied upon for diagnosis of meningitis/myelitis, because neither may be seen in affected animals.

Bacterial or fungal meningitis has been reported to result in moderate to severe CSF pleocytosis that reflects the degree of leptomeningeal or ependymal involvement.[13] A finding of more than 5000 WBCs/μL may be noted in some cases. Polymorphonuclear (PMN) cells predominate. Mixed mononuclear and PMN pleocytosis occurs with fungal meningitis, and eosinophils may be present, especially in cases of cryptococcal meningitis. The CSF appears turbid if the cell count is greater than 500 WBCs/μL. Disseminated bacterial meningomyelitis is rarely recognized antemortem in dogs or cats. Focal bacterial epidural, meningeal, or parenchymal infections more commonly occur.

CSF protein may be moderately to markedly increased as a result of increased capillary permeability and leakage of serum proteins into the CSF and probably also owing to local production of immunoglobulins.[13,43] If the CSF protein content is high, fibrin clots may develop. The CSF pressure is usually normal but occasionally is increased, especially in animals with cryptococcal meningitis. Hemorrhage into the CSF may occur; a red or pink supernatant is indicative of recent hemorrhage. Xanthochromia develops if more than 48 hours have elapsed since the hemorrhage. The CSF glucose content (normally 60% to 80% of a simultaneously determined plasma glucose concentration) may be decreased as a result of glucose utilization by micro-organisms and possibly by PMN leukocytes. However, a low CSF glucose concentration is not a consistent finding in animals with bacterial meningitis.

Bacteria or fungal organisms may be identified by staining (i.e., Gram stain or acridine orange) of sedimented or centrifuged CSF. Cryptococcal organisms often are observed in cell preparations of CSF and can be identified with Wright's stain or Gram stain or by use of a wet mount preparation with India ink.

CSF from all animals with CSF abnormalities consistent with meningitis should be submitted for both aerobic and anaerobic bacterial culture and for antibiotic sensitivity testing of any cultured bacterial isolates. CSF fungal culture may also be performed. Negative CSF culture results are common, even in animals in which bacteria or fungal organisms have been

identified in the cerebrospinal fluid. Culturing the sediment of centrifuged CSF or filtering CSF and culturing the filter may increase the likelihood of obtaining a positive CSF culture. Causative organisms may be isolated from blood cultures of animals that are bacteremic or that have a systemic fungal infection. *Histoplasma* organisms may be found in buffy coat or bone marrow neutrophils or monocytes. A large volume of CSF (preferably 2 or 3 mL) should be collected for bacterial and/or fungal culture. If a delay in processing of a CSF sample is anticipated, CSF may be aseptically inoculated into a blood culture bottle for submission to a diagnostic laboratory.

Serology may also be useful in the diagnosis of CNS fungal infections. The titer of antibody-coated latex agglutination to cryptococcal (capsular) antigen may be useful in supporting a diagnosis of cryptococcal meningitis and in assessing the response to therapy. The latex cryptococcal agglutination titer (LCAT) is more sensitive than the indirect fluorescent antibody test and may be used on CSF. However, animals with a localized CNS infection may have a negative titer.[44]

Focal epidural inflammatory lesions may appear as an extradural mass on myelography. Chronic focal meningitis may result in obstruction of CSF flow and blockage of contrast material on myelography as a result of arachnoid adhesions.

Rickettsial infections The characteristic histopathologic lesions of RMSF are necrotizing vasculitis, perivascular accumulation of PMN cells, and lymphoreticular cell infiltration into most tissues of the body, including the meninges and CNS. The histopathologic lesion in canine ehrlichiosis is generalized lymphoid and plasma cell accumulation in the bone marrow, meninges, kidneys, and other organs. The results of CSF analysis of dogs with RMSF may be normal or may show a mild increase in protein (less than 60 mg/dL) and nucleated cells (fewer than 80 cells/μL) with lymphocytes the predominant cell type. Currently, little information is available on the expected CSF findings in animals with ehrlichiosis. In one reported case, the CSF protein and nucleated cell levels were increased, with lymphocytes the predominant cell type. Diagnosis of both diseases is based on serology.[45]

Prototheca infections Neutrophilic or eosinophilic leukocytes often are increased in the CSF of animals with protothecosis. Culture of CSF on fungal media may result in isolation of the organism. Rectal scrapings should also be performed. Fluorescent antibody examination may demonstrate the organism in tissue sections.[40]

Treatment

Bacterial infections In the treatment of bacterial meningitis and/or myelitis, it is desirable to use an antimicrobial that is specific for the causative organism and that crosses the blood-brain barrier (or the blood–spinal cord barrier) in therapeutic concentrations, so that drug concentrations may be maintained after the acute phase of inflammation has subsided[46] (Box 193-5). The blood-brain, blood-spinal cord, and blood–spinal fluid barriers are most permeable to antimicrobials with high lipid solubility, low ionization potential, and low protein-binding affinity.[41,46,47] Antibiotics may be administered to animals suspected of having bacterial meningitis before the results of culture and sensitivity testing have been obtained. The selection of antibiotic should be based on tentative organism identification (by Gram or acridine orange staining) from the CSF, the suspected source of infection, and on the drug's ability to reach effective tissue concentrations in the CNS. High-dose intravenous therapy with a bactericidal drug should be used when possible, although many bactericidal drugs penetrate the CSF poorly. Penicillin and penicillin derivatives in high doses have been recommended for the treatment of CNS infections caused by gram-positive cocci (e.g., penicillin G, 10,000 to 20,000 U/lb given intravenously every 6 hours for at least 7 days). Oxacillin may be used for the treatment of meningitis caused by penicillin-resistant *Staphylococcus* strains (Box 193-5).

Box • 193-5

Antibiotic Penetration of the Cerebrospinal Fluid

Good Levels without Meningeal Inflammation
Chloramphenicol
Sulfonamides
Metronidazole
Trimethoprim-sulfamethoxazole
Isoniazid
Rifampin
Pyrazinamide

Therapeutic Levels with Meningeal Inflammation
Penicillin
Ampicillin
Nafcillin
Oxacillin
Cefotaxime
Ceftriaxone
Ceftizoxime
Vancomycin

Poor or No Penetration, Even with Meningeal Inflammation
Aminoglycosides
Erythromycin
Tetracycline
Clindamycin
First-generation cephalosporins

From Gormley WB et al: Cranial and intracranial bacterial infections. *In* Youmans JR (ed): Neurological Surgery, 4th ed. Philadelphia, WB Saunders, 1996, p 3191.

Most cephalosporins penetrate the CNS poorly.[48] Several third-generation cephalosporins (e.g., cefotaxime) reach effective CNS concentrations and are considered the drugs best suited for treatment of gram-negative meningitis. First- and second-generation[48,49] cephalosporins do not reach effective CSF concentrations and should not be used in the treatment of CNS infections.

Metronidazole is useful for the treatment of most anaerobic infections, is bactericidal, and diffuses well into all tissues, including the CNS.[50] Metronidazole has played an increasingly greater role in the therapy of brain abscesses of humans and is used in combination with high doses of penicillin when aerobes are present. Toxicity (central vestibular signs and cerebellar dysfunction) has been reported in dogs treated with metronidazole.[51] Chloramphenicol reaches higher CSF concentrations than most other antibiotics; however, it is bacteriostatic, and many *Staphylococcus* strains have been shown to be resistant to this drug.[52] Most sulfonamides penetrate the CSF effectively. Sulfadiazine (which is less protein bound than other sulfonamides) penetrates the CSF and nervous tissue better than sulfamethoxazole and is effective if given orally. Data are not available on the concentration of trimethoprim in the CSF of dogs.

Intrathecal administration of antibiotics has been used in humans. Although its use is possible in dogs or cats, multiple CSF

punctures, each requiring anesthesia, are needed. Some drugs are toxic when introduced directly into the CNS (e.g., penicillin may cause seizures), and drugs may not diffuse freely through the cerebrospinal fluid, especially if CSF flow is blocked.

Treatment with antibiotics should be started as soon as possible after submission of CSF for culture. After the results of culture and sensitivity are known, therapy may be altered. Treatment is continued for 4 to 6 weeks; however, treatment for longer periods often is necessary, and relapses are possible. It is also important to identify possible sources of infection outside the CNS (e.g., endocarditis, discospondylitis, and paravertebral abscess). Localized spinal cord or meningeal infections that are well encapsulated may be resistant to antibiotic therapy. Surgical exploration is indicated if focal meningeal or epidural infection refractory to medical therapy is suspected.

Use of corticosteroids in cases of bacterial meningitis and myelitis is controversial. Corticosteroids may reduce inflammation and thereby decrease the resulting spinal cord and nerve root damage; however, such treatment may also decrease host defense mechanisms, resulting in worsening of clinical signs and a higher incidence of relapse.

The prognosis in cases of bacterial meningitis and myelitis depends both on the ability to eliminate the causative organism and on the extent of neurologic deficits. Neurologic deficits that occur as a result of spinal cord or nerve root inflammation may be permanent.

Fungal infections Fungal infection of the CNS of dogs or cats is extremely difficult to eliminate.[40,41] The disease is often multisystemic and is seldom recognized in the early stages of CNS involvement. Amphotericin B is frequently used to treat systemic fungal infections, although it is poorly absorbed into the CSF and nervous tissue. Intrathecal administration of amphotericin B has been recommended, especially in animals with *C. immitis* meningitis, but it may result in arachnoiditis and cranial nerve toxicity.

Combinations of drugs have been recommended. Amphotericin B, ketoconazole (poor CNS penetration), and flucytosine (good CNS penetration) are the main agents used. Rifampin has been used to enhance amphotericin B activity. Combined treatment with amphotericin B and 5-fluorocytosine (5-FU) has been recommended for use in cases of cryptococcosis. Long-term, high-dose ketoconazole therapy is reported to be effective for treatment of cryptococcosis in cats.[53] Sequential LCAT determinations may provide a quantitative indication of the clinical response to treatment of cryptococcosis.[44,54]

Because obtaining therapeutic concentrations of antifungal agents in nervous tissue is difficult, the prognosis for CNS mycotic infections is poor.[55] Newer generation azole antifungal agents (e.g., fluconazole, itraconazole) are currently under investigation for treatment of fungal infections of the CNS.[56-60]

Rickettsial infections Rickettsial organisms appear to be extremely sensitive to tetracyclines (10 mg/lb given orally three times a day for 14 days).[40] Tetracyclines are bacteriostatic, and elimination of the organisms from the body depends on the immunocompetence of the affected animal. Doxycycline has better CNS penetration than oxytetracycline or tetracycline and is used in animals with meningitis or myelitis resulting from RMSF or ehrlichiosis. Chloramphenicol, rather than tetracycline, is used to treat young dogs prior to the eruption of permanent teeth. Severely affected dogs, especially those with neurologic involvement, may die despite therapy. Neurologic deficits may be permanent in affected dogs. Recovery may be prolonged, and pancytopenia persistent, in dogs with chronic ehrlichiosis.

Protothecal infections Treatment of cutaneous protothecosis in a dog with a 6-month course of oral ketoconazole has been reported.[61] Effective therapy for disseminated protothecosis has not been described.

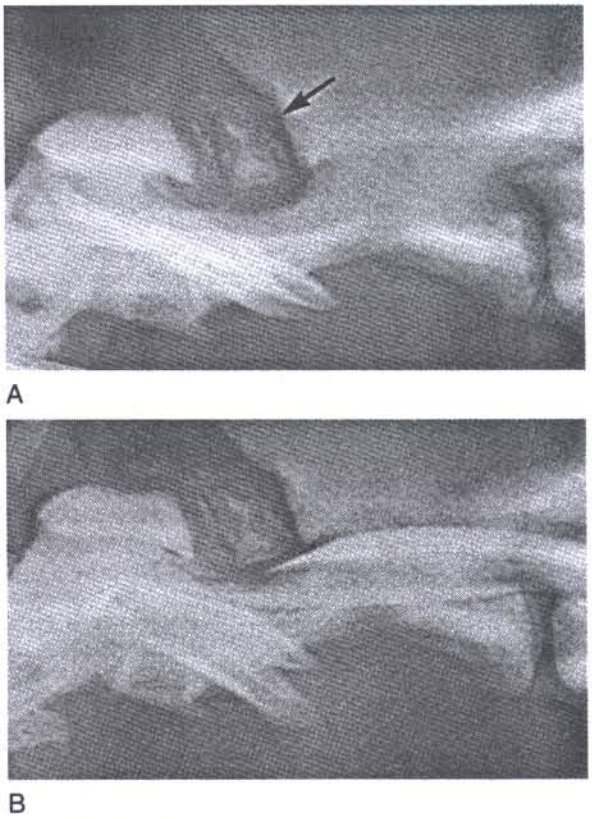
Calcinosis Circumscripta

Calcinosis circumscripta is usually an idiopathic condition that results in circumscribed single or multiple calcium deposits, often in periarticular connective tissue.[62] It occurs mainly in young dogs of large breeds, with an apparently high incidence in German shepherds.[63-65] The clinical signs of spinal cord compression caused by these slow-growing deposits vary, depending on the location of the mass. The diagnosis is made on the basis of radiography. Myelography usually reveals a solitary, rounded, mineralized mass dorsal to the spinal cord that results in extradural spinal cord compression (Figure 193-3). Advanced imaging (CT or MRI) may further delineate the extent of mass lesions. Complete surgical removal of the mass provides long-term resolution of clinical signs.[62-64]

Cervical Spondylomyelopathy

Etiology and Pathogenesis

Several terms have been used to describe this disease of the cervical vertebral column of Great Danes, Doberman pinschers, and other large breed dogs.[66-71] These terms include *wobbler syndrome, caudal cervical malformation-malarticulation, cervical spondylopathy, cervical vertebral instability,* and *cervical vertebral stenosis.* The term *wobbler* is nonspecific; it describes a dog with generalized ataxia and tetraparesis that may be seen with



A

B

Figure 193-3 Calcinosis circumscripta. Lateral radiograph (A) and myelogram (B) of the cranial cervical vertebrae of a 10-month-old neutered male German shepherd with signs of worsening tetraparesis and generalized ataxia. The radiograph (A) confirms a focal area of soft tissue mineralization between the dorsal arch of C1 and the spinous process of C2 *(arrow)*. The myelogram (B) shows dorsal spinal cord compression caused by this mass.

a variety of cervical myelopathies. The number of different terms that have been used reflects the many unanswered questions that remain regarding the etiology and pathogenesis of this condition. The term *cervical spondylomyelopathy* accurately reflects the complexity of the syndrome and therefore has become widely accepted. Although the etiology remains undetermined, the high incidence of the syndrome in certain dog breeds suggests that heredity is a contributing factor. Osteochondrosis resulting from overnutrition and rapid growth may also be a factor.[66-71] In humans, stenosis of the vertebral canal may be clinically "silent" as long as it is not complicated by other factors, such as vertebral instability or intervertebral disk protrusion.

Vertebral instability, either alone or in combination with vertebral malformation and/or soft tissue stenosis, has been suggested as an initiating cause of spinal cord compression and associated neurologic abnormalities.[68] The histopathologic alterations seen in the spinal cord are characteristic of chronic compression and usually involve both white and gray matter. White matter degeneration is noted in tracts cranial and caudal to the level of focal compression. Myelin degeneration appears to predominate over axonal degeneration.

Cervical spondylomyelopathy occurs most frequently in young Great Danes (less than 2 years of age) and middle-aged or older Doberman pinschers (3 to 9 years of age).[66-71] Other breeds that have been reported to be affected are the Saint Bernard, weimaraner, Labrador retriever, German shepherd, boxer, basset hound, Rhodesian ridgeback, Dalmatian, Samoyed, Old English sheepdog, and bull mastiff. Males appear to be affected more often than females. The C5–C6 and C6–C7 vertebrae and disks appear to be affected most commonly, although alterations consistent with a diagnosis of cervical spondylomyelopathy may be seen at the level of C4–C5 and less frequently at C3–C4. Spinal cord compression may be present at more than one site in the cervical spine. Stenosis of the vertebral canal of basset hounds has been reported to occur at C2–C3. Although the lesions seen in all breeds of dogs of all age groups are similar, certain pathologic changes are more characteristic of each particular group. Younger Great Danes frequently have dorsal spinal cord compression as a result of elongation of the cranial aspect of the dorsal arch of affected vertebrae. Older Doberman pinschers frequently have severe ventral spinal cord compression centered over the anulus fibrosus of the affected intervertebral disk.

Clinical Findings

The clinical signs reflect chronic compression of the cervical spinal cord. These signs are most often gradually progressive over several months or years; however, they sometimes may develop acutely, perhaps after an apparently insignificant traumatic episode. Gait deficits are frequently noted initially in the pelvic limbs. A mild pelvic limb ataxia progresses in severity until a wide-based, crouching stance and dragging or knuckling of the toes of the pelvic limbs may be seen. Abnormalities may be more easily observed when an affected dog rises from a lying position, turns, or negotiates stairs or a curb.

Neurologic abnormalities that may be noted in the pelvic limbs include depression or loss of proprioceptive positioning reactions and exaggerated spinal reflexes. Thoracic limb abnormalities most often occur after the development of neurologic deficits in the pelvic limbs, and thoracic limb deficits seldom progress to the level of severity of the pelvic limb abnormalities. Thoracic limb deficits usually are mild and may be evident only during intensive evaluation of postural reactions, particularly thoracic limb hopping reactions. Neurogenic atrophy of the supraspinatus or infraspinatus muscles may be detected; however, widespread LMN involvement in the thoracic limbs is rarely seen. In dogs with a chronic course, a stiff, "choppy" thoracic limb gait may be seen, often in combination with a rigid flexion of the neck. Although affected dogs may resist extension of the neck, apparent neck pain, as seen frequently with an acute cervical disk protrusion, seldom is elicitable.

Diagnosis

Radiography is the most accurate means of delineating the pathologic alterations of cervical spondylomyelopathy.[72,73] A diagnosis of cervical vertebral canal stenosis has been made on the basis of noncontrast lateral radiographs of the cervical spine; however, numerous studies have emphasized that noncontrast radiographs of the cervical spine may be normal in affected dogs. Abnormalities that may be present on noncontrast radiographs include malalignment of vertebrae, remodeling of vertebrae with cranial stenosis of the vertebral canal, new bone formation (spondylosis deformans), narrowing or collapse of one or more intervertebral disk spaces, calcification of the nucleus pulposus of one or more intervertebral disks, sclerosis of vertebral endplates, and degenerative changes of vertebral articular facets. It is important to note that features such as vertebral remodeling with spondylosis deformans, narrowing of intervertebral disk spaces, and asymmetry of articular facets may not be associated with clinically significant vertebral canal stenosis. "Tilting" of adjacent vertebrae, which may be apparent on plain spinal radiographs, may be within normal limits.

Myelography is essential for determining the location or locations, nature, and extent of spinal cord compression. Myelographic findings are essential in the consideration of treatment options and any surgical repair that is to be attempted. The importance of ventrodorsal projections in defining lateral spinal cord compression, and that of dynamic or "stressed" radiographs in outlining dorsal spinal cord compression, in combination with myelography, has been emphasized by several authors. Lateral and ventrodorsal "traction" radiographs are recommended as a method of showing the dynamic nature of a lesion.[68-71]

The myelographic abnormality most frequently recognized in Doberman pinschers is ventral spinal cord compression resulting from a hypertrophied, hyperplastic, or "redundant" dorsal anulus fibrosus. Other findings include dorsal spinal cord compression resulting from hypertrophied or hyperplastic ligamentum flavum, dorsolateral spinal cord compression resulting from malformed articular processes, and spinal cord compression resulting from malformed or malaligned vertebrae.

Dynamic or "stress" radiography, after myelography, may be of value in demonstrating instability, ventral spinal cord compression as a result of dorsally protruding intervertebral disks, or dorsal spinal cord compression as a result of ventrally protruding interarcuate ligament or joint capsule. A dorsal extended view is appropriate for demonstrating dorsal spinal cord compression due to interarcuate ligament hypertrophy/hyperplasia. It has been reported, however, that routine use of "stressed" views is not warranted because of the possibility of misinterpretation of alterations and because of the risk of further injury to a spinal cord that may already be severely compromised.

"Traction" radiography, for which firm traction is placed on the cervical spine during exposure of a lateral or ventrodorsal radiograph, may further delineate the dynamic nature of a lesion. With this technique, spinal cord compression resulting from "redundant" or protruding anulus fibrosus may be relieved by the procedure. Failure to relieve the compression with "traction" may indicate a static lesion, such as a disk protrusion. It should be noted that "traction" may relieve the compression evident on lateral radiographs, whereas the lateral compression seen on ventrodorsal radiographs may remain. "Traction" views in both the lateral and ventrodorsal projections are recommended

after myelography, because they do not appear to increase spinal cord compression and they provide useful information for the selection of an appropriate surgical technique.

Advanced imaging modalities (e.g., CT or MRI) may be useful for further defining the nature and extent of spinal cord and nerve root involvement in caudal cervical spondylomyelopathy and for differentiating this condition from other causes of caudal cervical spinal cord compression.[74]

Treatment

Numerous regimens have been recommended for the management of dogs with cervical spondylomyelopathy.[66-78] Treatment is directed toward relief of clinical signs through medical therapy and management practices or toward surgical relief of spinal cord compression. The large number of recommended treatments reflects the variety of lesions demonstrated by various diagnostic techniques, the variable results achieved by investigators, and the personal bias of individual surgeons. In most dogs the disease course is chronic and progressive, and the prognosis, in the absence of treatment, is guarded to poor.

Medical therapy consists of the use of anti-inflammatory medications and management procedures that reduce neck movement, such as close confinement or use of a neck brace.[68-71] Some affected dogs may be maintained at an acceptable level of neurologic function for months to years with corticosteroid administration. In some dogs, corticosteroid therapy may be discontinued during periods of improved neurologic function and re-established during periods of relapse of neurologic abnormalities. The adverse effects of long-term corticosteroid therapy must be considered, and it must be remembered that in most cases, this approach does not address the underlying sustained spinal cord compression.

Techniques for surgical management attempt to correct the underlying spinal cord compression.[66-82] The high potential for morbidity and postoperative complications associated with surgical management of cervical spondylomyelopathy must be considered before surgery is recommended. These considerations must be balanced against the current knowledge of the natural progression of the disease. Surgical procedures may use either a dorsal or a ventral approach to the vertebral column. The primary objective of all surgical procedures is decompression of the spinal cord or stabilization of affected vertebrae, or both.

The prognosis for dogs with cervical spondylomyelopathy is difficult to determine. In general, medical therapy may be expected to provide clinical improvement for a variable period (weeks to years). Medical therapy does not alter sustained and often progressive spinal cord compression. Surgical therapy that relieves spinal cord compression may be associated with postoperative complications; however, the following statements may be made: (1) The prognosis for dogs with a chronic history of worsening signs is not as favorable as for dogs with an acute onset of signs; (2) mildly affected dogs have a fair prognosis for recovery; (3) dogs with a single level of compression appear to have a better prognosis after surgery than those with multiple-level compressions; (4) long-term follow-up of dogs treated by fusion reveals that up to 19% of dogs develop spinal cord compression at an adjacent interspace an average of 20 months after surgery.[83]

Overall, the prognosis for long-term resolution of clinical signs must be considered guarded, regardless of the type of therapy.

Congenital Vertebral Anomalies

Etiology and Pathogenesis

Vertebral anomalies frequently occur in cats or dogs as a result of disturbances in embryonic development.[31,84,85] Most such anomalies are not clinically significant. If a vertebral anomaly causes instability or deformity of the vertebral canal, or spinal cord or nerve root compression, clinical signs may result. Multiple spinal anomalies may occur in a single dog or cat.

The most frequently recognized vertebral anomalies are alteration in location of the anticlinal vertebrae, anomalies of articular processes, variations in numbers of vertebrae, transitional vertebrae, butterfly vertebrae, block vertebrae, nonfusion of sacral vertebrae, or hemivertebrae. Of these anomalies, hemivertebrae are the most significant as a cause of neurologic abnormalities.[31]

Hemivertebrae Hemivertebrae are wedge shaped, and the apex may be directed dorsally, ventrally, or medially across the midline.[31] Hemivertebrae may be associated with moderate to severe angulation of the spine and may be displaced dorsally during growth by pressure from adjacent vertebrae. Hemivertebrae occur most commonly in the thoracic spine of "screw-tailed" brachycephalic breeds (French and English bulldogs, pugs, and Boston terriers), but they may occur at any location in any breed of dog. Thoracic hemivertebrae are the development of caudal hemivertebrae. Kyphosis, scoliosis, and lordosis are commonly associated with hemivertebrae.

Block vertebrae Block vertebrae may involve the vertebral bodies, vertebral arches, dorsal spinous processes, or entire vertebrae, at any level of the vertebral column. The sacrum is considered a "normal" block vertebra. Block vertebrae may be the same length as the number of involved vertebrae or shorter and can result in abnormal angulation of the spine. Partial "blockage" of vertebral bodies may occur, allowing partial development of an intervertebral disk.

Butterfly vertebrae Butterfly vertebrae result from persistence of the notochord. In some instances, sagittal cleavage of the notochord may result in a sagittal cleft dorsoventrally through the vertebral body. On a dorsoventral radiograph, such vertebrae resemble a butterfly with wings spread. Compensatory growth of the adjacent normal vertebrae often fills in the funnel-shaped depression of the vertebral endplates. Butterfly vertebrae are most commonly seen in brachycephalic "screw-tailed" breeds.

Transitional vertebrae Dogs may have variations in the number of cervical, thoracic, lumbar, or sacral vertebrae. Furthermore, congenital absence or alteration in the shape of vertebral articular processes and variation in the location of the anticlinal (usually T11) and diaphragmatic (usually T10) vertebrae may occur. Vertebrae that have the characteristics of two major divisions of the vertebral column are referred to as *transitional vertebrae.* Observed alterations include transverse processes of C7 resembling a rib, a transverse process on the most caudal thoracic vertebra in place of a rib, the first sacral vertebra having a transverse process, and the last lumbar vertebra having a transverse process that has fused with the ilium. These alterations may be accompanied by an alteration in the size and shape of the vertebral body or in the plane of the vertebral body or intervertebral disk.

Clinical Findings, Diagnosis, and Treatment

Congenital vertebral anomalies frequently occur; however, clinical signs related to anomalous vertebrae are not present in most affected animals. In most animals in which clinical signs develop, trauma to the spinal cord has occurred secondary to vertebral instability or progressive deformity with growth. Diagnosis of a vertebral anomaly is made using radiographs of the vertebral column (Figure 193-4). Radiographically, hemivertebrae and adjacent vertebrae appear to be formed of normal bone, and disk spaces are usually normal or widened. Vertebral bodies appear to have a portion absent and do not appear to be compressed. Adjacent vertebrae frequently have

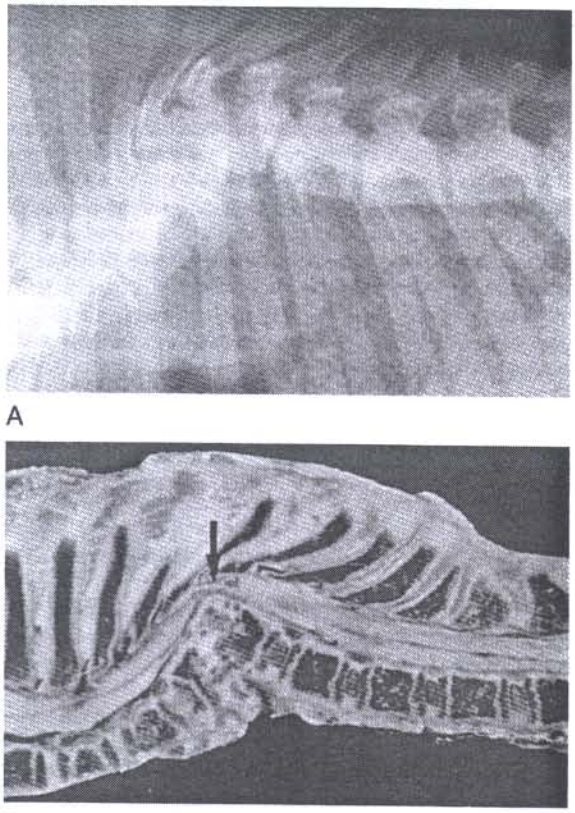


Figure 193-4 Hemivertebrae. Lateral radiograph **(A)** of the midthoracic region of the vertebral column of a 3-month-old male malamute that had a history of inability to use the pelvic limbs since birth. Pain perception was absent in the pelvic limbs. Note the kyphosis associated with hemivertebrae affecting three midthoracic vertebrae. Severe spinal cord compression *(arrow)* is seen in a gross necropsy specimen **(B)** of the vertebral column sectioned in the midsagittal plane.

an altered shape that conforms to the defect found in the congenitally affected segment. Vertebral endplates are smooth and of normal thickness. Hemivertebrae should be differentiated from vertebral compression caused by a traumatic fracture, pathologic fracture as a result of vertebral neoplasia, or osteomyelitis. In most cases myelography is necessary to detect spinal cord compression resulting from a congenital anomaly. Advanced imaging (CT or MRI) may be useful in further defining the extent of vertebral and spinal cord involvement. Vertebral anomalies resulting in spinal cord compression and instability of the vertebral column may be treated through surgical decompression, vertebral realignment, and stabilization.[86]

Corticosteroid-Responsive Meningitis-Arteritis

Etiology and Pathogenesis

Corticosteroid-responsive meningitis-arteritis, which occurs in young, medium to large breed dogs, may be the most frequently occurring form of meningitis.[87-89] The etiology is unknown; however, immunopathologic mechanisms are suspected, because IgA seems to play a central role in the pathogenesis.[21,90-92] It has been suggested that repeated vaccinations with multivalent modified live vaccines may be a cause. The clinical and clinicopathologic findings associated with this disease are similar to those seen in dogs with necrotizing vasculitis of the spinal meningeal arteries.[49,93-98]

Clinical Findings

Affected dogs are usually 7 to 16 months of age. Clinical signs include reluctance to move, arched back, stiff gait, apparent cervical and/or thoracolumbar pain, fever, muscle rigidity or spasms, apparent pain on opening the mouth and, less commonly, neurologic deficits, such as decreased proprioceptive positioning, paraparesis, or tetraparesis. Optic neuritis has been reported in an affected animal.[87] The clinical signs are indistinguishable from those of meningitis and myelitis of other causes (bacterial, fungal, viral) and from necrotizing vasculitis of spinal meningeal arteries. Clinical signs may be acute in onset and progressive, or they may follow a waxing and waning course over a period of weeks or months.

Diagnosis

The diagnosis is made on the basis of increased white blood cells in the CSF, failure to isolate an infectious agent from the CSF, and response to therapy with corticosteroids. Most affected dogs may have a mature neutrophilia in peripheral blood. The WBC count of the cerebrospinal fluid may be normal or may range from 50 to more than 3000 cells/μL, with predominantly mature neutrophils. Neither bacteria nor fungi are seen in the white blood cells. The CSF protein concentration most often is increased (40 to 350 mg/dL). Bacterial (aerobic and anaerobic) and fungal cultures of the CSF, urine, and blood are negative. It may be difficult to differentiate this disease from granulomatous meningoencephalomyelitis on the basis of CSF analysis. Examination of the IgG index and the IgM and IgA contents of the CSF may be useful in distinguishing corticosteroid-responsive meningitis from other causes of meningitis, such as chronic distemper encephalitis or granulomatous meningoencephalitis of dogs.[21]

Treatment

Early diagnosis is essential for successful treatment.[92] Initially, a corticosteroid is given at a dosage sufficient to produce remission of clinical signs (prednisone, 1 to 2 mg/lb/day). Corticosteroids are reduced slowly over several months to the lowest dose necessary to maintain remission of the clinical signs. Maintenance treatment using every other day dosing is preferred. Approximately 50% of affected animals have recurrence of clinical signs after corticosteroid therapy is discontinued. Increasing the corticosteroid dose may be necessary if clinical signs recur. Therapy for up to 6 months may be necessary to prevent recurrence of clinical signs. Ideally, CSF analysis results should be within normal limits before therapy is stopped.[92] The prognosis for eventual resolution of clinical signs is good. Treatment with antibiotics may be indicated initially if the diagnosis is uncertain and bacterial meningitis is suspected.

Degenerative Myelopathy

Etiology and Pathogenesis

Degenerative myelopathy is characterized by slowly progressive ataxia and paresis of the pelvic limbs. Histologically, demyelination, axonal degeneration, and astrocytosis in the white matter of the spinal cord are seen. These changes are found throughout the spinal cord and are most severe in the thoracic spinal cord segments, especially in the dorsolateral and ventromedial funiculi.[99-101] The etiology of degenerative myelopathy is unknown in dogs.[102,103] Dural ossification, spondylosis deformans, chronic intervertebral disk protrusion, or infectious or vascular disorders may occur concurrently with degenerative myelopathy. The occurrence of degenerative myelopathy predominantly in German shepherds suggests a genetic basis for the disease, although there is no direct evidence to support this.

Clinical Findings

Degenerative myelopathy generally occurs in dogs 6 years of age or older, although a similar condition has been reported in German shepherds 6 and 7 months of age.[104] Males are affected more often than females. It has been reported most commonly in German shepherds and German shepherd–mixed breed dogs, although it does occur in other large and medium breeds.[99-101]

Affected dogs usually have a slowly progressive paraparesis and pelvic limb ataxia. The onset of clinical signs is gradual. Neurologic deficits often are more noticeable when the dog walks on a smooth surface. Affected dogs may have worn pelvic limb toenails. Although neurologic deficits are most often present bilaterally, they may be asymmetric. Paraparesis and ataxia progressively worsen, so that most affected dogs become nonambulatory within several months to 1 year after neurologic deficits are first detected. Paralysis of the pelvic limbs rarely occurs, probably because most large dogs are euthanized if they become nonambulatory.

Apparent pain or discomfort is not evident in affected dogs. Voluntary control of urination and defecation is retained, although affected dogs may not be able to urinate or defecate in an appropriate place owing to severe paraparesis or inability to assume a voiding posture. This is important, because some dogs have apparent incontinence in the house, which may suggest a lesion of the cauda equina or sacral spinal cord segments. Muscle atrophy is not severe in the initial stages of the disease but may become noticeable in later stages; it is due to disuse rather than denervation. Cutaneous and deep pain perception remain intact throughout the course of the disease.

The neurologic examination findings usually are indicative of a transverse myelopathy between T3 and L3. Abnormalities include decreased or absent conscious proprioception and placing reactions in the pelvic limbs, normal to exaggerated patellar reflexes, normal to exaggerated withdrawal reflexes in the pelvic limbs, normal anal sphincter tone and anal reflex, normal muscle tone in the tail and, in some cases, crossed extensor reflexes in the pelvic limbs. The panniculus reflex usually is normal bilaterally. It is important to note that patellar reflexes may be decreased or absent unilaterally or bilaterally in some cases, possibly as a result of degeneration of the dorsal root ganglia or dorsal gray matter of the lumbar spinal cord (i.e., an afferent rather than a LMN lesion).

Diagnosis

Diagnosis of degenerative myelopathy is based on the clinical findings, the age and breed of the dog, and the ruling out of all other causes of a transverse myelopathy in the T3 to L3 region of the spinal cord. Diseases to be considered in the differential diagnosis include discospondylitis, myelitis, spinal cord compression due to type II intervertebral disk protrusion, and spinal neoplasia. Radiographs of the vertebral column may be normal or may demonstrate degenerative changes, such as dural ossification, spondylosis deformans, or narrowed intervertebral disk spaces. An increased protein content (40 to 100 mg/dL) is often found in CSF collected from the lumbar subarachnoid space. The CSF protein level is usually normal in samples collected from the cisternal subarachnoid space. The WBC count is normal in both lumbar and cisternal CSF. Significant myelographic abnormalities are not found.

Treatment

Effective treatment has not been reported, and affected dogs usually progress to severe nonambulatory paraparesis within a year of initial diagnosis. Therapy with vitamin supplementation, epsilon-aminocaproic acid (EACA), N-acetylcysteine, and exercise has been recommended by one author.[99-101] However, to date no controlled studies have shown that this therapeutic regimen is of any benefit.

Diffuse Idiopathic Skeletal Hyperostosis

Etiology and Pathogenesis

Diffuse idiopathic skeletal hyperostosis (DISH) is a diffuse ossifying condition of young dogs (predominantly large and giant breeds) or cats.[105,106] It has been suggested that four of the following five criteria be met for confirmation of DISH in dogs: (1) flowing calcification and ossification along ventral and lateral aspects of three contiguous vertebral bodies, leading to segmental bony ankylosis; (2) relative preservation of disk width in involved areas, and absence of extensive radiographic changes of degenerative disk disease (e.g., endplate sclerosis, nuclear calcification, or localized spondylosis deformans); (3) periarticular osteophytes surrounding true vertebral joints; (4) formation of pseudoarthrosis between the bases of spinous processes; and (5) periarticular osteophytes and calcification and ossification of soft tissue attachments (enthesiophytes) in both the axial and the peripheral skeleton.[105] Other associated findings may include periarticular osteophytes, sclerosis and ankylosis of sacroiliac joints, and bony ankylosis of the symphysis pubis.

The etiology of this condition is obscure. DISH is a disease that most likely represents a "vulnerable state" in which extensive vertebral ossification results from some stimulus that causes only modest new bone formation in most animals. These "bone formers" have a high incidence of associated extraspinal hyperostosis at the sites of ligament or tendon attachment. The pathologic alterations in DISH include findings consistent with spondylosis deformans; however, DISH differs quantitatively and qualitatively from spondylosis deformans and represents a regional ossification encompassing ligaments, paraspinal connective tissue, and anulus fibrosus, as well as periosteal new bone formation on the ventral surface of the vertebrae.[107-109] Spinal rigidity of several vertebrae resulting from DISH may result in syndromes caused by "dynamic overload" of an adjacent "mobile segment" of the vertebral column. Typically, a rigid fusion of several lumbar vertebrae may result in degenerative changes (e.g., sclerosis, spondylosis deformans, disk protrusion) that affect the "overloaded" disk immediately cranial to the fused segments. The degenerative changes in the adjacent disk may result in clinical signs associated with spinal cord compression or nerve root entrapment.

Clinical Findings

Clinical signs, which may be minimal compared with the dramatic radiographic changes, include mild apparent spinal pain, stiff or stilted gait, and difficulty jumping. Rarely, clinical signs of spinal cord compression resulting from extreme bony proliferation and spinal canal stenosis may result in a transverse myelopathy between T3 and S3. Nerve entrapment may result from bony proliferation at the level of the intervertebral foramen.

Diagnosis and Treatment

The diagnosis is based on radiographic confirmation of the diagnostic criteria listed above (Figure 193-5).[105] Analysis of CSF and myelography are necessary to rule out other disorders that may result in similar clinical signs. Advanced imaging (CT or MRI) may be useful for accurately investigating the possibility of spinal cord compression or nerve root entrapment resulting from bony proliferation.

Treatment for DISH has not been described. Conservative (medical) management is recommended unless clinical signs of spinal cord compression or nerve root entrapment are present, in which case surgical decompression may be considered.

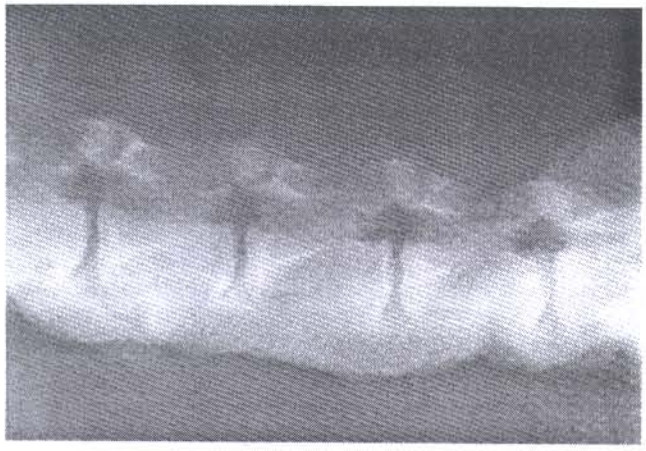


Figure 193-5 Diffuse idiopathic skeletal hyperostosis (DISH). Lateral radiograph of the lumbar region of a 4-year-old neutered male Akita. Note the smooth proliferative laminar bridging of the ventral aspects of L4 through L7, consistent with a diagnosis of DISH. The intervertebral disks in this region do not appear to be narrowed. Spondylosis deformans is present at L7–S1. Proliferative remodeling changes are observed at multiple articular facets along the lumbar spine.

Discospondylitis (Spondylitis, Vertebral Osteomyelitis)

Etiology and Pathogenesis

Bacterial or fungal infection of the intervertebral disks and adjacent vertebral bodies (discospondylitis) or of only the vertebral bodies (spondylitis) may cause extradural spinal cord or cauda equina compression as a result of granulation tissue, bony proliferation, or pathologic fracture or luxation. Less commonly, discospondylitis may lead to diffuse or focal meningitis and myelitis.[110-113] These conditions result from implantation of bacteria or fungi introduced by migrating plant awns (grass seeds, foxtails), hematogenous spread, extension of a paravertebral infection, a penetrating wound, or previous disk or vertebral surgery.

Discospondylitis and spondylitis occur more commonly in dogs in areas where grass awn infections are a problem. Several theories attempt to explain the migration of grass awns to the vertebral column. Awns may be swallowed and migrate through the bowel wall (possibly at the caudal duodenal flexure), through the mesentery to the attachment to ventral epaxial muscles, and to the vertebral column. Evidence of scarring, however, has not been found in the gut or abdomen of dogs with discospondylitis. Because dogs with discospondylitis thought to be due to plant awn migration have lesions most commonly in the cranial lumbar spine (L2–L4), it has been suggested that awns may be inhaled and migrate through the lungs to the diaphragm, lodging at the crural insertion on the lumbar vertebrae. Plant awns may also migrate through skin and paravertebral or abdominal muscles to the vertebral column. Grass seeds are able to travel long distances owing to the direction of the barbs. Forward progress may be aided by muscle movements.

Hematogenous spread of bacteria or fungi is probably the most common cause of discospondylitis. Sources of infection include bacterial endocarditis, dental disease, and urinary tract infections. Retrograde flow in the vertebral veins has been suggested as a possible route of infection to the vertebral column. It is not known whether discospondylitis associated with urinary tract infection is due to venous or arterial dissemination of bacteria or whether a direct causal relationship exists between urinary tract infection and discospondylitis. Many dogs with discospondylitis have concurrent urinary tract infection. Discospondylitis caused by *Brucella canis* infection most likely results from bacteremic spread from a genital infection.

Affected intervertebral disks may show evidence of degeneration (collapsed disk space, spondylosis deformans) or trauma (traumatic disk protrusion, vertebral luxation). Discospondylitis may occur with increased frequency in immunocompromised animals.[114-116] The organisms most commonly isolated from the blood, affected vertebrae, and urine of dogs with discospondylitis are coagulase-positive *Staphylococcus* spp. *(S. aureus, S. intermedius)*, although a number of other organisms have been identified.[110-112,116-120] Discospondylitis has been reported to occur in cats.[121]

Clinical Findings

Discospondylitis may occur in dogs or cats of any age, but it is most commonly seen in giant and large breed dogs. Any level of the vertebral column may be affected, and multiple lesions may be seen in either adjacent or nonadjacent vertebrae. Discospondylitis occurs more commonly in the thoracic and lumbar spine than in the cervical spine. The lumbosacral disk space frequently is involved.

Clinical findings depend on the location of the affected vertebra or vertebrae. The most common clinical signs are weight loss, anorexia, depression, fever, reluctance to run or jump, and apparent spinal pain (which may be severe). Hyperesthesia may be present only over the site of the lesion or may be poorly localized, especially with involvement of multiple sites.[110]

Diagnosis

Diagnosis may be difficult, because clinical signs often are nonspecific. Discospondylitis should always be considered in an animal with fever of unknown origin. If the lumbosacral intervertebral disk is involved, dogs often show a stilted, short-strided pelvic limb gait and shifting pelvic limb lameness. Clinical signs may be present for several weeks or months before diagnosis.

Neurologic deficits associated with spinal cord or cauda equina compression may be present and may reflect either a transverse or a multifocal myelopathy. Neurologic deficits associated with a transverse myelopathy (T3–L3) occur most commonly and include paraparesis, decreased conscious proprioception, exaggerated spinal reflexes and, much less commonly, paraplegia. Cervical lesions most commonly cause only apparent cervical pain, and lumbosacral lesions may cause neurologic deficits due to compression of nerves of the cauda equina. Rarely, animals may demonstrate clinical signs of diffuse suppurative meningitis associated with extension of infection to involve the spinal meninges. Dogs may have a history of draining tracts in the paravertebral area associated with grass seed migration. Discospondylitis has been described in dogs with osteomyelitis in other sites (femur and sternum).

Affected animals may have a normal or elevated peripheral WBC count. Typical radiographic findings are destruction of the bony endplates adjacent to an infected disk, collapse of the intervertebral disk, and varying degrees of new bone production. Early lesions may consist only of lytic areas in affected vertebral endplates. More advanced lesions show a mixture of bone lysis and extensive new bone production, with osteophytes bridging adjacent vertebrae containing a central destructive focus (Figure 193-6). Affected vertebral bodies may be shortened, and bony proliferation may result in fusion of one or more vertebrae. Discospondylitis may be superimposed on other vertebral abnormalities, including fracture and associated callus formation, spondylosis deformans, or a surgical site.

Because discospondylitis may be present in more than one site in the vertebral column, it is important that the entire

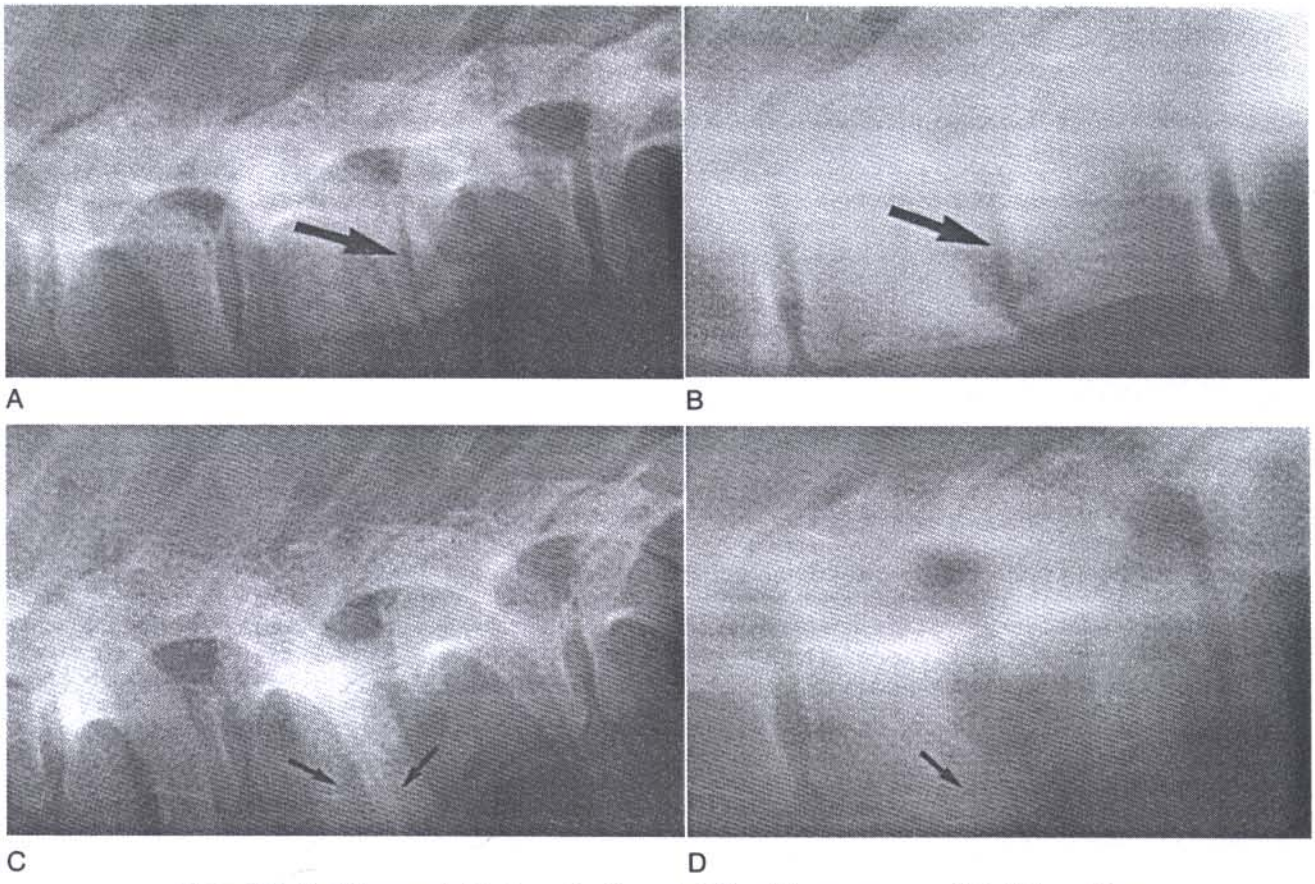


Figure 193-6 Discospondylitis. Lateral radiograph **(A)** and linear tomogram **(B)** of the midthoracic vertebral column of a 1-year-old female Doberman pinscher 8 weeks after the onset of apparent back pain. Note the collapse of the T6–T7 disk *(large arrow)*, the destruction of the vertebral endplates, and the well-delineated lysis of the T6 and T7 vertebral bodies. These changes are easily observed on the tomogram, where superimposed ribs are not a factor. Lateral radiograph **(C)** and linear tomogram **(D)** of the midthoracic vertebrae completed 3 months after **A** and **B**. The dog had undergone a 4-week course of a broad-spectrum antibiotic that resulted in clinical improvement after the initial radiographic examination; however, signs of spinal pain had returned. Note the progression of the radiographic changes seen 3 months earlier and the bony proliferation *(small arrows)* at T6–T7. After surgical biopsy and culture of the T6–T7 disk, therapy with an appropriate antibiotic drug was commenced. Complete radiographic resolution of the discospondylitis and fusion of the T6–T7 vertebrae were apparent after 6 months of continued antibiotic therapy.

spine be radiographed in animals suspected of having discospondylitis. Occasionally clinical signs may occur before characteristic radiographic changes are evident. Tomography may also be a useful method of radiographic diagnosis of discospondylitis, particularly at the lumbosacral junction (Figure 193-7). Bone scintigraphy may be useful for detection of early lesions prior to the development of radiographically evident lesions and for investigation in animals in which it is uncertain whether lesions are due to infection or other causes (e.g., severe spondylosis deformans). Advanced imaging (CT or MRI) may be useful in the identification of subtle vertebral lesions.[110,122]

Collection of CSF is indicated for animals with neurologic deficits. The CSF may be normal or may have an increased WBC count and/or protein content when discospondylitis lesions cause extradural compression of the spinal cord or result in meningitis and/or myelitis. Myelographic findings usually indicate extradural compression that results from extension of granulation tissue and bony proliferation in the spinal canal. Clinical signs do not always correlate well with the degree of compression seen on myelography and depend on factors such as the rate, duration, and degree of compression. Aerobic, anaerobic, and fungal cultures of blood and urine should be done prior to treatment in an attempt to isolate causative organisms. Some authors consider any organism other than *S. intermedius* cultured from the urine unlikely to be the causative organism unless it is also cultured from the blood or a vertebral lesion. Cultures of CSF are indicated if the WBC count is elevated. Cultures of fluid from draining sinuses may also be performed. In all dogs with discospondylitis, efforts should be made to determine whether *B. canis* infection is present.[117]

Surgical biopsy may be indicated in affected dogs in which a causative organism is not isolated from blood or urine and/or in animals that are unresponsive to treatment with broad-spectrum antibiotics. Fluoroscopy-guided needle aspiration of lesions is possible in some animals.[123] However, cultures of samples collected in this way are often negative, especially if animals have been treated with antibiotics prior to the biopsy.

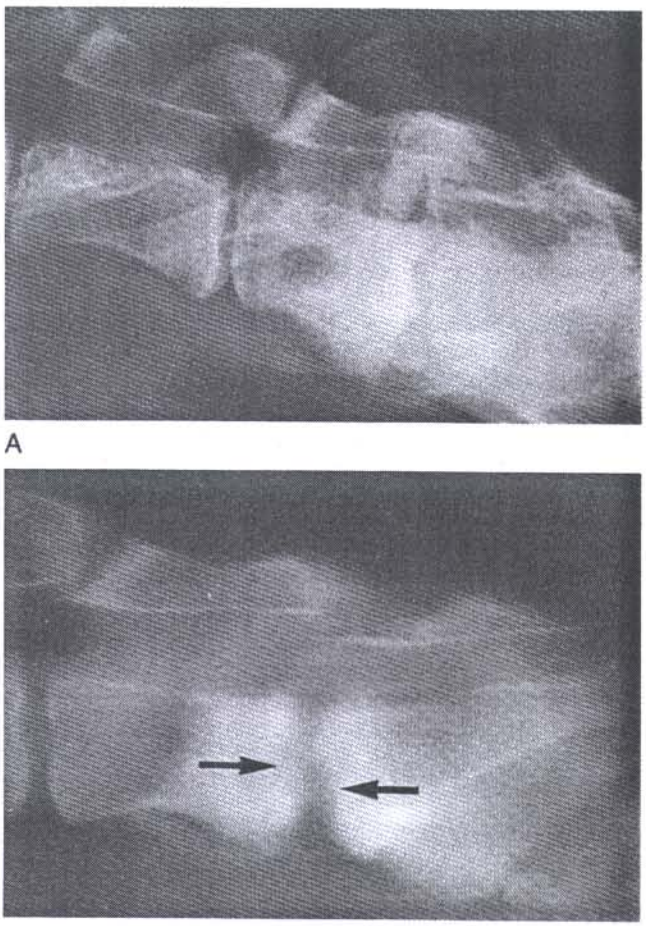


Figure 193-7 Discospondylitis. Lateral radiograph **(A)** and linear tomogram **(B)** of the lumbosacral region of the vertebral column of a 4-year-old German shepherd that had a 1-month history of apparent pain and pelvic limb weakness. Note the sclerosis of the vertebral endplates, spondylosis deformans, new bone formation, and collapsed disk seen on the radiograph of L7–S1. A tomogram of this region confirms the presence of bone lysis *(arrows)* consistent with a diagnosis of discospondylitis. *Staphylococcus aureus* was cultured from the urine and blood and from material obtained from the L7–S1 disk by needle aspiration.

Treatment

Treatment consists of long-term use of an antimicrobial that is effective against the causative organism or organisms detected by blood and/or urine cultures. If an organism is not cultured, dogs without severe neurologic deficits may be treated empirically, assuming infection with the most common organism isolated from animals with discospondylitis (coagulase-positive *Staphylococcus* spp.). The antibiotics most effective for this purpose are cephalosporins or beta lactamase–resistant penicillins (e.g., oxacillin and cloxacillin). A trimethoprim/sulfonamide combination or chloramphenicol is less effective, but it is less expensive and may be effective in some cases.

Clinical signs may recur if the infection is not completely eliminated prior to cessation of antibiotic therapy, and repeated cultures of blood and urine, as well as ongoing treatment with an appropriate antibiotic, may be necessary. Treatment is continued for at least 6 weeks, and vertebral radiographs are taken every 2 to 3 weeks to monitor the progression or regression of a lesion and to monitor for the development of new lesions. Antibiotic administration may be necessary for up to 6 months before radiographic evidence of resolution of lesions is seen. Clinical improvement in animals with discospondylitis (resolution of fever, improved appetite, reduction of apparent spinal pain) should be seen within 2 weeks of initiation of antibiotic therapy. Surgical exploration of a lesion should be considered in animals that are unresponsive to treatment or that have persistent draining tracts suggestive of grass seed migration. The objectives of surgery are curettage of lesions and harvesting of material for bacterial and fungal culture. A cancellous bone graft has been recommended after curettage of a disk space. Decompressive surgery is indicated if evidence of spinal cord compression is found on myelography and if the animal shows severe or progressive neurologic deficits. Surgical stabilization of the vertebrae may be necessary after decompression.[124]

Distemper Myelitis

Etiology and Pathogenesis

Canine distemper (CD) virus is a neurotropic virus that may cause focal or diffuse demyelination in both gray and white matter of the CNS.[125] The mechanism by which demyelination occurs is not known, but the condition may be a primary effect of the virus on glial cells or may occur secondary to immunologic mechanisms. The white matter of the cerebellum, cerebellar peduncles, optic nerves, optic tracts, and spinal cord are most severely affected. Focal or diffuse demyelination may occur in the white matter of the spinal cord.[126,127] Further histopathologic changes seen in the spinal cord and throughout the CNS include perivascular cuffing by mononuclear cells, gliosis, microglial proliferation, inflammatory cell infiltration of the pia arachnoid, and neuronal changes (nuclear pyknosis, chromatolysis, shrunken cells, and neuronophagia). Intranuclear and intracyloplasmic inclusions may or may not be present.

Clinical Findings

Affected animals may or may not have a history of systemic illness. Dogs of any age may be affected, but those with myelitis due to CD infection are usually less than 3 years of age. Dogs that have been vaccinated according to recommended schedules may be affected. Clinical signs of CD myelitis reflect the location of the lesion or lesions, which may be focal or diffuse, at any point in the spinal cord. The T3 to L3 spinal cord segments are affected most often, and clinical signs indicative of a transverse myelopathy in this region are seen. Neurologic abnormalities include paraparesis or paraplegia and normal to exaggerated reflexes in the pelvic limbs. Neurologic deficits are progressive and bilateral; however, they may be asymmetric. Affected dogs may have clinical signs indicative of current or previous systemic CD infection. Neurologic deficits commonly seen in dogs with CD infection are vestibular and/or cerebellar abnormalities and visual deficits.[128] Self-mutilation occasionally is seen in dogs with CD infection. The limbs and tail are the common sites of mutilation. Paresis or paralysis of the limbs may also be present.

Distemper myoclonus Myoclonus, the rhythmic twitching of a muscle or muscle group, is most often associated with CD infection.[129] Any muscles may be involved, including the facial and masticatory muscles or the limb muscles. The pathogenesis of myoclonus is unknown. It is thought to result from an abnormality in the motor neuron and interneuron pools of the medulla and spinal cord. Animals may recover from systemic CD infection and occasionally from CNS infection; however, myoclonus may persist. Myoclonus is generally permanent and may persist during sleep. It may be alleviated by oral therapy with procainamide.

Diagnosis

Antemortem diagnosis often is difficult.[130] Clinical signs of multifocal CNS disease, particularly neurologic deficits indicative of

spinal cord and cerebellovestibular disease, are highly suggestive of CD infection. Hematologic findings in dogs with CD infection are nonspecific. Abnormalities of the cerebrospinal fluid may be useful in the diagnosis of CD infection; however, the CSF may be normal. The WBC count and protein content of the cerebrospinal fluid are usually mildly to moderately increased. Cells seen in the CSF are predominantly lymphocytes (10 to 60 cells/μL). The presence of interferon in the CSF appears to be a reliable indicator of virus persistence.[129] CSF electrophoresis may also be performed and is useful for predicting the histopathologic changes in dogs with CD encephalomyelitis.[131] Determination of the IgG index may also aid the diagnosis of CD encephalomyelitis.[126]

Increased CD virus–specific antibody titers in the CSF may be useful in the diagnosis of CD infection. Increased anti–CD virus antibody in the CSF may offer evidence of chronic CD infection, because antibody is produced locally in the CNS, and significantly increased titers have rarely been present in vaccinated dogs or dogs with systemic CD infection without CNS involvement. Cerebrospinal CD antibody may be artifactually increased if whole blood contamination of the CSF occurs during collection. Negative CD antibody results do not rule out a diagnosis of CD.[40,129]

Treatment

Clinical signs of CD myelitis may be either rapidly or more slowly progressive. Periods of apparent improvement may be followed by progression of clinical signs. A specific antiviral drug that has an effect on CD in dogs is not currently available. Favorable results have been reported by some investigators with short-duration (1 to 3 days) corticosteroid therapy.[40] Intravenous administration of a modified live vaccine in dogs with CD is effective only if given before clinical signs appear. Treatment of CD myelitis is almost always unrewarding. The prognosis for recovery is poor. In dogs that recover from CD infection, residual signs such as myoclonus or optic neuritis may improve with time. Immunization by vaccination is the only effective approach to the prevention of CD.[126]

Dural Ossification

Etiology and Pathogenesis

Dural ossification is the formation of bony plaques on the inner surface of the dura mater.[6] Bony plaques are found most commonly in the cervical and lumbar spine and may occur laterally, ventrally, or dorsally. Dural ossification is found in more than 40% of large and small breed dogs over 2 years of age and in more than 60% of dogs 5 years of age or older. Although many dogs with dural ossification also have spondylosis deformans, no direct correlation exists between the two conditions. The etiology of dural ossification is unknown.

Clinical Findings

Dural ossification rarely results in neurologic deficits or apparent spinal pain in dogs. Other causes of spinal cord disease should be ruled out before clinical significance is attributed to dural ossification.

Diagnosis and Treatment

Radiographically, bony plaques appear as thin, radiopaque lines (linear shadows) that are most easily viewed at the site of intervertebral foramina. These linear shadows must be distinguished from calcified herniated disk material in the spinal canal, from vertebral osteophytes, and from the accessory processes of the lumbar vertebrae. No specific treatment exists for dural ossification; however, in rare cases surgical removal of a bony plaque from the vicinity of a nerve root may be necessary to alleviate apparent pain due to nerve root compression.

Feline Infectious Peritonitis, Meningitis, and Myelitis

Etiology and Pathogenesis

Feline infectious peritonitis is a serious, almost always fatal disease caused by a coronavirus.[132-137] Pyogranulomatous meningitis and myelitis may occur in cats with FIP, which is most commonly seen in younger animals between 6 months and 5 years of age. Meningeal and spinal cord lesions are probably the result of immune complex–mediated vasculitis. Involvement of the CNS is more frequently observed in the noneffusive (dry) form than in the effusive (wet) form of the disease.

Clinical Findings

Focal, multifocal, or diffuse involvement of the spinal cord, brain, and meninges may occur with FIP, and clinical signs reflect the location of these lesions. The most commonly recognized neurologic signs are pelvic limb ataxia, hyperesthesia (especially over the back), and generalized ataxia.[137] Affected animals usually manifest other clinical signs indicative of disseminated disease, such as persistent fever (frequently exceeding 105° F), weight loss, enlarged kidneys, chorioretinitis, panophthalmitis, or anterior uveitis.[137]

Diagnosis

Histopathologic examination of biopsy specimens is the only conclusive method for diagnosing FIP. Short of this, a variety of factors may be considered to support a diagnosis of FIP.[138-140] The CSF usually is abnormal, with an elevated WBC count and protein level. The differential WBC count for the CSF is variable, but PMN cells, lymphocytes, and monocytes usually are present.

PMNs may be the predominant cell type in the CSF. The protein concentration may be high (greater than 2000 mg/dL), and the CSF may be viscous and may clot. This should be taken into consideration when a CSF puncture is performed, because fluid may flow into the needle slowly. The results of cytologic examination of the CSF depend on the degree of meningeal involvement. Meningeal inflammation may be extensive, and the CSF in these cases is generally highly abnormal. With focal or parenchymal inflammation, the CSF may be normal.

Treatment

The prognosis for cats with FIP of the central nervous system is poor. The feline leukemia virus (FeLV) status of cats suspected of having FIP should be determined before treatment is started, because the prognosis for cats with both viruses is hopeless.[141] The most effective treatment protocols combine high levels of corticosteroids (prednisolone, 1 to 2 mg/lb given orally once daily in the evening), cytotoxic drugs (either cyclophosphamide [1 mg/lb given orally once daily for 4 consecutive days of each week] or melphalan [1 mg given orally every third day]), and broad-spectrum antibiotics (ampicillin, 10 mg/lb given orally every 8 hours), together with maintenance of nutrient intake and electrolyte balance. Cats receiving cytotoxic drugs should be routinely monitored for evidence of kidney dysfunction or bone marrow suppression. If a positive response to therapy is seen, treatment should be continued for at least 3 months.[141]

Feline Polioencephalomyelitis (Feline Nonsuppurative Meningoencephalomyelitis)

Feline polioencephalomyelitis is a chronic, slowly progressive encephalomyelitis of unknown etiology that has been described in immature and mature cats.[40,142] A viral etiology is suspected based on the histopathologic changes, although a specific viral agent has not been isolated. The chronic clinical course, distribution of lesions, and lack of inclusions distinguish this disease from rabies, pseudorabies, and FIP. It has

been proposed that a tick-borne virus may be the causative agent in Sweden.[143-146]

Clinical signs include ataxia, paraparesis, tetraparesis, hypermetria, head tremors, and localized hyperesthesia. Spinal reflexes, pupillary light reflexes, and postural reactions may be normal or depressed. Clinical signs usually are indicative of multifocal CNS disease but may be suggestive of focal transverse myelopathy in the thoracolumbar region or lumbar enlargement. Clinical signs are slowly progressive over several months. Antemortem diagnosis is difficult and is made by ruling out other multifocal CNS diseases. Treatment of affected cats has not been reported.

Globoid Cell Leukodystrophy (Krabbe-Type Leukodystrophy)

Etiology and Pathogenesis

Globoid cell leukodystrophy is an inherited lysosomal storage disease that results from a deficiency of galactocerebrosidase (GALC) activity.[6,147] Globoid cell leukodystrophy is characterized by bilaterally symmetric demyelination of the white matter of the brain, spinal cord, spinal nerve roots, and peripheral nerves and by accumulation, especially perivascularly, of large phagocytic cells with foamy-appearing cytoplasm (globoid cells). Globoid cell leukodystrophy is inherited as an autosomal recessive trait in cairn terriers and West Highland white terriers, and findings in other dog breeds suggest a recessive factor. The condition may not be inherited as a simple autosomal recessive trait in cats. Cloning of the GALC cDNA has been completed and the disease–Causing mutation identified in both West Highland white and cairn terriers.[147]

Clinical Findings

Clinical signs generally are first seen between 2 and 6 months of age and are progressive. However, neurologic abnormalities were not evident in an affected basset hound until 4 years of age. Affected cats usually show abnormalities by 6 weeks of age. Progressive paraparesis and paraplegia predominate in some affected animals, whereas cerebellar signs predominate in others. Spinal reflexes in the pelvic limbs may be normal or exaggerated, indicative of T3–L3 transverse myelopathy. Neurologic signs in affected animals usually progress to quadriparesis, dysmetria, head tremor, behavioral changes, and/or blindness. Spinal reflexes may be decreased or absent and muscle atrophy may be evident in some animals, indicative of LMN disease. Clinical signs usually progress over 2 to 6 months, although they were observed to progress for 2 years in one dog. Clinical signs in cats with globoid cell leukodystrophy are generally more indicative of cerebellar disease and are more rapidly progressive than in dogs.

Diagnosis

The diagnosis is made on the basis of the animal's age and breed and the presence of progressive neurologic deficits, as well as by ruling out other causes of progressive myelopathy (e.g., CD myelitis). The CSF may have phagocytic cells containing periodic acid–Schiff (PAS)-positive material (globoid cells), and the CSF protein content may be increased. In some animals the CSF may be normal. Brain and/or peripheral nerve biopsy may show characteristic demyelination and globoid cell accumulation and may be done to confirm a diagnosis of globoid cell leukodystrophy. A rapid test for identification of the genotype at cDNA position 473 has been developed.[147] The results of this test may allow breeders to screen their dogs for this problem and may result in elimination of this disease in the future.

Treatment

Treatment for globoid cell leukodystrophy has not been described.[6] Selective breeding based on genetic testing may eventually eliminate this disease.[147]

Granulomatous Meningoencephalomyelitis

Etiology and Pathogenesis

Granulomatous meningoencephalomyelitis (GME) is a nonsuppurative meningoencephalomyelitis of undetermined etiology in dogs.[6,148-150] It is characterized histopathologically by large perivascular accumulations of mononuclear cells throughout the brain, spinal cord, and meninges. A recent immunomorphologic study suggested that inflammatory lesions in canine GME consist of a heterogeneous population of major histocompatibility complex (MHC) class II antigen–positive macrophages and predominantly CD3 antigen–positive lymphocytes.[151] These data suggest T cell–mediated, delayed-type hypersensitivity of an organ-specific autoimmune disease.[151]

Clinical Findings

A higher incidence of GME has been found in female dogs, small breed dogs, poodles, poodle–mixed breed dogs, and Airedale terriers. Affected dogs usually are between 1 and 9 years of age, although dogs may be affected at any age. Clinical signs may indicate focal or multifocal cerebral, brain stem, cerebellar, and/or spinal cord involvement. GME may involve the spinal cord at any level; however, lesions appear to be most severe in the cervical spinal cord, and clinical findings are often indicative of cervical spinal cord disease. Findings include apparent cervical pain, rigidity, reluctance to move, hyperesthesia, cervical paraspinal muscle spasms, exaggerated spinal reflexes, decreased conscious proprioception, paraparesis, tetraparesis, and paraplegia. Affected animals usually have an acute onset of clinical signs, which progress over several days to months.[148,149]

Diagnosis

Antemortem diagnosis is difficult and usually is made on the basis of clinical findings and the results of CSF analysis. Dogs with GME may have intermittent fever. The findings for a complete blood count and on spinal and skull radiographs frequently are within normal limits. The CSF is abnormal in most affected dogs. The WBC count of the cerebrospinal fluid is usually increased (may be greater than 1000 WBCs/μL). Mononuclear cells predominate. The percentage of lymphocytes and monocytes varies considerably. PMN cells may also be present and in one study constituted 0 to 62% of the differential WBC count.[152] In the same study, less than 1% of the differential WBC count consisted of macrophages with ingested debris, plasma cells, and cells undergoing mitosis. The total and differential CSF white blood cell counts do not reflect the severity of meningeal involvement or the degree of necrosis. The CSF protein concentration is usually elevated, and the CSF pressure may be normal or increased. Alterations in the CSF were similar in untreated and corticosteroid-treated dogs in one study.[152]

Meningeal lesions may render CSF collection from cisternal puncture difficult. Although CSF collected from the lumbar subarachnoid space of affected dogs may have fewer white blood cells than cisternal CSF, it is useful for diagnosis. The difference in WBC counts probably reflects the greater distance of the lumbar subarachnoid space from the site of most lesions. Bacterial and fungal cultures are negative, and organisms are not identified in CSF cell preparations. Noncontrast radiography, myelography, and advanced imaging (CT or MRI) may confirm an intramedullary space-occupying lesion of the spinal cord.

Treatment

GME is either continuously or episodically progressive, and the prognosis for recovery is poor. Treatment with corticosteroids may result in improvement of clinical signs for several days to several months or years. Immunosuppressive doses of corticosteroids should be given, and therapy must be

sustained indefinitely. The corticosteroid regimen used for treatment of corticosteroid-responsive meningitis should be used for therapy of dogs with GME. Clinical remissions of greater than 1 year occur in some cases; however, clinical signs usually recur with discontinuation of treatment with corticosteroids. Radiation therapy may be an effective treatment for dogs with focal GME.[150] Alternative immunomodulatory drugs may also play a role in the treatment of GME in the future.[153]

Hemorrhage

Etiology and Pathogenesis

Intramedullary, intrameningeal, or epidural hemorrhage may be due to coagulopathies, including thrombocytopenia, clotting factor deficiencies, disseminated intravascular coagulation, and anticoagulant poisonings (e.g., warfarin).[154] Acute hemorrhage may also occur in association with tumors, vascular malformations, acute intervertebral disk protrusion, trauma, parasitic migration, or meningitis (Figure 193-8). Spontaneous intramedullary hemorrhage with hematoma formation has been reported in the cervical spinal cord of a dog.[155] Spontaneous subperiosteal vertebral hemorrhage and hematoma formation associated with spinal cord compression and transverse myelopathy have been reported in dogs.

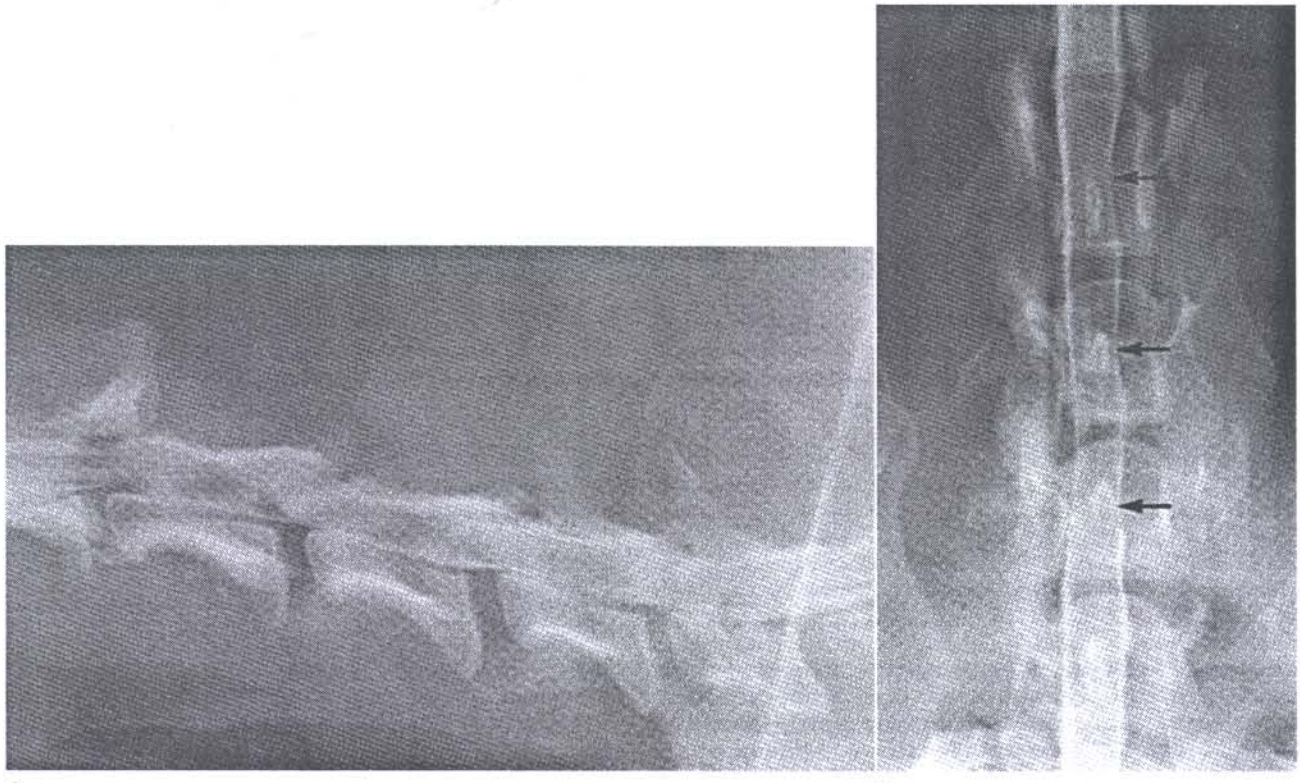
Clinical Findings

Neurologic deficits depend on the location of the hemorrhage and usually indicate a focal or multifocal myelopathy. Clinical signs most often are acute in onset, and neurologic deficits may be severe. Extensive gray matter necrosis may occur with intramedullary hemorrhage, resulting in LMN signs over a relatively large area of the spinal cord, especially if the cervical or lumbosacral spinal cord is involved. Subarachnoid hemorrhage may result in clinical signs suggestive of meningitis, including cervical rigidity, hyperesthesia, and elevated body temperature.

Diagnosis

Animals with coagulopathies may have evidence of hemorrhage elsewhere in the body. Diagnostic tests for coagulopathies should be undertaken. Subarachnoid CSF puncture may be contraindicated in animals with a coagulopathy because of the high probability of inducing further hemorrhage. Red blood cells may be present in the CSF for a short time after subarachnoid hemorrhage, and CSF supernatant may be red or pink in color. Xanthochromia may be present in the CSF 48 hours or more after the hemorrhage. The CSF white blood cell count and protein concentration may also be elevated.

Myelography is indicated when epidural hemorrhage is suspected to be the cause of spinal cord compression and when noncontrast radiographs and the results of CSF analysis are normal and no evidence of coagulopathy has been found. Epidural hemorrhage is not distinguishable from other extradural space-occupying lesions on myelography. Hemorrhage may occur secondary to other abnormalities, such as intervertebral disk extrusion, as a result of laceration of a vertebral venous sinus.



A B

Figure 193-8 Hemorrhage. Lateral (A) and ventrodorsal (B) myelogram of the cervical vertebrae of a 10-year-old neutered male mixed-breed dog with an acute onset of tetraparesis. Narrowing of the C5–C6 intervertebral disk can be seen. The lateral myelogram (A) demonstrates inconsistent filling of the subarachnoid space. The ventrodorsal projection (B) confirms lateral deviation of the right contrast column and attenuation of the left contrast column *(arrows)*, owing to an extradural space-occupying mass. Exploratory surgery demonstrated that the extradural compression was caused by hemorrhage that had occurred secondary to the acute C5–C6 disk extrusion.

Treatment

Treatment is directed at the underlying cause in animals with coagulopathies. Epidural and intramedullary hematomas not associated with coagulopathy may be removed surgically. The prognosis depends on the severity of the neurologic deficits at the time of diagnosis.

Hereditary Ataxia (Ataxia in Smooth-Haired Fox Terriers and Jack Russell Terriers)

Etiology and Pathogenesis

An inherited, progressive, generalized ataxia has been reported to occur in young, smooth-haired fox terriers and Jack Russell terriers.[6] This disease is characterized pathologically by demyelination bilaterally throughout the dorsolateral and ventromedial white matter of the spinal cord. In Jack Russell terriers, wide-spread wallerian-type degeneration in the white matter of the brain and degenerative changes in the central auditory pathways and peripheral nerves may be seen. Hereditary ataxia is inherited as an autosomal recessive trait in smooth-haired fox terriers. The etiology of ataxia in Jack Russell terriers is not known; however, clinical and pathologic findings suggest that it may be congenital. Degenerative myelopathies have been described in several dog breeds other than fox terriers and Jack Russell terriers, including English foxhounds, harriers, beagles,[156-158] boxers,[1] German shepherds,[99-104] poodles,[1] Afghan hounds,[1] a Pyrenees mountain dog,[159] a cairn terrier,[160] Dutch Kooiker dogs,[161] and Australian cattle dogs.[162] The pathogenesis of these conditions is unclear.

Clinical Findings, Diagnosis, and Treatment

Both males and females are affected. Neurologic abnormalities, first seen between 2 and 6 months of age, include pelvic limb ataxia and swinging of the hindquarters. The ataxia progressively worsens over 6 months to 2 years and involves all four limbs. Affected animals often have a prancing pelvic limb gait. Dysmetria may be severe, and affected dogs fall to the ground with a slight change in position. The diagnosis is made on the basis of the animal's age and breed and the clinical findings. Treatment is not effective. Affected animals are eventually unable to walk.

Hypervitaminosis A of Cats

Etiology and Pathogenesis

Hypervitaminosis A in cats is characterized by extensive, confluent exostosis that is most prominent in the cervical and thoracic spine.[6,7,163] It is caused by a chronic excess of dietary vitamin A and is usually a result of feeding of a diet consisting largely of liver. Exostosis may extend to involve the entire spine, ribs, and pelvic and thoracic limbs, with complete fusion of the spine and joints. Compression of spinal nerve roots or nerves may occur if new bone formation extends into the intervertebral foramina.

Clinical Findings, Diagnosis, and Treatment

Clinical signs in affected cats include apparent cervical pain and rigidity, thoracic limb lameness, ataxia, reluctance to move, paralysis, and hyperesthesia or anesthesia of the skin of the neck and forelimbs. The three most proximal diarthrodial joints of the cervical spine are almost always first affected. Osseous lesions develop insidiously, and clinical disease usually is advanced in cats older than 2 years of age before significant clinical features are recognized. Radiographic evidence of extensive exostosis of the cervical vertebral column and a history of excessive dietary intake of vitamin A or liver are necessary for the diagnosis. Reduction of dietary intake of vitamin A prevents the development of further exostosis, but it may be difficult to persuade affected cats to eat anything other than liver.

Intervertebral Disk Disease

Etiology and Pathogenesis

Degeneration of intervertebral disks may result in protrusion or extrusion of disk material into the spinal canal, causing spinal cord compression and clinical signs ranging from apparent pain to complete transverse myelopathy. Degenerative changes may occur in any of the intervertebral disks; however, they occur most commonly in the cervical, caudal thoracic, and lumbar spine. Because the intervertebral disks between T1 and T11 are stabilized dorsally by the intercapital ligaments, disk protrusion or extrusion is less likely in this region.[164-166]

Two types of disk herniation have been reported to occur in dogs.[167] Type I disk herniation occurs with degeneration and rupture of the dorsal anulus fibrosus and extrusion of the nucleus pulposus into the spinal canal. Type I disk extrusion is most commonly associated with chondroid disk degeneration (Figure 193-9). Although chondroid disk degeneration and type I disk extrusion occur most commonly in chondrodystrophoid breeds (dachshund, beagle, Pekingese, Lhasa apso, Shih Tzu) and in breeds with chondrodystrophoid tendencies (miniature poodle and cocker spaniel), these conditions may occur in any breed, including large breeds. Type II disk protrusion is characterized by bulging of the intervertebral disk without complete rupture of the anulus fibrosus. Type II disk protrusion is most commonly associated with fibroid disk degeneration (Figure 193-10). Chondroid metaplasia of the nucleus pulposus, chondroid disk degeneration, and type I disk extrusion may occur in any breed, including large breeds. The author (RAL) has noted an unusually high incidence of type I disk extrusion in Doberman pinschers. The smaller lumbar epidural space in dachshunds may explain the severe clinical signs seen in this breed in association with apparently small amounts of extruded disk material. Likewise, the larger epidural space in large breed dogs may account for the fact that small amounts of extruded disk material in the spinal canal in these breeds may not cause spinal cord compression and associated clinical signs.[168]

Chondroid degeneration of disks is characterized by an increase in the collagen content of the disk, alteration of the specific glycosaminoglycan concentration of the nucleus pulposus, and a decrease in the water content of the disk. The normally gelatinous nucleus pulposus becomes progressively more cartilaginous and granular and eventually may mineralize (calcify). Extrusion of degenerative nucleus pulposus occurs through fissures in or rupture of the anulus fibrosus. In chondrodystrophoid breeds of dog, 75% to 100% of all disks undergo chondroid metaplasia by 1 year of age.[169]

Fibroid disk degeneration occurs in older dogs of all breeds; however, it is most often recognized as a clinical problem in older, large breed, nonchondrodystrophoid dogs and is characterized by fibrous metaplasia of the nucleus pulposus. An increase in the noncollagenous glycoprotein content of the intervertebral disks occurs in nonchondrodystrophoid breeds with aging. Calcification of the disk may occur but is rare. Protrusion of the disk occurs, with a bulging of the anulus fibrosus as a result of partial rupture of the anular bands. Rupture of the anulus fibrosus and extrusion of the nucleus pulposus (characteristic of type I disk extrusion) infrequently is seen in association with type II disk protrusion.

Intervertebral disk protrusion or extrusion may occur in a ventral, dorsal, or lateral direction. In most instances only dorsal protrusions or extrusions are of clinical significance, because meningeal irritation and nerve root and/or spinal cord compression may occur. Occasionally a lateral disk protrusion or extrusion may result in nerve root or spinal nerve compression with associated clinical signs. The cause of intervertebral disk degeneration is unknown. Trauma does not appear to play a major role; mechanical and anatomic factors are

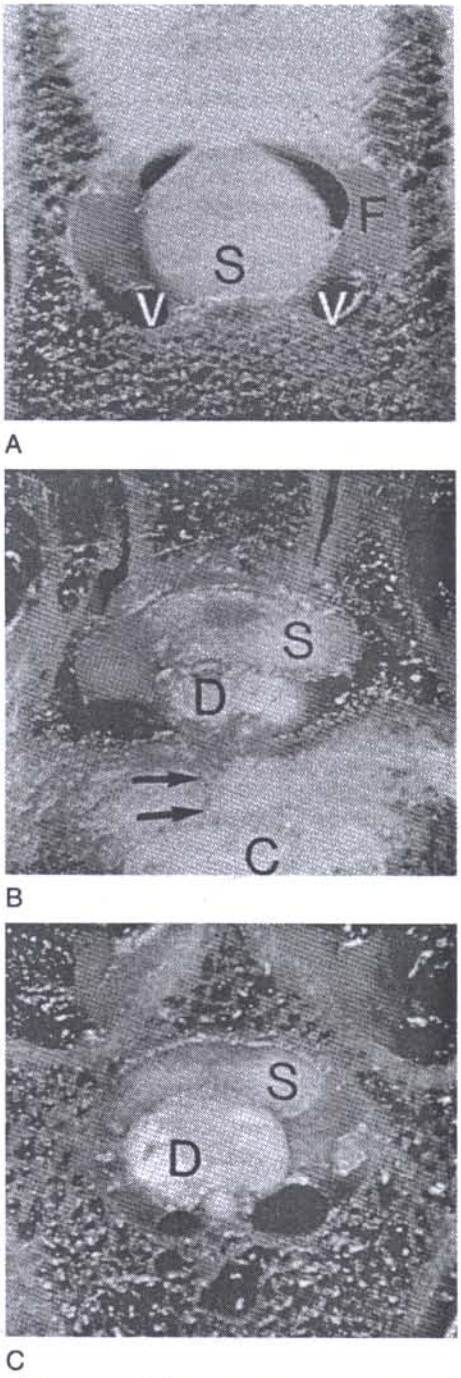


Figure 193-9 Type I disk extrusion. Gross necropsy specimens from a 4-year-old male dachshund that had an acute onset of pelvic limb paralysis. Pain perception was absent in the pelvic limbs. Myelography confirmed acute disk extrusion at T11–T12 that had caused severe spinal cord compression. **A,** Transverse section of the T12 vertebral canal 1 cm caudal to the extruded T11–T12 disk. Note the normal appearance of the spinal cord *(S)* in the spinal canal. Epidural fat *(F)* and internal vertebral venous plexus or vertebral sinuses *(V)* are also present in the spinal canal. **B,** Transverse section of the vertebral canal at the level of the T11–T12 disk. Calcified material *(C)* is present in the nucleus pulposus. A fissure (*arrows*) is present in the dorsal anulus fibrosus, and calcified material from the nucleus pulposus *(D)* has extruded through the fissure into the spinal canal. Dorsal displacement and compression of the spinal cord *(S)* have occurred. **C,** Transverse section of the vertebral canal 5 mm cranial to **B.** Extruded calcified material *(D)* from the nucleus pulposus is compressing the spinal cord *(S)* at this level.

probably important. Disk extrusions are most common in the cervical and T11 to L3 regions of the vertebral column. Genetic factors probably also play a role.

Type I disk extrusion often results in more severe clinical signs than type II protrusion, although the mechanical distortion and compression of the spinal cord caused by type II protrusion may be greater. The nucleus pulposus is most often extruded into the spinal canal acutely (minutes to hours) or subacutely (days) from disks undergoing chondroid degeneration, whereas slowly progressive spinal cord compression most often accompanies protrusion of disks undergoing fibroid degeneration, as the bulging fibrous mass increasingly enlarges within the spinal canal. The spinal cord changes seen in acute versus chronic spinal cord compression differ and are reflected in the difference in clinical signs and response to treatment seen in these two types of intervertebral disk disease. The severity of spinal cord injury depends on the velocity at which

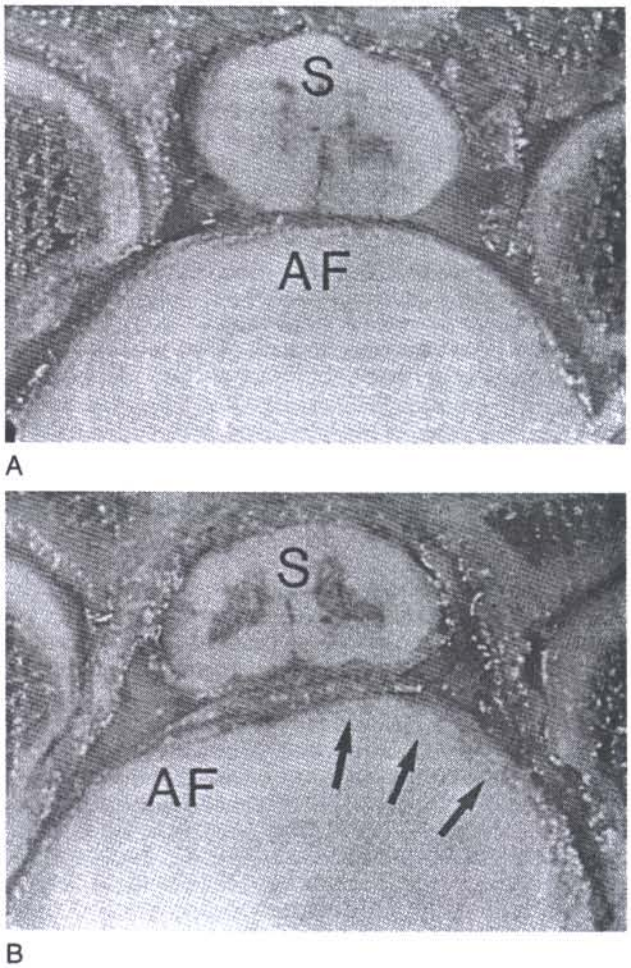


Figure 193-10 Type II disk protrusion. Gross necropsy specimens from a 7-year-old female Doberman pinscher that had a history of progressively worsening tetraparesis and generalized ataxia. Myelography confirmed type II disk protrusion at C6–C7. The disk protrusion appeared to be predominantly on the left. **A,** Transverse section of the vertebral canal at the level of the C5–C6 disk. Note the normal appearance of the spinal cord (*S*) in the spinal canal, and the close anatomic relationship of the dorsal anulus fibrosus (*AF*) to the spinal cord. **B,** Transverse section of the vertebral canal at the level of the C6–C7 disk. Note the compression of the left spinal cord (*S*), caused by dorsal bulging (*arrows*) of the anulus fibrosus (*AF*) at this level.

the compressive force is applied, the degree of compression, and the duration of the compression. Vascular factors, as well as mechanical distortion of the spinal cord as a result of herniated disk material, are important in the pathogenesis of resulting spinal cord lesions. Severe spinal cord lesions may be found without evidence of compression, presumably as a result of vascular changes.

Hemorrhage, edema, and necrosis of spinal cord gray and white matter are characteristic of acute spinal cord injury associated with acute type I disk extrusion. Hemorrhage and edema are not major features of chronic spinal cord compression in which white matter changes (e.g., demyelination, focal malacia, vacuolization, and loss of axons) are seen. Type I disk extrusions often are associated with rupture of vertebral venous sinuses, and hemorrhage into the epidural space may increase the degree of spinal cord compression. Pulmonary emboli arising from the nucleus pulposus have been described in three chondrodystrophoid dogs with acute thoracolumbar transverse myelopathies as a result of type I disk extrusions, presumably as a result of disk material entering the vertebral venous sinuses. The nucleus pulposus may also penetrate the dura mater. Traumatic rupture of the anulus fibrosus and extrusion of normal nucleus pulposus may occur, resulting in spinal cord compression and acute onset of clinical signs indicative of a transverse myelopathy.[170,171]

Degenerative disk disease also occurs in cats,[7,170,171] although the incidence of clinical signs associated with disk protrusion is low. The degenerative changes, distribution of disk protrusions, and clinical signs are similar to those seen with type II disk protrusions in nonchondrodystrophoid dogs. Type I disk extrusion associated with a calcification of intervertebral disks and an acute onset of neurologic deficits may occur in cats.

Clinical Findings

Chondroid degeneration and type I disk extrusion most commonly occur in dogs 3 years of age and older. Fibroid degeneration and type II disk protrusion most commonly occur in dogs older than 5 years of age. Clinical signs seen in association with type I disk extrusion include apparent pain and/or motor and/or sensory deficits. These clinical signs usually develop rapidly, within minutes or hours of disk extrusion. However, clinical signs may progress slowly over several days or may manifest periods of improvement and subsequent worsening over weeks or months. These findings are probably associated with extrusion of small amounts of disk material into the spinal canal over a period of time.

Clinical signs associated with type I disk extrusion in the cervical spine usually are less severe than those associated with extrusions in the thoracolumbar region because the vertebral canal in this region is larger in diameter in relation to the spinal cord than is the case in the thoracolumbar region. Apparent neck pain is the most common clinical finding in dogs with cervical disk extrusion. Affected dogs often hold the head and neck rigidly and cry out when moved, and they may show spasms of cervical musculature. Neurologic deficits indicative of a cervical myelopathy (e.g., proprioceptive deficits, tetraparesis, or tetraplegia) are seen less commonly.

Ipsilateral Horner's syndrome and hyperthermia have been described in cases of acute, severe, dorsolateral cervical disk extrusions. LMN deficits in the thoracic limbs may be seen in caudal cervical disk extrusions. Thoracic limb lameness may also be seen in caudal cervical disk extrusions as a result of nerve root compression, particularly from lateral disk extrusions in which disk material enters an intervertebral foramen.

Clinical findings with thoracolumbar type I disk extrusion, which depend on the severity of spinal cord injury, range from apparent back or abdominal pain to complete paraplegia and loss of deep pain perception. Neurologic deficits usually are indicative of a transverse myelopathy between T3 and L3, because most disk extrusions in this region occur between T11 and L3. LMN signs may be seen in the pelvic limbs if disk extrusion occurs caudal to L3 as a result of compression of the lumbosacral spinal cord or the nerves of the cauda equina. LMN signs also may be seen in paraplegic animals with progressive hemorrhagic myelomalacia (PHM).

The panniculus reflex may be depressed or absent caudal to the site of disk extrusion. The site of a lesion is usually one or two vertebral spaces cranial to the loss or depression of the panniculus reflex. The Schiff-Sherrington sign may be seen in animals with acute type I disk extrusion caudal to T2.

The clinical signs seen in both cervical and thoracolumbar type I disk extrusion may be asymmetric, especially if the extrusion occurs dorsolaterally within the spinal canal.[172,173] Apparent pain associated with disk extrusions results from inflammation and/or ischemia caused by compression of meninges and/or spinal nerve roots. Extruded disk material initiates an extradural inflammatory reaction that results in fibrous adhesions between the dura mater and the extruded disk material. Pain may also arise from stimulation of sensory nerve endings in the anulus fibrosus and dorsal longitudinal ligament. The nucleus pulposus of each disk does not contain nerve fiber endings.

The clinical signs associated with type II disk protrusion generally progress slowly over a period of months. However, in some animals they may develop acutely over days. Neurologic deficits usually are indicative of a cervical or thoracolumbar myelopathy. Paraparesis or tetraparesis, depending on the site of the lesion, is the most common clinical finding, and deficits may be asymmetric. In the cervical spine, type II protrusions most commonly occur in caudal cervical disks. In some cases caudal cervical type II disk protrusion may be part of the spectrum of abnormalities associated with cervical spondylomyelopathy. Apparent neck or back pain may or may not be a feature of type II disk protrusion.

Diagnosis

A tentative diagnosis of type I disk protrusion or extrusion may be made on the basis of the patient's age, breed, history, and clinical signs; however, other causes of transverse myelopathy or apparent pain should be considered in the differential diagnosis. It must be remembered that apparent spinal pain is seen in animals with meningitis. Dogs with thoracolumbar disk extrusions may appear to have abdominal pain. The differential diagnosis in animals with type II disk protrusion includes other causes of progressive transverse myelopathy, the most likely being neoplasia or degenerative myelopathy.

Spinal radiographs and, in almost all cases, CSF analysis and myelography are necessary to confirm a diagnosis of disk extrusion or protrusion. General anesthesia is required to achieve the precise positioning needed to obtain radiographs of diagnostic value. Foam wedges or sandbags are usually needed to align the vertebral column parallel to the table top for lateral projections. Care must be taken, however, in anesthetizing and positioning animals suspected of having acute type I disk extrusions, because further extrusion of disk material and further spinal cord compression may occur with manipulation and movement of the spine.

Calcification of the nucleus pulposus is best seen on lateral radiographic views and usually is seen in one or more disks of most chondrodystrophoid dogs more than 1 year of age. Calcified disks also may be seen in older nonchondrodystrophoid breeds. The presence of calcified material in the nucleus pulposus is indicative of disk degeneration but by itself is not of clinical significance.

The disk space of an extruded disk may be narrower than adjacent disk spaces; it may be wedge shaped, with a decrease in the width of the disk space dorsally. However, positioning

is important, because some disk spaces (C7–T1, T9–T10 or T10–T11, and L7–S1) are normally narrower than adjacent spaces, and cervical and lumbosacral disks are normally wedge shaped on hyperextension and flexion of the spine. "Spikes" of calcified material suggestive of disk extrusion may extend dorsally from a disk. Calcified material may be present in the vertebral canal, but it often is difficult to visualize because of overlying vertebral articular processes or ribs. The intervertebral foramina are larger in the lumbar spine, and calcified material often is easily visualized in the spinal canal in this region. Disk material in the spinal canal may appear as a hazy, indistinct shadow or as a dense mass with distinct margins. In many cases of disk extrusion, calcified material is not visualized in the spinal canal, because the disk material is probably not sufficiently mineralized to be visible on radiographs. Ventrodorsal views, and in some cases oblique views, are important for determining the laterality of any visible mineralized material in the spinal canal. Vertebral osteophytes and vertebral endplate sclerosis may be seen in association with chronic disk degeneration and extrusion or, in cases of chronic disk degeneration, without disk extrusion or protrusion.

Type II disk protrusion may be associated with narrowing of the disk space, osteophyte production, and endplate sclerosis. Calcification of disk material rarely is seen with type II disk protrusion. In some animals with type I or type II disk herniation, obvious abnormalities are not seen on noncontrast vertebral radiographs (Figure 193-11).

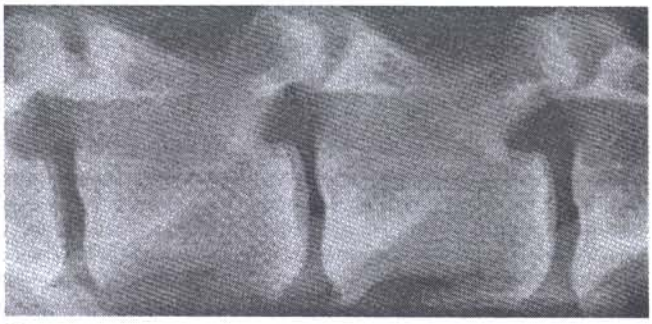
Myelography is almost always necessary to confirm that disk material has herniated into the spinal canal, resulting in spinal cord compression.[173-175] Myelography is most important for determining the site (or sites) of disk herniation and for lateralizing disk material in the spinal canal prior to surgical decompression.[176] Myelography is necessary to distinguish disk protrusion from other causes of slowly progressive transverse myelopathy, such as spinal neoplasia and degenerative myelopathy.

CSF should be collected and analyzed before myelography to rule out inflammatory or infectious disease of the spinal cord and/or meninges.[177] Clinical signs in animals with GME, distemper myelitis, FIP, spinal lymphoma, and other disorders may mimic those of cervical or thoracolumbar disk disease.

The characteristic myelographic findings in both type I and type II disk herniation into the spinal canal are extradural compression of the spinal cord with displacement of the spinal cord and narrowing of the subarachnoid space on lateral and/or ventrodorsal views, depending on the location of the compressive mass. Type II and most type I disk herniations result in a ventral or ventrolateral epidural mass that causes dorsal displacement of the spinal cord. Disk material may extend over more than one vertebral segment in type I extrusions and may result in deviation or narrowing of contrast columns over more than one vertebral length. Disk material may completely encircle the spinal cord. Acute type I disk extrusions often are accompanied by spinal cord edema and swelling and occasionally by dural laceration.[178] The spinal cord may be widened over several segments, and the myelographic appearance is similar to that of an intramedullary mass, making precise determination of the site of disk extrusion difficult. In some animals, disk material is scattered along the spinal canal without obvious mechanical distortion of the spinal cord.

Rarely, in the cervical region type I disk extrusion may occur laterally or intraforaminally, resulting in neck pain or thoracic limb pain due to nerve root compression. In such cases myelograms may be normal; however, increased density associated with calcified disk material may be visualized intraforaminally on ventral oblique radiographs of the cervical spine. Traumatic disk protrusion is usually associated with narrowing of the intervertebral disk space on radiographs. Other abnormalities, such as vertebral fracture, luxation, or instability, also may be seen. Myelography is useful for determining whether spinal cord compression is present in such cases and therefore whether surgical decompression is indicated.

The use of advanced imaging techniques (CT or MRI) may aid in the exact localization of intervertebral disk extrusions, particularly in cases of intraforaminal disk extrusion.[179-181]



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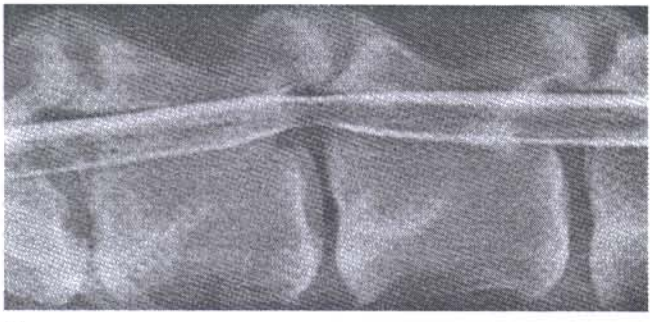

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Figure 193-11 Type II disk protrusion. Lateral radiograph (A) and myelogram (B) of the midlumbar vertebral column of a 7-year-old castrated male Great Dane with a 3-month history of corticosteroid-responsive back pain. The dog was neurologically normal at the time of this study. Slight narrowing of the L2–L3 disk and mild ventral spondylosis deformans are seen on the lateral radiograph. The myelogram confirms severe ventral spinal cord compression at the level of L2–L3 associated with a type II disk protrusion.

Treatment

Type I disk extrusion The appropriate treatment for animals with type I disk extrusion depends on the individual animal's neurologic status. Medical treatment directed at reducing spinal cord edema with corticosteroid therapy is indicated only in animals with an acute onset of neurologic deficits that are examined within 8 hours of injury. The recommended agents and dosages are the same as those described for spinal cord trauma. The use of corticosteroids in dogs with type I disk extrusion has been associated with pancreatitis, gastrointestinal bleeding, and colonic perforation.

Nonsurgical (medical or conservative) treatment is recommended for animals with apparent pain only or animals that have mild neurologic deficits but are ambulatory and have not had previous clinical signs associated with disk disease. These animals should be strictly confined to a small area, such as a hospital cage or a quiet place away from other pets, for at least 2 weeks and walked (on a leash or harness) only to urinate and defecate. The objective of confinement is to allow fissures in the anulus fibrosus to heal, thus preventing further extrusion of disk material and allowing resolution of the inflammatory reaction caused by the small amounts of extruded disk material.

The use of analgesics, muscle relaxants, or nonsteroidal anti-inflammatory agents is not recommended in most cases,

because it is believed that the pain relief they bestow encourages animals to exercise and thus risk further disk extrusion. Cautious use of analgesics or nonsteroidal anti-inflammatory agents occasionally may be indicated; however, strict confinement, followed by a period of restricted exercise, is imperative. Owners should also be warned that an animal's neurologic status may deteriorate, owing to extrusion of further disk material, despite this treatment. If the neurologic status worsens, treatment should be re-evaluated immediately. Owners should also be warned that recurrence of clinical signs is common, as a result of further disk extrusion at the same or a different site, and subsequent episodes may be more severe, especially in the thoracolumbar spine.

Animals with severe cervical pain frequently do not respond to cage rest. These dogs often have large amounts of disk material in the spinal canal. Dogs that do not show improvement after 7 to 10 days of confinement should be evaluated further using radiography and myelography, and ventral cervical decompression should be considered.

Surgical disk fenestration has been recommended as a prophylactic measure to prevent further extrusion of disk material into the spinal canal.[182,183] Fenestration of the disks most likely to herniate (C2–C3 through C6–C7 in the cervical spine and T11–T12 through L3–L4 in the thoracolumbar spine) is recommended in animals that have had one or more episodes of apparent neck or back pain and that have radiographic evidence of intervertebral disk disease. Various surgical techniques have been described.[164-166] However, fenestration of disks does not remove disk material from the spinal canal and therefore is not recommended as the sole surgical procedure in dogs that have radiographic and myelographic evidence of disk material in the spinal canal and of spinal cord compression.

The role of disk fenestration in the management of intervertebral disk disease is controversial.[182-185] Disk fenestration in the thoracolumbar region is not easily accomplished, and complications such as scoliosis, pneumothorax, and hemorrhage may occur. Disk fenestration in the cervical region is achieved more easily and rarely is associated with such complications. Fenestration does not prevent the recurrence of disk extrusion in all animals. The effectiveness of fenestration depends largely on the amount of nucleus pulposus removed. Completion of disk fenestration is recommended at the time of spinal cord decompression.

Animals with neurologic deficits such as paresis or paralysis in which deep pain perception is intact; animals with recurrent bouts of apparent back or neck pain; and animals with apparent back or neck pain (or mild neurologic deficits) unresponsive to strict confinement should be evaluated by means of spinal radiographs, CSF analysis, and myelography. Surgical decompression of the spinal cord and removal of disk material from the spinal canal should be considered. Although many dogs with moderate or severe paresis improve neurologically if treated with cage rest, neurologic recovery is often more rapid and more complete after surgical decompression of the spinal cord. In addition, the neurologic status of some dogs with type I disk extrusion, especially in the thoracolumbar spine, suddenly worsens over a period of hours or days despite medical treatment. Such deterioration usually results from further disk extrusion, which may cause irreversible spinal cord damage and permanent paralysis. This progression of signs always is a risk with medical treatment of animals with thoracolumbar disk disease. Progression is impossible to predict on the basis of the history, clinical signs, or radiography. Owners should be made aware of treatment options and offered the opportunity of referral to an appropriate surgical facility when animals are initially presented. Surgical decompression should be performed as soon as possible to prevent further spinal cord damage from sustained compression or further extrusion of disk material. Also, if surgery is delayed 2 to 3 weeks, disk material hardens and becomes adherent to the dura mater and is difficult or impossible to remove from the spinal canal.

The prognosis for neurologic recovery in animals that retain deep pain perception after surgery is fair to very good. The major factors that correlate with the degree of postsurgical neurologic improvement are the animal's neurologic status before surgery, the rapidity of onset of clinical signs, and the time interval between the onset of clinical signs and surgical decompression. Animals that have severe neurologic signs, a rapid onset of clinical signs (hours), and a long period before surgery generally have a prolonged recovery and may have varying degrees of permanent neurologic deficit.

The incidence of recurrence of clinical signs due to disk extrusion is greater in nonsurgically than surgically treated dogs. One author found that one third of dogs with type I disk herniation that were treated nonsurgically had a recurrence of clinical signs and generally showed greater severity of neurologic deficits at the time of recurrence.[1] Another author reported a recurrence rate of 40% in nonsurgically treated dogs.[1]

The advantages and disadvantages of various techniques for spinal cord decompression have been discussed.[125-127] Surgical treatment is not without risks. Anesthesia is necessary, and surgery occasionally results in further spinal cord damage, incurred through surgical manipulation. Nonsurgical treatment should be attempted in animals that are poor anesthesia or surgical candidates or if surgical treatment is not possible financially.

In animals that have clinical signs of a complete transverse myelopathy and in which deep pain perception has been absent for more than 24 hours, the prognosis for return of spinal cord function is poor despite medical or surgical treatment. Some of these animals may improve neurologically if given sufficient time; however, it is a matter of controversy whether surgical treatment increases the probability of improvement. When deep pain perception has been absent for less than 24 hours, the prognosis for return of spinal cord function is poor; however, surgical treatment may increase the likelihood of neurologic improvement.

Regardless of whether medical or surgical treatment is instituted, animals that are paretic or paralyzed require intensive nursing care.[186] Neurologic improvement may take weeks or months, and this requires owner co-operation and enthusiasm regarding care and physical therapy. Manual expression, intermittent catheterization, and/or indwelling catheterization of the bladder are often required to ensure emptying of the bladder. Weekly urinalysis, especially in animals that do not have voluntary control of micturition, is important in monitoring for urinary tract infection. It is also important to keep animals well padded, clean, and dry to prevent the formation of pressure sores, and to ensure that caloric and water intake is adequate. Physical therapy does not result in neurologic improvement but helps prevent disuse muscle atrophy associated with paraplegia or tetraplegia. Physical therapy should not be attempted in animals treated medically for at least the first 2 weeks after the onset of signs, because further extrusion of disk material may occur.[140]

Type II disk protrusion Treatment with corticosteroids may result in neurologic improvement for variable periods in animals with type II disk protrusion. However, corticosteroid therapy is not curative. The reason for this improvement is not clear, because the intramedullary hemorrhage and edema seen in cases of acute spinal cord injury are not a feature of chronic spinal cord compression. In the thoracolumbar spine, surgical removal of protruded disk material may result in clinical improvement; however, the neurologic status of some dogs is worsened permanently despite careful surgical technique. The reasons for this are not known, but increased vascular permeability in the spinal cord has been described in association

with release of chronic spinal cord compression, and this probably plays a role in the phenomenon. Ventral decompression in the cervical spine allows removal of protruded type II disk material, and neurologic improvement may occur over several months; however, some dogs, especially those with moderate to severe neurologic deficits prior to surgery, may manifest temporary or permanent worsening of clinical signs postoperatively.

Acupuncture The use of acupuncture for the treatment of intervertebral disk extrusion in dogs is controversial. Acupuncture may be an excellent adjunctive therapy in nonsurgical management of affected dogs.[187] However, the use of acupuncture as an alternative to surgery for dogs that have severe spinal cord compression resulting from disk extrusion is not recommended.

Chemonucleolysis Injection of the proteolytic enzyme chymopapain into the nucleus pulposus of intervertebral disks to cause discolysis has been used infrequently in veterinary medicine.[81,188-191] The precise mechanism by which chymopapain causes dissolution of the nucleus pulposus is unknown. In one study in dogs, dissolution of the nucleus pulposus was demonstrated histologically in all cervical intervertebral disks injected with chymopapain via a ventral surgical approach. Similar pathologic findings were found in the lumbar disks of dogs injected with chymopapain transcutaneously under fluoroscopic guidance via a lateral approach. Significant postoperative clinical complications were not seen. Radiographic narrowing of the intervertebral disk spaces was found in both the cervical and lumbar chymopapain-injected spaces. Cervical injection resulted in a more noticeable narrowing than did lumbar injection. However, successful injection, as determined histologically, was not always detected radiographically. These studies have described only the acute response to chymopapain. Another study has shown that chymopapain injection results in progressive dissolution of the nucleus pulposus and eventual regeneration of nuclear ground material.

Chemonucleolysis may be of benefit in animals with intervertebral disk disease when the nucleus pulposus is still contained within an intact or partly ruptured anulus fibrosus. Dissolution of the nucleus pulposus in these cases may relieve the pressure exerted by the protruding disk on the spinal cord and nerve roots. Chemonucleolysis may also be useful as a prophylactic measure in animals with evidence of intervertebral disk degeneration to prevent acute type I disk extrusion.

Chemonucleolysis is not indicated in cases of type I disk extrusion, because the enzyme is unable to reach sequestered nucleus pulposus in the spinal canal. Chemonucleolysis has been used in the treatment of type II disk protrusion in the cervical spine of large breed dogs. Most of the dogs in one study improved clinically despite a persistence or only slight decrease in the degree of spinal cord compression on myelography. Injection of chymopapain to the intervertebral disks via a surgical approach is recommended to prevent inadvertent intrathecal injection or accidental penetration of the vertebral arteries, spinal arteries, or spinal nerve roots. Further evaluation of the effect of chemonucleolysis in dogs with intervertebral disk disease is needed; however, it seems likely that this technique may have advantages over the methods used at present for surgical disk fenestration.

Ischemic Myelopathy Caused by Fibrocartilaginous Embolism

Etiology and Pathogenesis

Ischemic myelopathy results from ischemic necrosis of spinal cord gray and white matter associated with fibrocartilaginous emboli that occlude arteries and/or veins of the leptomeninges and spinal cord parenchyma of dogs[192-194] or cats.[195,196] This disease is characterized by an acute onset of neurologic deficits and is generally nonprogressive after several hours. In most cases the substance occluding the spinal cord arteries and veins has histologic and histochemical properties similar to those of fibrocartilage of intervertebral disks and is presumed to originate from the nucleus pulposus of an intervertebral disk. The pathogenesis of this fibrocartilaginous embolism is not known. Acute spinal cord infarction has been reported secondary to neoplastic emboli and intravascular coagulation.[197] Most affected animals do not have evidence of degenerative intervertebral disk disease and are dog breeds that have a low incidence of degenerative disk disease and type I disk extrusion.

Clinical Findings

Ischemic myelopathy most commonly occurs in large and giant breed dogs, generally between 1 and 9 years of age, of either gender, but it has also been described in many other breeds, including smaller dogs such as miniature schnauzers and Shetland sheepdogs.[192-194] It has been described in cats.[195,196]

Ischemic myelopathy is characterized by an acute onset of neurologic deficits that may be severe. Clinical signs may progress over several hours but are generally not progressive after 12 hours. Affected animals usually do not have a history or evidence of trauma but may have a history of exercise prior to the onset of clinical signs. Apparent pain usually is not present at the time of examination or during the course of the disease, although dogs are often reported to cry out at the onset of clinical signs.

Neurologic deficits usually are bilateral and are often but not always asymmetric. The clinical signs seem to depend on the location and extent of the spinal cord lesion. Many spinal cord segments may be involved, and the neurologic deficits present may indicate extensive gray and white matter necrosis. If fibrocartilaginous embolism occurs in the cervical enlargement, unilateral or bilateral LMN signs in the thoracic limbs and UMN signs in the pelvic limbs are seen. The absence of the panniculus reflex unilaterally or bilaterally often is noted in lesions involving the T1 spinal cord segment. An ipsilateral Horner's syndrome commonly is seen in dogs with fibrocartilaginous embolism of the cervical enlargement as a result of damage to preganglionic sympathetic cell bodies in spinal cord segments T1 and T2. Horner's syndrome may also be seen in severe lesions in the cervical spinal cord, owing to interruption of the tectotegmental spinal tract.

Fibrocartilaginous embolism in the lumbosacral spinal cord causes unilateral or bilateral LMN signs in the pelvic limbs, anal and urinary sphincters, and tail. Lesions may also occur in the C1 to C5 and T3 to L3 spinal cord segments and may result in symmetric or asymmetric UMN signs in all four limbs or in the pelvic limbs, respectively. Neurologic deficits may range from decreased conscious proprioception and mild paresis to complete paralysis and analgesia in affected limbs.

Diagnosis

Ischemic myelopathy should be suspected in any dog (especially large and giant breed dogs) with an acute onset of nonprogressive neurologic deficits that are not associated with apparent spinal pain, especially if the deficits are asymmetric or indicate that at least several spinal cord segments are involved. A diagnosis is made by ruling out other causes of myelopathy. Spinal radiographs are normal. The CSF may be normal or may have an elevated protein concentration as a result of leakage of protein through damaged vascular endothelium. Xanthochromia may be present 48 hours or more after a subarachnoid hemorrhage. The myelographic appearance usually is normal, although mild intramedullary swelling as a result of spinal cord edema may be seen for as long as 24 hours after the onset of clinical signs.

Treatment

Corticosteroids (as recommended for spinal trauma) may be given initially to reduce any secondary spinal cord edema; however, such edema usually resolves after several days. Good nursing care is essential in recumbent animals to prevent pressure sores, urinary tract infections, and contracture of denervated muscles. The prognosis depends on the severity of an animal's neurologic deficits. Animals that retain pain perception in the affected limbs and tail usually regain neurologic function, although recovery may take several weeks to months, and LMN signs may persist (muscle atrophy and/or paresis). Animals with absent pain perception for 24 hours are likely to have irreversible spinal cord damage and have a poor prognosis for return of function in the affected limb or limbs. Many animals show improvement within 2 weeks of the onset of signs unless extensive gray matter destruction has occurred.

Leukoencephalomyelopathy of Rottweilers

Etiology and Pathogenesis

Leukoencephalomyelopathy is a demyelinating disorder of the brain and spinal cord that has been reported to occur in rottweilers. It is characterized by progressive tetraparesis and hypermetria, especially of the thoracic limbs.

Leukoencephalomyelopathy has been reported in two dogs in the United States,[198] and a similar disorder has been reported in 16 rottweilers in the Netherlands.[199] Histopathologic examination showed demyelination in the white matter of the spinal cord, brain stem, and cerebellum, with intact naked axons and thinly myelinated axons accompanied by reactive astrogliosis. The spinal cord lesions were found in the lateral funiculi and occasionally the dorsal funiculi, predominantly in the cervical and thoracic spinal cord, and tended to be bilaterally symmetric. The lack of neuronal fiber degeneration makes primary demyelination more likely than secondary demyelination.

The etiology of this disease is unknown. It may be the result of an acquired primary demyelinating disease, but whether the lesions seen are due to a single demyelinating event or are the result of repeated demyelination and remyelination is not known. The lesions' bilaterally symmetric character indicate that toxic, metabolic, and nutritional mechanisms may be involved. Infectious causes (e.g., CD virus) may also result in demyelination. Vascular mechanisms may be involved, because the lesions have a segmental distribution; however, axon degeneration would be expected. An inherited condition in which myelin formation is defective and cannot be maintained (leukodystrophy) is also possible. The two dogs in the U.S. report were related, as were the 16 dogs in the Netherlands.

Other leukodystrophies have been reported in young animals, although an adult-onset leukodystrophy has not been described in dogs. The relationship of this disease to neuroaxonal dystrophy of rottweilers is not known.[200] Histopathologic lesions and clinical findings differ from those described in dogs with neuroaxonal dystrophy; however, a dog related to a dog with leukoencephalomyelopathy was diagnosed as having neuroaxonal dystrophy.

Clinical Findings

Both males and females have been reported to be affected. Clinical findings included tetraparesis, hypermetria (especially of the forelimbs), decreased conscious proprioception (especially of the pelvic limbs), and exaggerated spinal reflexes. The clinical signs became apparent between 18 and 42 months of age, and the abnormalities progressed slowly over several months to 1 year. The neurologic abnormalities were consistent with a transverse myelopathy of the cervical spinal cord. Neurologic deficits referable to structures rostral to the foramen magnum were not detected.

Diagnosis and Treatment

The diagnosis may be made on the basis of the dog's age and breed and by ruling out other causes of cervical myelopathy, such as CD myelitis, GME, cervical spondylomyelopathy, and spinal neoplasia. The results of radiography, CSF analysis, and myelography were normal in the dogs reported. Treatment of leukoencephalomyelopathy of rottweilers has not been effective.

Lumbosacral Vertebral Canal Stenosis

Etiology and Pathogenesis

The term *lumbosacral vertebral canal stenosis* encompasses a spectrum of disorders that result in narrowing of the lumbosacral vertebral canal, with consequent compression of the cauda equina. The term *cauda equina syndrome* describes a group of neurologic signs that result from compression, destruction, or displacement of the nerve roots and spinal nerves that form the cauda equina and that have a variety of causes, including lumbosacral vertebral canal stenosis (Box 193-6).[201]

Lumbosacral vertebral canal stenosis is defined as an acquired disorder of large breed dogs that results from several or all of the following: type II disk protrusion (dorsal bulging of the anulus fibrosus), hypertrophy and/or hyperplasia of the interarcuate ligament, thickening of the vertebral arches or articular facets and, infrequently, subluxation/instability of the lumbosacral junction. It is likely that several separate disorders currently are included in this definition. Other terms have been used to describe this syndrome, including *lumbosacral spondylolisthesis, lumbar spinal stenosis,* and *lumbosacral instability.* In humans, the term *spondylolisthesis* refers specifically to a forward (anterior) movement of a lower lumbar vertebra relative to a lumbar vertebra or sacrum directly below it. This problem rarely occurs in dogs, in which the most frequently encountered problem is a ventral slippage of the sacrum relative to the body of the L7 vertebra. The term *retrolisthesis* has been proposed to describe this "reverse spondylolisthesis" of dogs. *Lumbar spinal stenosis* is a term that perhaps is best used to describe a congenital ("idiopathic") syndrome reported to occur in young dogs. *Lumbosacral instability* is a misleading term, because instability is not demonstrated consistently in association with lumbosacral vertebral canal stenosis.

Box • 193-6

Disorders that Produce Signs of Cauda Equina Dysfunction in Dogs

Congenital Disorders
Vertebral and/or nerve root anomalies (e.g., spina bifida)
Idiopathic lumbar stenosis

Acquired Disorders
Infections (e.g., discospondylitis)
Neoplasia (e.g., malignant nerve sheath neoplasia)
Intervertebral disk disease
Iatrogenic stenosis (e.g., postsurgical scarring)
Lumbosacral vertebral canal stenosis (with/without "retrolisthesis")

Combined Disorders
Combination of congenital and acquired disorders (e.g., disk degeneration and lumbosacral vertebral canal stenosis)

Certain similarities between vertebral and soft tissue alterations seen in dogs with lumbosacral vertebral canal stenosis and in Doberman pinschers with caudal cervical spondylomyelopathy have been noted. Because the etiology and pathogenesis of both conditions are incompletely understood, such comparisons are of little significance at the present time. An association has been reported between lumbosacral stenosis and transitional vertebrae in German shepherds.[202] In another report, more than 30% of German shepherds with clinical signs of cauda equina compression had radiographic and pathologic abnormalities consistent with osteochondrosis of the sacral endplate.[203]

Clinical Findings

Acquired degenerative lumbosacral vertebral canal stenosis occurs most commonly in large breed dogs, especially German shepherds.[204] Males appear to be affected more frequently than females. The congenital ("idiopathic") form appears to affect smaller breed dogs. Affected dogs in both categories are between 3 and 7 years of age, although the problem can occur at any age. Degenerative lumbosacral vertebral canal stenosis is rarely recognized in cats.[7,171,193]

Signs of cauda equina compression seen frequently in affected dogs include apparent pain on palpation of the lumbosacral region, on caudal extension of the pelvic limbs, or on elevation of the tail; difficulty rising; pelvic limb lameness (often unilateral); pelvic limb muscle atrophy; paresis of the tail; scuffing of the toes; urinary and/or fecal incontinence or inappropriate voiding as a result of an inability to assume a voiding posture; self-mutilation of the perineum, tail, or pelvic limbs; and rarely, paraphimosis. These signs most often are insidious in onset and progress gradually over months, and they are easily confused with the signs of hip dysplasia or degenerative myelopathy.[204-206]

Abnormalities detected on neurologic examination include gait deficits related to sciatic nerve paresis (e.g., dragging of toes). Depression or loss of conscious proprioception, normal or slightly exaggerated patellar reflexes ("pseudoexaggeration" related to loss of antagonism to femoral nerve–innervated muscles by sciatic nerve–innervated muscles), depressed or absent flexion reflexes in pelvic limbs, decreased anal tone and anal sphincter reflexes, atonic bladder, hypesthesia of the perineum and tail, and muscle atrophy may be seen. These abnormalities relate to deficits of the sciatic, pudendal, caudal, and pelvic nerves, the nerve roots of which make up the cauda equina.[204-206]

Diagnosis

Characteristic clinical findings may be consistent with a diagnosis of degenerative lumbosacral vertebral canal stenosis. Careful mapping of areas of loss of cutaneous sensation may assist the detection of involved nerve roots. However, the syndrome must be confirmed with plain radiographs and special radiographic procedures.[207] Rarely can this condition be diagnosed on the basis of plain radiographic findings alone. Plain radiographic findings include spondylosis deformans ventral and lateral to the lumbosacral articulation, sclerosis of vertebral endplates, "wedging" or narrowing of the L7–S1 disk space, and secondary degenerative joint disease in the region of the L7–S1 articular facets (Figure 193-12). Ventral displacement of the sacrum with respect to L7 (retrolisthesis) and diminished dorsoventral dimensions of the lumbosacral spinal canal may be seen; however, such findings must be interpreted with caution, because they may be seen in normal dogs in association with slight rotation of the vertebral column on lateral radiographs. General anesthesia is mandatory for obtaining radiographs of the lumbosacral vertebral column. A ventrodorsal projection also is recommended.

"Stressed" plain radiographic projections (flexed and extended views), obtained with careful attention to avoid rotation, often help detect instability or retrolisthesis. Several attempts to separate normal dogs from dogs with lumbosacral vertebral canal stenosis by means of objective measurements made from radiographs have not been successful.[208] The appearance on plain radiographs helps eliminate other causes of cauda equina syndrome (e.g., discospondylitis or vertebral neoplasia). Linear tomography, when available, may provide specific information about the diameter of the lumbosacral vertebral canal that cannot be obtained from plain radiographs.

Electromyography may complement information available from a neurologic examination and from plain spinal radiographs by confirming denervation in muscles innervated by the nerves of the cauda equina. Motor nerve conduction velocity determinations in the sciatic and tibial nerves and measurement of evoked spinal cord potentials may also provide indirect evidence of cauda equina dysfunction.[209,210] Several contrast radiographic techniques can be used to examine the lumbosacral vertebral canal. Such techniques must be used to demonstrate soft tissue vertebral canal stenosis.[209,211] Myelography most often is useful in the diagnosis of lumbosacral problems, because the terminal portion of the subarachnoid space of dogs may fill with contrast material at this level. Many investigators have used transosseous vertebral sinus venography (filling of vertebral sinuses with contrast material) and epidurography (filling of the lumbosacral epidural space with contrast material) in an attempt to outline soft tissue stenosis of the lumbosacral vertebral canal. Th results obtained with either of these techniques must be interpreted cautiously, because false-positive studies occur with both.

Discography is useful for confirming the presence of lumbosacral soft tissue stenosis.[209,212] Discography consists of radiography performed after injection of contrast material into the nucleus pulposus of an intervertebral disk (Figure 193-13). This technique has special application in the lumbosacral disk space.

CT, either alone or combined with the contrast techniques listed above, and MRI may provide further information about soft tissue stenosis of the lumbosacral vertebral canal, particularly with regard to the L7–S1 intervertebral foramen.[213-217]

Surgical exploration may be indicated in dogs (with the appropriate history and clinical signs) in which the results of ancillary diagnostic tests do not provide a definitive diagnosis of soft tissue stenosis.

Treatment

Some affected dogs in which the clinical signs are mild or the apparent lumbosacral pain is the sole problem improve temporarily after strict confinement and restricted leash exercise for 4 to 6 weeks. The use of analgesic drugs or corticosteroids has been recommended; however, such use must be accompanied by strict confinement.

Clinical signs commonly recur in affected dogs treated only with medical therapy. Dogs with recurrence of signs and dogs that are moderately to severely affected at the time of initial presentation (especially those with urinary/fecal incontinence) should be considered candidates for surgery. Dorsal decompressive laminectomy of the L7 and S1 vertebrae is recommended. This procedure may be combined with foraminotomy or facetectomy in dogs in which compression of the spinal nerves at the level of the intervertebral foramina is suspected. In animals with radiographically confirmed instability or significant retrolisthesis, fusion of the lumbosacral articulation may be necessary. A dorsal approach for fusion has been recommended.[218]

Patients should be confined for 2 to 4 weeks after surgery. Postoperative complications include seroma formation at the surgical site and formation of a laminectomy scar at the site of the laminectomy. Both may be avoided by use of appropriate surgical technique and postoperative patient management.

Attention to bladder emptying may be necessary in dogs with bladder atony prior to surgery. The bladder should be manually expressed three times a day in such dogs. Urine should be submitted for culture and sensitivity testing before and 2 weeks after surgery, and appropriate antibiotic therapy should be instituted as indicated by the results.

The prognosis for affected dogs depends on the severity of signs before surgery. Return to normal function may be expected in dogs that are mildly affected prior to surgery. Dogs with bladder atony or a flaccid anal sphincter prior to surgery have the poorest prognosis.

Mucopolysaccharidosis

Etiology and Pathogenesis

The mucopolysaccharidoses are a group of genetic diseases that result from defects in the metabolism of glycosaminoglycans. Two subclasses have been recognized in cats, and paraparesis associated with spinal cord compression has been reported in Siamese cats with mucopolysaccharidosis VI (MPS VI).[6,7] MPS VI is the result of a deficiency of the lysosomal enzyme arylsulfatase B; in addition to causing characteristic physical deformities, it can result in (1) skeletal changes, including fusion of the cervical vertebrae, variable fusion of thoracic and

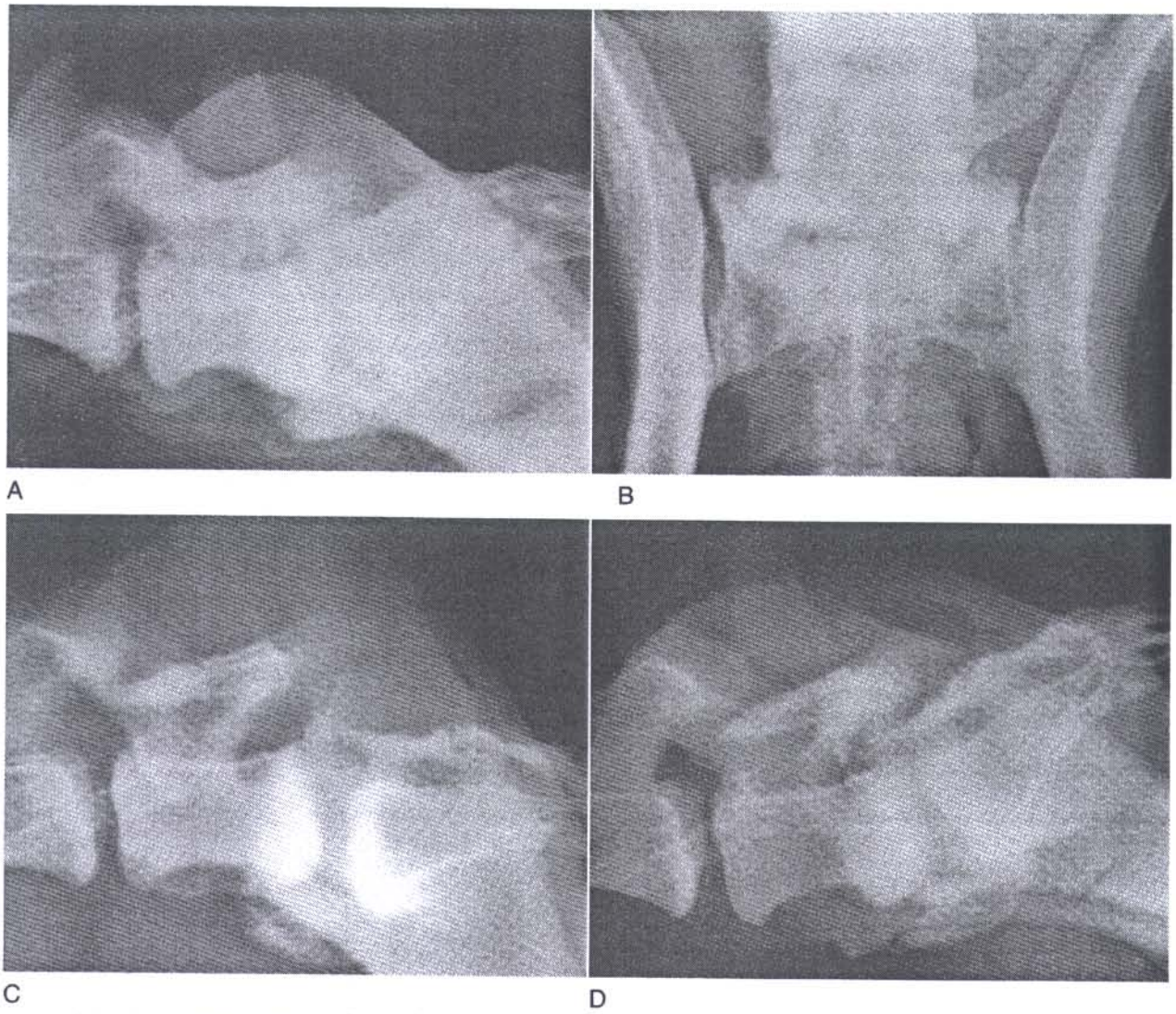
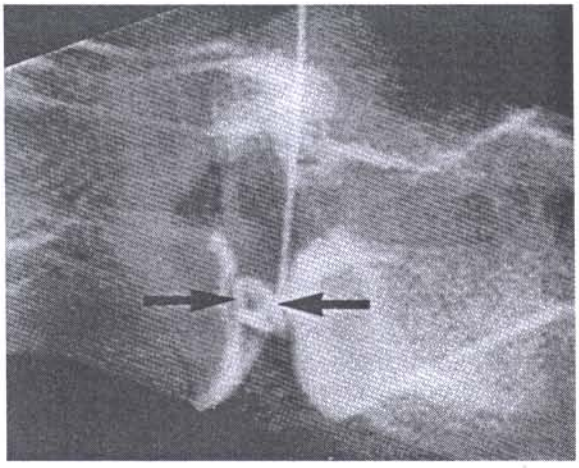
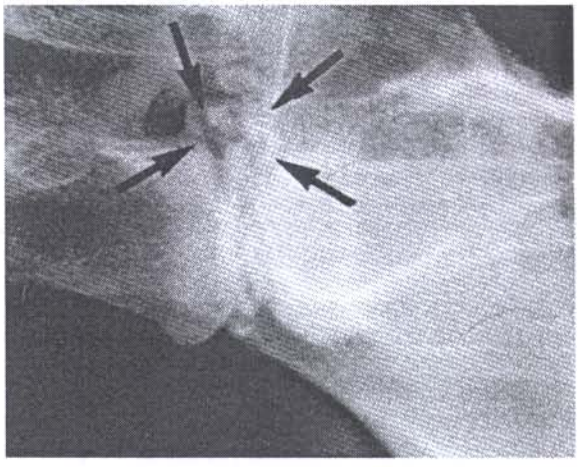


Figure 193-12 Lumbosacral vertebral canal stenosis. Lateral (**A**) and ventrodorsal (**B**) radiographs of the lumbosacral region of the vertebral column of a 7-year-old female vizsla. The dog had a history of apparent spinal pain, hypotonic tail, urinary incontinence, and pelvic limb paresis. Sclerosis of the vertebral endplates of L7 and S1, L7–S1 spondylosis deformans, "wedging" of the L7–S1 disk, and malalignment of L7–S1 are evident on the neutrally positioned lateral projection. Spondylosis deformans is seen lateral to the L7–S1 vertebral articulation on the ventrodorsal projection. A flexed lateral projection (**C**) confirms the presence of "retrolisthesis" with excessive ventral movement of the sacrum with respect to the body of L7. Instability of the lumbosacral articulation is further suggested by the extended projection (**D**), in which "wedging" of the L7–S1 disk can be seen. Use of these stressed projections is essential for confirmation of instability associated with lumbosacral vertebral canal stenosis.



A



B

Figure 193-13 Lumbosacral vertebral canal stenosis. A, Discogram at L7–S1 in a normal 5-year-old male Saint Bernard. Note the placement of a spinal needle in the nucleus pulposus of the L7–S1 disk. Contrast material (0.2 mL) is confined to the region of the nucleus pulposus *(arrows)*. B, Discogram at L7–S1 in a 6-year-old male Great Dane with a history of apparent spinal pain and self-mutilation of the right side of the tail. Note the irregular pattern of contrast filling of the disk and the dome-shaped region of contrast material that has accumulated in the vertebral canal *(arrows)*. This abnormal discogram is consistent with a diagnosis of L7–S1 disk degeneration with bulging of the dorsal anulus fibrosus into the vertebral canal. This diagnosis was confirmed through dorsal laminectomy over this site.

lumbar vertebrae, and bony proliferation and protrusion into the vertebral canal in the thoracic and lumbar spine, causing compression of the spinal cord, and (2) bony proliferation in the intervertebral foramina, causing nerve root compression.[219] Bony proliferative changes and associated spinal cord compression occur prior to or at the time of epiphyseal closure (about 9 months of age) and are probably nonprogressive after this time. MPS VI is an inherited abnormality with an autosomal recessive mode of inheritance.

MPS I, which is due to a deficiency of alpha$_1$-iduronidase, has been reported in a domestic short-hair cat. The clinical features were similar to those of MPS VI, but bony proliferative changes and associated spinal cord compression were not found. Although vacuolar changes were observed in the neurons of the brain and cervical spinal cord, presumably as a result of storage of glycosaminoglycans, neurologic deficits were not found clinically. MPS I probably has an autosomal recessive mode of inheritance.

Clinical Findings

The characteristic physical findings with MPS VI are a small head; a flat, broad face; widely spaced eyes; corneal clouding; small ears; depressed bridge of the nose; large forepaws; and a concave deformity of the sternum. Affected kittens are smaller than normal littermates, and physical deformities are noticeable by 8 weeks of age. Neurologic deficits due to skeletal changes and spinal cord compression are seen between 4 and 7 months of age and progress over 2 to 4 weeks. Neurologic findings, which are indicative of a transverse myelopathy between T3 and L3, include absent conscious proprioception, normal to exaggerated pelvic limb reflexes, and decreased pain perception in the pelvic limbs. The thoracic limb gait may be normal, or affected cats may have a crouching posture. Spinal reflexes in the thoracic limbs are normal.

Diagnosis

Radiographs of the spine show vertebral fusion and bony protrusions into the spinal canal and intervertebral foramina of the thoracolumbar spine.[219] However, bony proliferation is not an indication of neurologic dysfunction. Myelography is necessary to demonstrate spinal cord compression. Subarachnoid CSF puncture may be difficult, owing to proliferative changes around the vertebrae. MPS VI can be confirmed by measurement of arylsulfatase B activity in leukocytes.

Treatment

Because skeletal changes are nonprogressive after about 9 months of age, decompressive surgery may result in improvement in neurologic signs. However, spinal cord compression may be present at more than one site. The underlying lysosomal enzyme deficit is not amenable to treatment at present. Bone marrow transplantation is being investigated as a possible therapy for MPS VI.[220]

Myelodysplasia

Etiology and Pathogenesis

The term *myelodysplasia* describes a number of malformations of the spinal cord believed to result from incomplete closure or development of the neural tube.[6,7,221] Malformations identified histopathologically include anomalies of the central canal (hydromyelia, duplication of the central canal, or absence of the central canal); anomalies of the central gray matter, ventral median fissure, and dorsal median septum; gray matter ectopias, chromatolysis, and loss of nerve cell bodies; and syringomyelia, usually in the dorsal columns. Lesions are found throughout the spinal cord but are more severe in the lumbar region.

Myelodysplasia is considered to be an inherited condition in the weimaraner, transmitted by a mutant gene.[222] Both males and females are affected. Myelodysplasia has been described in other breeds of dogs and cats, including a Dalmatian, a rottweiler, a West Highland white terrier, an English bulldog, mixed-breed dogs, and Manx cats.[7,221,223] The etiology and pathogenesis of the condition in these animals are unknown.

Clinical Findings

Clinical signs vary in severity and usually are referable to a transverse myelopathy between T3 and L3. Clinical abnormalities usually are evident at 4 to 6 weeks of age, when puppies become ambulatory, although abnormal reflexes have been reported in affected newborn puppies. The major clinical finding in affected dogs is a symmetric, "bunny hopping" pelvic limb gait. Other clinical findings are crouching stance, abduction or overextension of one or both pelvic limbs, decreased

conscious proprioception in the pelvic limbs, scoliosis and, in one case, torticollis. The spinal reflexes and pain perception usually are normal. In weimaraners, other findings include abnormal hair "streams" in the dorsal neck region, koilosternia (a gutterlike depression in the chest) and, occasionally, a head tilt.

Diagnosis

The diagnosis is made on the basis of the history, signalment, clinical signs, plain radiography, CSF analysis, and myelography. Advanced imaging techniques (CT and MRI) have also been used.[223]

Treatment

No effective treatment exists. In weimaraners, and probably in other dogs and in cats, the clinical signs are not progressive, and affected animals may be acceptable pets.

Neoplasia

Etiology and Pathogenesis

The spinal cord may be a site of primary or metastatic neoplasia, or it can be compressed or invaded by primary or metastatic tumors arising from the vertebrae and surrounding tissues.[224-227] Primary neural tumors include astrocytoma, glioma, ependymoma, neuroepithelioma, malignant nerve sheath neoplasm (schwannoma, neurofibroma, neurofibrosarcoma), meningioma, meningeal sarcoma, and reticulum cell sarcoma. Primary lymphosarcoma of the spinal cord also has been reported in a dog.

Tumors of spinal nerves that extend into the spinal canal or spinal nerve roots may cause extradural or intradural compression of the spinal cord.[228] These tumors may also invade the spinal cord parenchyma. The distinction between schwannoma, Schwann cell sarcoma, neurofibroma, and neurofibrosarcoma is difficult to make histologically, but all have similar features clinically and on gross pathology.[224] The term *malignant nerve sheath neoplasm* has been proposed for this tumor.[224] These tumors may involve any cranial or spinal nerve or dorsal or ventral nerve root and commonly spread to involve adjacent nerves and nerve roots. Malignant nerve sheath tumors commonly arise from nerve roots or spinal nerves contributing to the brachial plexus. The tumors may arise from more than one site. Lymphosarcoma may also involve peripheral nerves and may extend along spinal nerves and nerve roots into the spinal canal, resulting in clinical signs of spinal cord disease.[229] Meningeal sarcomatosis is a rare condition characterized by diffuse infiltration of the leptomeninges by neoplastic mesenchymal cells.

The spinal cord may also be compressed by tumors originating from surrounding structures. These tumors most commonly arise from bone, cartilage, fibrous tissue, and blood vessels of vertebrae and less commonly from the hematopoietic elements of bone and tissue outside the vertebral column, including muscle, fat, and paraganglia.[224] Primary vertebral tumors, which may cause compression of the spinal cord as a result either of extension of the tumor mass into the spinal canal or of pathologic fracture of the vertebra, include osteosarcoma, chondrosarcoma, fibrosarcoma, hemangioma, hemangiosarcoma, plasma cell myeloma, giant cell sarcoma (arising from primitive stromal elements of bone marrow), and undifferentiated sarcomas.[224] Tumor metastases from sites elsewhere in the body may also be found in vertebrae, epidural space, meninges, and rarely the parenchyma of the spinal cord.

Secondary tumors, which result from hematogenous or lymphatic spread of tumor emboli, include hemangiosarcoma, lymphosarcoma, mammary adenocarcinoma, pulmonary carcinoma, prostatic carcinoma, and malignant melanoma. Clinical signs associated with secondary spinal tumors may occur early or late in the course of the disease. With the prolonged survival times that accompany recent therapeutic regimens for osteosarcoma of long bones, an increased frequency of vertebral metastases can be expected, particularly in cranial thoracic vertebrae. Embolic tumor cells may pass directly to the lumbar vertebrae from tumors in the pelvic area by reversal of blood flow in the vertebral veins with increases in central venous pressure.

Retrospective studies have shown the most commonly occurring spinal tumors in dogs to be primary and secondary bone tumors and tumors of spinal nerves and nerve roots. Primary intramedullary tumors occur less commonly than extradural or intradural-extramedullary tumors. Spinal tumors of all types occur more frequently in large breed dogs. Epidural lymphosarcoma is the most commonly occurring spinal tumor in cats.[229-233] Primary intramedullary tumors rarely occur in cats. The etiology of vertebral and spinal cord tumors is unknown. Lymphosarcoma in cats may be associated with FeLV or feline immunodeficiency virus (FIV) infection; however, not all cats with spinal lymphosarcoma test positive for FeLV or FIV.[230]

Spinal tumors may occur in animals of any age. Although tumors more commonly occur in animals more than 5 years of age, spinal cord blastoma (nephroblastoma) in dogs[234] and lymphosarcoma in cats are found most commonly in young animals. Spinal cord blastoma has been reported in large breed dogs 6 months to 3 years of age. German shepherds have a higher incidence of this tumor than other breeds. These tumors are generally found in an intradural and extramedullary location, closely associated with the pia mater of the spinal cord and separated from the spinal cord by a thin band of connective tissue. The tumor may replace most of the spinal cord and may also have an intramedullary component. These tumors occur in the T10 to L2 spinal cord segments and may be the result of neoplastic transformation of remnants of embryonic medullary (neuro)epithelium in this region of the spinal cord. However, immunocytochemical studies do not support a neuroectodermal origin. The mixed epithelial and mesenchymal patterns seen in these tumors are similar to those of nephroblastomas.[234]

Metastatic spinal tumors have also been reported to occur in dogs.[226] Primary spinal cord, meningeal, and nerve root tumors rarely metastasize outside the spinal canal; however, tumors may arise from multiple sites or may metastasize along CSF pathways (meningioma, ependymoma). Primary vertebral tumors commonly metastasize to other organ systems.

Clinical Findings

The clinical signs depend on the location of the tumor. Tumors may involve more than one spinal cord segment, and more than one spinal tumor may be present, resulting in multifocal signs. However, most animals have clinical signs referable to a transverse myelopathy. Tumors may occur anywhere in the spinal cord or spinal canal and usually result in progressive neurologic deficits. The duration of clinical signs may vary considerably (from 1 week to 1 year in one study). Animals may have acute onset of severe neurologic deficits associated with pathologic fracture of a vertebra, resulting in spinal cord compression; epidural, subarachnoid, or intramedullary hemorrhage; or spinal cord ischemia associated with tumor expansion. Neurologic deficits are usually bilateral but may be asymmetric.

Tumors of nerves of the brachial plexus initially cause progressive LMN signs in the ipsilateral thoracic limb, including muscle atrophy and paresis. The affected limb is often painful on palpation or movement; cutaneous sensation generally remains intact.[224] If the tumor extends into the spinal canal, UMN signs in the pelvic limbs may become apparent. Tumors of nerves of the cauda equina or lumbosacral plexus, with extension into the spinal canal, may cause unilateral or bilateral LMN signs in the pelvic limbs, tail, perineum, urinary bladder, and anal sphincter.

Apparent pain is a common finding with extradural and intradural tumors[227] and was the predominant clinical sign in a study of dogs with vertebral tumors. Apparent pain may be intractable, especially in animals with a tumor that affects spinal nerve roots. This may be due to stretching or inflammation of the meninges surrounding the expanding tumor. Intramedullary tumors are reported to cause a more rapid progression of clinical signs and are much less likely to be painful than extradural or intradural-extramedullary tumors. In general, however, extradural, intradural-extramedullary, and intramedullary tumors cannot be distinguished on the basis of clinical findings.

Diagnosis

A tentative diagnosis of spinal tumor can be made on the basis of radiographic, CSF, and myelographic findings. A definitive diagnosis can be made only after biopsy of a suspected lesion.

Radiography Bone lysis with a cortical break is the most common radiographic finding in animals with vertebral tumors. Other radiographic findings include destruction of vertebral endplates, collapse of an adjacent disk space, collapse and shortening of a vertebral body, pathologic fracture, bone sclerosis and bony production, cystlike expansile lesions, and adjacent soft tissue masses. Bone tumors most commonly occur in the vertebral body but may also be found in the dorsal spinous processes, transverse processes, and articular facets. Primary and secondary bone tumors or specific tumor types cannot be distinguished radiographically. Primary bone tumors usually but not always involve one vertebra. More than half of the secondary bone tumors in one study involved more than one vertebra. Rarely, metastatic tumors (e.g., carcinoma) may arise in a disk space. The radiographic appearance of such tumors may resemble that of discospondylitis. Metastases from intrapelvic soft tissue tumors often produce periosteal new bone on the ventral aspect of multiple lumbar vertebral bodies in association with the formation of a paravertebral soft tissue mass. The characteristic vertebral lesions of multiple myeloma are "punched out" lytic lesions.

Vertebral lesions may also occur with the spread of tumors from surrounding soft tissues into the vertebrae. Bone tumors are not always easily detected radiographically because of inconsistent vertebral shape, overlying rib and soft tissue shadows, and improper positioning. Other diseases, such as bacterial or fungal discospondylitis, spondylitis, or vertebral osteomyelitis, must be considered in the differential diagnosis of vertebral tumors.

Expanding tumors in the spinal canal may result in widening of the vertebral canal and loss of bone density because of ischemia and necrosis of overlying bone. Similarly, tumors of spinal nerves extending into the spinal canal may cause widening of intervertebral foramina.

Cerebrospinal fluid analysis The CSF may be normal or may have an elevated protein concentration and/or WBC count.[13] A mild to moderate increase in the WBC count of the cerebrospinal fluid may occur in animals with tumors that arise from or invade the leptomeninges. PMN cells may predominate, probably as a result of meningeal inflammation and necrosis. Tumor cells rarely are found in the CSF, except in CSF from animals with lymphosarcoma, in which abnormal lymphocytes are often present in association with meningeal infiltration. Collection of CSF from the lumbar subarachnoid space may yield more cells than cisternal collection, owing to probable caudal flow of the CSF in animals. Inability to demonstrate tumor cells in the CSF may be the result of the methods used to analyze it. Cell-concentrating techniques, which show a greater percentage of cells present in the CSF, may result in preservation of more neoplastic cells. Xanthochromia, which suggests previous subarachnoid hemorrhage, occasionally is present. The CSF protein concentration may be increased because of abnormal permeability of the blood–spinal cord or blood–meningeal barrier, the result of extradural compression or meningeal or parenchymal tumor infiltration.

Myelography Myelography may be helpful in differentiating intramedullary, intradural-extramedullary, and extradural tumors. Cisternal and lumbar injection of contrast material may be necessary to outline both the cranial and caudal extent of a tumor. It is important to obtain survey radiographs of the entire vertebral column prior to and after the injection of contrast, because more than one tumor may be present, and the neurologic deficits of one tumor may mask those produced by another. Several radiographic views (at least lateral and ventrodorsal views) are necessary to determine whether a tumor is intramedullary, intradural-extramedullary, or extradural. Tumors may have a mixed myelographic appearance, with extradural, intradural, and/or intramedullary components (e.g., nerve root tumors, meningioma, and spinal cord blastoma). Myelographic findings may also be misleading, because extradural tumors may appear intramedullary on some views, or spinal cord edema associated with acute extradural compression may appear the same as an intramedullary mass. Other mass lesions that result in spinal cord compression, intramedullary swelling, and intradural lesions must be considered in the differential diagnosis of spinal tumors.

Both CT (Figure 193-14) and MRI aid the exact determination of the location and extent of spinal tumors.[235,236] Use of these advanced imaging modalities also helps in the planning of precise surgical approaches and radiation therapy.

Biopsy Biopsy of suspected lesions is necessary to differentiate neoplasms from other vertebral and spinal cord abnormalities and to determine the histologic type.[237]

Treatment

Most vertebral tumors are not surgically resectable because of their malignant characteristics and because of the decreased stability of the vertebral column that may result from extensive surgery. Surgical decompression of the spinal cord and debulking of the tumor mass may be palliative in some cases. Some tumors in the spinal canal are surgically resectable,

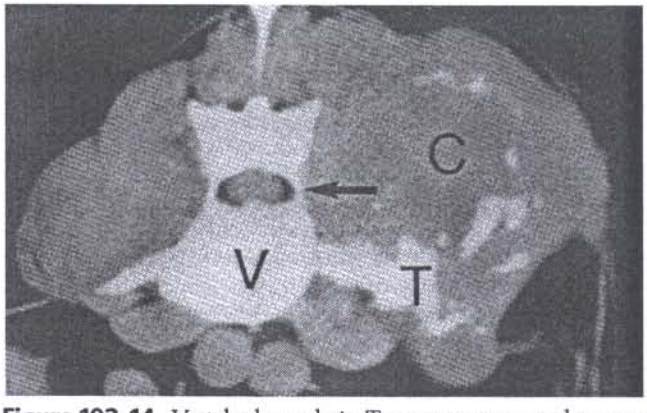


Figure 193-14 Vertebral neoplasia. Transverse computed tomography (CT) image of the vertebral column of a 13-year-old spayed female Old English sheepdog at the level of the L4 vertebral body *(V)*. Note the chondrosarcoma *(C)* arising from the transverse process *(T)* of L4. Areas of calcification can be seen in the neoplasm. The tumor involves the lateral lamina *(arrow)* of L4. CT allows exact determination of the location and extent of a neoplasm.

including some tumors that appear intramedullary on myelography, such as spinal cord blastoma.[238] Surgical exploration of solitary tumors in the spinal canal is recommended for animals with clinical signs indicative of an incomplete transverse myelopathy, even those in which myelographic findings are consistent with an intramedullary mass.[231] Intradural nerve root tumors are rarely completely surgically resectable, and the recurrence rate is high. Resection of ventral nerve roots that contribute to the brachial or lumbosacral plexus may necessitate amputation of the affected limb.[224]

No direct correlation exists between tumor size and the severity or rate of progression of clinical signs. The spinal cord is able to compensate for pressure applied gradually, and animals with spinal tumors may remain ambulatory despite having little normal spinal cord tissue remaining. Compression applied to the spinal cord rapidly, such as may occur with a pathologic fracture, may cause severe, irreversible spinal cord damage.

Corticosteroids may reduce spinal cord edema associated with spinal cord tumors and may produce clinical improvement for a variable period. Radiation therapy and chemotherapy may be helpful in animals with spinal lymphosarcoma. Most chemotherapeutic agents do not cross the blood–spinal cord or blood-CSF barrier in concentrations sufficient to eliminate tumor cells in the meninges or spinal cord. Several chemotherapeutic agents, including methotrexate and cytosine arabinoside, may be given intrathecally and have been used in the treatment of meningeal lymphosarcoma and leukemic meningitis. Complications of intrathecal use of chemotherapeutic agents include arachnoiditis and seizures. Chemotherapy may be helpful in the treatment of plasma cell myeloma.

Chemotherapy and radiation therapy have not been used in the treatment of a sufficient number of primary spinal cord, nerve root, or meningeal tumors to allow assessment of the results; however, initial experience suggests that further use of radiation therapy is warranted.[239] Various chemotherapeutic regimens have been used in the treatment of bone tumors and tumors that metastasize to bone, generally with poor results. Chemotherapy regimens in the future may offer more hope in the treatment of vertebral tumors. In general, the prognosis for animals with nonresectable spinal tumors is poor.

Neuroaxonal Dystrophy of Rottweilers

Etiology and Pathogenesis

Neuroaxonal dystrophy is a disease of rottweilers characterized by the accumulation of axonal spheroids throughout the neuraxis.[200,240,241] Clinically, affected animals have progressive ataxia in all limbs and severe hypermetria, especially of the thoracic limbs. Histologically, axonal spheroids are found in massive numbers throughout the brain and spinal cord, especially in the dorsal horns of the spinal cord and in the nucleus gracilis and nucleus cuneatus. The cerebellum is mildly atrophic in some dogs. Afferent fibers entering the sensory nuclei in the spinal cord, brain stem, and diencephalon are primarily affected. Electron microscopy has shown axonal spheroids to be enlarged, distal portions of axons and synaptic terminals that contain accumulations of smooth membrane–bound vesicles, membranous lamellae, dense bodies, and other organelles. Histologic lesions may be mild in young dogs.

A recessive mode of inheritance, with variable penetrance in rottweilers, is suspected from preliminary breeding studies. The etiology and pathogenesis of distal membranous axonopathies are not understood, but the location of the lesions suggests a derangement in the presynaptic portion of neurons or abnormalities in axonal transport. Axonal dystrophies have been associated with toxins, nutritional deficiency, aging, and genetic disorders in other species and in humans. A progressive neuroaxonal dystrophy was reported in a Jack Russell terrier pup, with pathologic alterations similar to those reported in rottweilers.[242]

Clinical Findings

Affected dogs may be clumsy as puppies, or clinical signs may not be seen until the dog is more than 12 months of age. Both male and female dogs are affected. Clinical signs may progress slowly over several years. The initial clinical finding is progressive ataxia of all limbs. Paresis or abnormalities in conscious proprioception have not been found in affected dogs. The patellar reflexes may be exaggerated, but other reflexes are normal. These findings are consistent with a transverse myelopathy of the cervical spinal cord or multifocal spinal cord disease. As the disease progresses, other signs become apparent, including hypermetria (especially of the thoracic limbs), incoordination, tremors of the head, positional nystagmus, decreased menace response, and crossed extensor reflexes. Thoracic limb hypermetria may be severe in older dogs, especially when they climb stairs. The neurologic deficits seen in older dogs are predominantly referable to abnormalities in the cerebellum or input to the cerebellum.

Diagnosis

The diagnosis is made on the basis of the animal's age and breed, as well as the neurologic findings, and by ruling out other causes of cervical spinal cord and cerebellar disease. This disease is unusual in that it is slowly progressive over several years, but in the initial stages it may appear clinically similar to other causes of a cervical myelopathy, including CD myelitis and cervical spondylomyelopathy. The CSF may have an elevated protein concentration (40 mg/dL was reported in one dog[240]). Spinal radiographs and myelograms are normal.

Treatment

Currently, no effective treatment is available. Clinical improvement has not been detected during treatment with corticosteroids. Owing to the slow progression of the disease, affected dogs may be acceptable pets for several years. Affected dogs should not be used for breeding, although a diagnosis of neuroaxonal dystrophy may not be made until after these dogs have produced litters.

Osteochondromatosis (Multiple Cartilaginous Exostoses)

Etiology and Pathogenesis

A skeletal osteochondroma is a cartilage-capped exostosis arising from the surface of a bone formed by endochondral ossification. An animal with a monostotic lesion has a *solitary osteochondroma*. Polyostotic skeletal involvement is called *osteochondromatosis* (also *multiple cartilaginous exostoses, hereditary multiple exostoses, multiple osteochondromatosis, diaphyseal aclasis, dyschondroplasia,* and *hereditary deforming chondrodysplasia*). Consistent differences exist between cats and dogs with regard to the age of onset of lesions, patterns of skeletal involvement, and pathogenesis.[243,244]

The incidence of feline osteochondromatosis is unknown.[7] Feline osteochondromatosis is characterized by an initial appearance of lesions in the skeleton of mature cats (2 to 4 years of age). Growth of the lesions is progressive. In cats, the disease has no apparent gender or breed predilection, and a hereditary pattern has not been demonstrated. Malignant transformation to osteosarcoma was reported to have occurred in an osteochondroma of a cervical vertebra in a cat.

The incidence of osteochondromatosis in dogs remains undetermined. The disease is frequently demonstrated in the skeleton of dogs radiographed for unrelated reasons. The onset of clinical disease usually occurs in dogs less than 18 months of age.[245] Onset in mature dogs is infrequently recognized.[246] A hereditary basis has been indicated in dogs, but a gender or breed predilection is not apparent. Continued growth or reactivation of growth of exostoses in dogs is suggestive of neoplastic transformation.

The etiology of canine osteochondromatosis is unknown. The current view of the pathogenesis of feline osteochondromatosis is that the disease is virus related and probably virus induced. The random distribution of the lesions is compatible with hematogenous distribution of a virus. The virus may be FeLV, feline fibrosarcoma virus acting in an atypical manner, or another member of the feline retrovirus family.

Clinical Findings

Osteochondromatosis may occur anywhere in the vertebral column but most commonly is found in the thoracic and lumbar spine. The disease may result in spinal cord compression and clinical signs indicative of a progressive transverse myelopathy between T3 and L3. Neurologic deficits are often asymmetric.

Diagnosis

Radiographically, vertebral lesions tend to be circular and smooth with sclerotic borders. The lesions are usually multiple and may be cystic or proliferative, with an increased radiodensity. Myelography is necessary to demonstrate associated spinal cord compression. Extension of exostoses into the spinal canal results in extradural compression of the spinal cord. Surgical biopsy is necessary to differentiate osteochondromatosis from benign bone tumors (osteomas), neoplastic lesions, or infectious processes.

Treatment

Treatment of canine osteochondromatosis affecting the vertebral column is unnecessary unless a lesion results in clinical sequelae. An osteochondroma should be removed if it impinges on the spinal cord or if malignant transformation is suspected. Surgical excision of cartilaginous exostoses and spinal cord decompression are the recommended treatments for lesions causing spinal cord compression and neurologic deficits. Intraoperative spinal stabilization may be indicated after removal of the lesion.[247] The prognosis for dogs that have stopped growing is good; however, the prognosis for animals that are still growing is guarded, because lesions may continue to expand and may subsequently cause spinal cord compression.

Treatment of feline osteochondromatosis is complicated by the association with FeLV and the progressive nature of the lesions in cats. It seems that at best, surgical removal of a lesion may provide only temporary relief to a cat because of the tendency for excised lesions to recur and for new lesions to develop.

Pilonidal Sinus, Epidermoid Cyst, and Dermoid Cyst (Dermoid Sinus, Pilonidal Cyst)

Etiology and Pathogenesis

A pilonidal sinus is an invagination of the skin dorsal to the spine that extends below the skin to variable depths and in some cases as far as the dura mater, where it may communicate with the subarachnoid space. The formation of pilonidal sinuses is related to failure of complete separation of the neural groove from the epidermis during embryonic development. Pilonidal sinuses may occur anywhere along the dorsal midline from the cervical to the sacrocaudal regions and may be single or multiple. Purebred and crossbred Rhodesian ridgeback dogs are most commonly affected, although other dog breeds may be affected.[248] There have been no reports of sinuses occurring along the ridge of hair of Rhodesian ridgebacks. The sinuses contain inspissated sebum, hair, and exfoliated cells and commonly become inflamed or infected. If the sinuses communicate with the subarachnoid space, extension of infection results in meningitis or myelitis. Pilonidal sinuses are likely to occur as a hereditary defect in Rhodesian ridgebacks, but the mode of inheritance is not definitely known.[6]

Dermoid cysts have been reported to occur in the brain and spinal cord of dogs and cats.[249] In one report, a dermoid cyst in the spinal cord of a cat at the level of T3 was considered a congenital anomaly.[1]

Epidermoid cysts have been reported to occur in the brain and spinal cord of dogs.[191] Such cysts are thought to arise from entrapment and subsequent growth of primordial epithelial cells during closure of the neural tube. Morphologically similar cysts have developed in humans after injury or after repeated lumbar subarachnoid punctures for CSF collection, presumably from mechanical implantation of epidermal cells. An intramedullary spinal epidermoid cyst reported in a dog was thought to have a congenital cause. Apparently, spinal epidermoid cysts rarely occur in dogs.[250]

Clinical Findings

Clinical signs of meningitis and myelitis may be seen in animals as a result of extension of infection from a pilonidal sinus to the subarachnoid space. Localized or generalized spinal pain and rigidity may be seen associated with meningitis. Neurologic deficits indicative of a transverse or diffuse myelopathy may be seen as a result of myelitis. Signs resulting from a spinal dermoid or epidermoid cyst depend on its location.

Diagnosis

A pilonidal sinus may be palpable as a cord of fibrous tissue under the skin of the dorsal midline. Palpation may be painful if the sinus is infected. An opening in the skin on the dorsal midline is usually found, and hair may or may not be seen protruding from this opening. The CSF in animals with meningitis or myelitis is generally abnormal and indicative of bacterial infection. Fistulography (performed by injecting a radiographic contrast material, such as metrizamide, which is not an irritant to nervous tissue, into the sinus) demonstrates whether pilonidal sinuses are continuous with the subarachnoid space. Myelography may also demonstrate communication.

The diagnosis of a spinal dermoid or epidermoid cyst is based on the clinical signs and on the results of plain spinal radiography, CSF analysis, and myelography. Typically an epidermoid cyst should be suspected with an intramedullary, expansile lesion on myelography in a young dog with progressive neurologic deficits. The diagnosis is confirmed by open surgical biopsy, which may provide the only means of ruling out spinal neoplasia (e.g., spinal cord blastoma). Advanced imaging (CT or MRI) may be useful for fully delineating the extent and location of these cystic structures.

Treatment

Animals with meningitis and/or myelitis associated with a pilonidal sinus should be treated as an animal with meningitis and myelitis due to another cause. Antibiotic therapy should be selected on the basis of the CSF culture, culture of the contents of the pilonidal sinus, and sensitivity testing. Complete surgical excision of the pilonidal sinus is essential.[251] Laminectomy may be necessary to remove portions of a pilonidal sinus from within the spinal canal. Recurrence of infection is likely in dogs in which a pilonidal sinus is incompletely removed. The prognosis depends on the severity of the neurologic deficits before surgery, the response to antibiotic therapy, and whether the pilonidal sinus was removed completely. Complications of surgical removal include wound dehiscence and seroma formation. Affected animals should not be used for breeding.

Treatment of spinal dermoid or epidermoid cysts of dogs has not been reported. Surgical excision may be possible in some animals.

Progressive Hemorrhagic Myelomalacia

Etiology and Pathogenesis

Acute, severe spinal cord injury may result in progressive ascending and descending infarction and hemorrhagic necrosis of the spinal cord parenchyma. Progressive hemorrhagic myelomalacia occurs infrequently and usually follows peracute explosive extrusion of a thoracolumbar disk, but it may also be seen after other types of spinal cord trauma.[6] PHM previously was known as hematomyelia. Most dogs with thoracolumbar disk extrusions have evidence of a localized myelopathy affecting up to four spinal cord segments. In animals with PHM, hemorrhagic necrosis of a large number of spinal cord segments may occur over a period of hours to days. The etiology of this syndrome is not known; however, spinal cord pathology indicates severe ischemia.

Clinical Findings

The clinical signs depend on the location of the lesion; however, most affected animals initially have clinical signs indicative of a transverse myelopathy between T3 and L3. Neurologic deficits usually are severe (paraplegia and absent deep pain perception in pelvic limbs) and peracute in onset (over several hours). Clinical signs indicating a diffuse myelopathy progress over a period of hours to 1 to 2 days. As infarction and hemorrhagic necrosis of the spinal cord progress caudally, LMN signs may be seen in the pelvic limbs and anus. As PHM progresses cranially, the level of cutaneous anesthesia and LMN signs in intercostal muscles extend cranially until thoracic limbs exhibit LMN signs. The Schiff-Sherrington sign may be present before involvement of the spinal cord cranial to T3. Diaphragmatic paralysis and bilateral Horner's syndrome may be seen with involvement of the cervical spinal cord. Affected animals often are in extreme pain, are anxious, and have an increased body temperature.

Diagnosis

The diagnosis is made on the basis of progressive clinical signs indicative of a diffuse myelopathy. Any animal with an acute onset of paraplegia due to a lesion between T3 and L3 that shows LMN signs in the pelvic or thoracic limbs should be suspected of having more than one lesion or PHM.

Treatment

In most cases PHM is fatal within 24 to 48 hours as a result of respiratory paralysis. There is no effective medical or surgical treatment, and euthanasia is recommended. Difficulty often arises in the treatment of animals that have an acute onset of paraplegia, with or without deep pain perception, within hours after the onset of clinical signs. Ideally, if decompressive surgery is indicated, it should be performed as soon as possible; however, a small percentage of these cases may show clinical signs of PHM after surgery. Hemorrhagic myelomalacia in some cases may not progress to involve the cervical cord, and affected animals may survive; however, the spinal cord damage incurred and the associated severe neurologic deficits are permanent.

Protozoal Myelitis

Etiology and Pathogenesis

Toxoplasma gondii is an obligate, intracellular, coccidian parasite. Cats are the only known definitive host of the organism and as such pass environmentally resistant oocysts in feces. The seroprevalence of infection varies by region but is approximately 30% in cats in the United States. Despite this high seroprevalence, clinical disease caused by *T. gondii* is rare.[252,253]

T. gondii infection may cause a focal or disseminated myelopathy in dogs or cats.[6] Animals are infected after ingesting meat containing *Toxoplasma* bradyzoites and/or tachyzoites; after ingesting cat feces containing sporulated oocysts; or by transplacental or congenital infection. The infective organism is spread hematogenously to most organs of the body, including the CNS. Although the incidence of disease associated with *T. gondii* is low, opportunistic infection in immunosuppressed animals may be more widespread than previously reported. Immaturity and concurrent CD virus infection may result in an increased susceptibility of dogs to toxoplasmosis. In dogs with systemic toxoplasmosis, the incidence of CNS involvement is high. In cats, concurrent infection with FeLV or FIV or administration of corticosteroids may predispose the animal to the development of clinical signs of toxoplasmosis through immunosuppression and reactivation of latent infection.[254-256]

Neospora caninum is a recently discovered, cyst-forming coccidium in the phylum Apicomplexa that is structurally similar to but distinct from *T. gondii*.[257-264] This protozoal parasite is associated most commonly with natural infection in dogs and cattle. The organism forms meronts in many tissues of dogs, especially the brain and spinal cord, resulting in meningoencephalomyelitis. Clinical signs result from host cell death caused by rapid intracellular multiplication of the parasite and the ensuing inflammatory response of the host. Cats have been infected experimentally and have been shown to develop clinical disease. *N. caninum* organisms do not react to *Toxoplasma* immunoperoxidase staining techniques, and the life cycle is unknown. Clinically, this protozoal disease appears similar to toxoplasmosis; however, CNS signs (progressive ascending paralysis) and myositis are seen more commonly than in toxoplasmosis, and *T. gondii* almost always has been associated with concurrent disease in dogs (e.g., CD infection), whereas *N. caninum* appears to be a primary pathogen.

Clinical Findings

Animals with CNS involvement by *T. gondii* usually have clinical signs of progressive multifocal or disseminated disease. Clinical signs indicating a focal transverse or diffuse myelopathy may be seen initially. Neurologic deficits depend on the site of involvement and may be either UMN or LMN deficits. If lower motor neurons are involved, denervation may result in severe muscle atrophy.

In dogs less than 1 year of age, a syndrome of progressive paralysis and rigid extension of one or both pelvic limbs may be seen in association with *T. gondii* infection. Muscle atrophy and contracture of affected limbs are seen, and limbs cannot be flexed. Muscle changes may be the result of myositis and myonecrosis and/or denervation caused by myelitis or radiculitis in the caudal lumbar and sacral spinal cord segments. Animals with CNS toxoplasmosis may or may not have other clinical signs indicative of systemic infection, such as fever, lymphadenopathy, pneumonia, apparent muscle pain, gastrointestinal tract disease, iritis, or chorioretinitis.

Overall, neosporosis is an increasingly prevalent infectious disease that merits consideration in juvenile and adult dogs with progressive paraparesis. Neosporosis may cause fatal disease in dogs of all ages (several weeks to 15 years). Puppies are affected more severely than older dogs. Young dogs develop an ascending paralysis, with the pelvic limbs affected more severely than the thoracic limbs. Other signs of dysfunction include difficulty swallowing, paralysis of the jaw, muscle flaccidity, and muscle atrophy.

Diagnosis

Antemortem confirmation of CNS toxoplasmosis or neosporosis in dogs or cats is extremely difficult and may be tentatively based on all of the following: (1) demonstration of serologic evidence of infection, (2) clinical signs of disease referable to toxoplasmosis or neosporosis, (3) exclusion of other common causes of these clinical signs, and (4) positive response to appropriate treatment.

Treatment

Several antibacterial agents have been recommended for the treatment of both toxoplasmosis and neosporosis in dogs as well as cats.

Sacrocaudal Dysgenesis in Manx Cats

Etiology and Pathogenesis

Manx cats have varying degrees of taillessness associated with sacral and/or caudal vertebral deformities.[6,7,267] Some tailless cats have a normal sacrum, spinal cord, and cauda equina. Others show varying dysgenesis or agenesis of the sacral and/or caudal vertebrae that may be associated with spina bifida and/or malformations of the terminal spinal cord and/or cauda equina. Spinal cord malformations include the absence or partial development of the sacral and caudal spinal cord segments or the cauda equina; myelodysplasia; meningocele; meningomyelocele; diastematomyelia of sacral segments (duplication); myeloschisis (cleft within the spinal cord); syringomyelia in the lumbar and sacral spinal cord segments; shortening of the spinal cord and subcutaneous cyst formation. These spinal cord and cauda equina malformations are associated with a variety of neurologic deficits.

Sacrocaudal dysgenesis is inherited as an autosomal dominant trait and may be lethal in some homozygote cats. Sacrocaudal dysgenesis and associated malformations have been recognized in most breeds of cats, many not of true Manx breeding.

Clinical Findings

Clinical signs vary, depending on the degree of spinal cord and cauda equina malformation; they include paraparesis, paraplegia, megacolon, atonic bladder, absent anal and urinary bladder sphincter tone, absent anal reflex, urinary and fecal incontinence, and perineal analgesia. Affected cats often walk plantigrade in the pelvic limbs with a "bunny hopping" gait. Vertebral abnormalities may be palpable in the lumbosacral region, and in some cats a meningocele (congenital or the result of necrosis of the overlying skin) may exit through the skin and drain CSF.

Clinical signs usually are evident soon after birth and may remain static or may progress. Worsening of neurologic deficits may be due to progressive syringomyelia in the lumbar and sacral spinal cord.

Diagnosis

The diagnosis is made on the basis of clinical findings, in addition to radiographic findings indicative of dysgenesis or agenesis of the sacral and caudal vertebrae. Myelography may demonstrate meningocele or attachment of the spinal cord to subcutaneous tissues in the lumbosacral region. The degree of spinal deformity does not always correspond with the degree of neurologic impairment. Clinical findings are the most important factors to consider in the determination of the prognosis.

Treatment

The prognosis for severely affected cats is hopeless, and treatment is not available. Cats with urinary and fecal incontinence may be managed with manual bladder expression and fecal softening agents; however, recurrent urinary tract infection, megacolon, and chronic constipation are common problems. Meningocele in cats with minimal neurologic deficits may be surgically correctable. Many tailless cats do not have neurologic deficits, and sacral and caudal deformities often are an incidental radiographic finding.

Spina Bifida

Etiology and Pathogenesis

Spina bifida, which occurs in both dogs and cats, describes a group of developmental defects characterized by failure of fusion of the vertebral arches with or without protrusion or dysplasia of the spinal cord and meninges.[6,7] This defect is part of the complex of spinal dysraphism and is the most commonly occurring dysraphic defect. *Dysraphism* is a defective fusion of parts that normally unite. Spina bifida is the absence of a portion of the dorsal elements of the vertebrae. The spinal cord and meninges may be normal (spina bifida occulta), or they may be abnormal, and the meninges and/or spinal cord may protrude through the vertebral defect.

Myelodysplasia consisting of hydromyelia, syringomyelia, anomalies of the dorsal septum, anomalies of the central gray matter, abnormal position of the central gray matter, anomalies of the dorsal and ventral horns, and myeloschisis (cleft in the dorsal part of the spinal cord) may occur in association with spina bifida. The most severe defects involve myelorachischisis, with superficial location of the neuroectoderm that is continuous with the skin. Spina bifida with myelorachischisis has been reported to occur in dogs and cats.

The etiology of spina bifida is unknown and probably is multifactorial, with genetic and environmental components. The relatively high incidence of spina bifida in some breeds of animals (e.g., bulldogs and Manx cats) suggests a heritable basis for the disorder. Teratogenic compounds, nutritional deficiencies, and environmental changes during pregnancy are also known to induce this defect.

Clinical Findings

Spina bifida is usually an incidental radiographic finding; however, if associated with spinal cord malformations, it may result in clinical signs of spinal cord or cauda equina dysfunction. English bulldogs have a high incidence of spina bifida. Spina bifida may be found anywhere in the spinal column but most commonly occurs in the caudal lumbar spine, where clinical signs are indicative of a transverse myelopathy from the L4 to the S3 spinal cord segments. Clinical signs usually become evident when affected animals start to walk.

Spina bifida also has been reported in the thoracic spine of a dog and may be associated with other spinal deformities, such as scoliosis. Other associated anomalies include dimpling of the skin or "streaming" (abnormal direction) of the haircoat over the affected region or a palpable abnormality in the spinal column. Meningoceles may cause necrosis of the overlying skin and drainage of CSF. Meningoceles may be present in the absence of clinical signs associated with spinal cord malformation.

Diagnosis

Radiographically, absence of the vertebral arch or failure of fusion of the spinous processes in one or more vertebrae may be seen (Figure 193-15). Myelography may demonstrate meningocele. Advanced imaging (CT or MRI) may be used to accurately define the location and extent of bony and soft tissue abnormalities in animals with spina bifida.

Treatment

Treatment of spina bifida rarely is attempted. Treatment is not effective for affected animals with clinical signs of spinal cord malformation. Meningocele may be amenable to surgery if neurologic abnormalities are not evident. Treatment is not necessary for animals with vertebral defects in the absence of spinal cord dysfunction. When planning therapy, the veterinarian must consider the possible existence of additional spinal cord malformations (e.g., hydromyelia) seen in association with spina bifida.

Spinal Intra-Arachnoid Cysts

Etiology and Pathogenesis

Intra-arachnoid cysts are intra-arachnoid membrane accumulations of CSF that may occur in any location along the cerebrospinal axis of cats or dogs.[268-273] The intra-arachnoid accumulation of CSF in the cyst results in expansion of the cyst between the overlying dura mater and the underlying pia mater, causing compression of the spinal cord. Intra-arachnoid

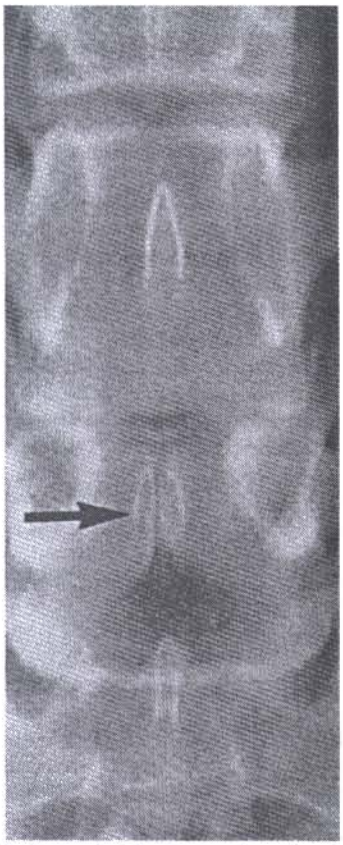


Figure 193-15 Spina bifida. Ventrodorsal radiograph of the caudal lumbar vertebral column of an 8-year-old spayed female chow chow. A deficit in fusion of the embryologic neural tube has resulted in nonfusion of the spinous process of L7 *(arrow)*. This congenital defect was an incidental finding in this dog.

cysts may be congenital in origin or may occur secondary to trauma, infection, inflammation, or subarachnoid hemorrhage.

Clinical Findings

A single intra-arachnoid cyst has been described in either the cranial cervical or caudal thoracic spinal canal. The author (RAL) has diagnosed multiple intra-arachnoid cysts in the caudal cervical region of three rottweilers. The neurologic deficits were indicative of a progressive transverse myelopathy in either the C1 to C5 or the T3 to L3 spinal cord region. Apparent cervical pain and spasms of the cervical muscles were a feature of cervical lesions; however, apparent pain was not evident in dogs with thoracic lesions. Neurologic deficits may be asymmetric.

Diagnosis

The diagnosis is made on the basis of myelographic or advanced imaging (CT or MRI) findings. Surgical findings and histopathologic examination of excised tissues confirm the diagnosis.

Plain radiographs of the spine may be normal or may show enlargement of the vertebral canal with smooth cortical margins, presumably as a result of pressure atrophy of bone overlying the cyst. Abnormalities in the results of CSF analysis have not been reported. Care should be taken in attempting a cisternal subarachnoid puncture in an animal suspected of having a cervical arachnoid cyst, because lesions may be located on the dorsal midline. One reported dog was injured inadvertently during an attempted cisternal puncture.

On myelography, pooling of contrast material in the subarachnoid space may be seen, resulting in a characteristic

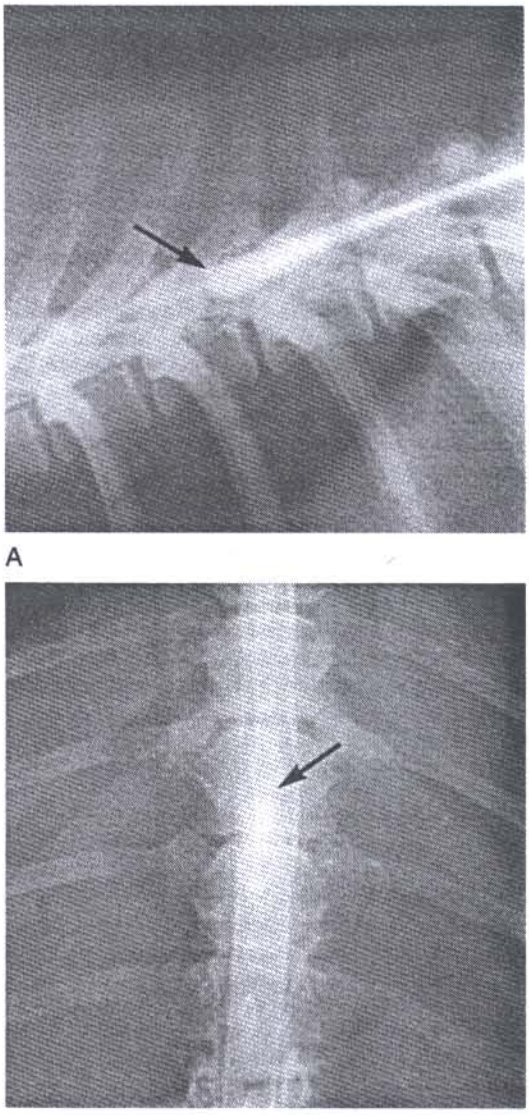


Figure 193-16 Spinal intra-arachnoid cyst. Lateral (A) and ventrodorsal (B) projections of a myelogram of the midthoracic region of a 2-year-old toy poodle that had a 1-year history of progressive pelvic limb paresis and ataxia. Note the widening of the dorsal subarachnoid contrast column at T9–T10 on the lateral projection *(arrow)*. The ventrodorsal projection shows apparent intramedullary expansion of this area *(arrow)*. An intra-arachnoid cyst was removed by dorsal laminectomy.

widening of the subarachnoid space and spinal cord compression (Figure 193-16). In all reported cases, the lesions have been intradural-extramedullary and located on the dorsal midline. The author (RAL) has seen intra-arachnoid cysts in dorsolateral and ventral locations in the cervical region of dogs. The lesions may extend over more than one spinal cord segment.

Advanced imaging (CT or MRI) may be used to fully delineate intra-arachnoid cysts. Although intra-arachnoid cysts have a characteristic appearance on advanced imaging, they must be differentiated from other cystic lesions (e.g., cystic neoplasms or cysts associated with infections).

Treatment

Surgical exploration is necessary to confirm a diagnosis of intra-arachnoid cyst and to decompress the spinal cord.

Complete surgical excision of an intra-arachnoid cyst usually is not possible, although partial excision of the cyst (called *surgical fenestration*) may result in decompression of the spinal cord and permanent clinical improvement.

Spinal Nematodiasis

Etiology and Pathogenesis

Aberrant migration and growth of parasites in the spinal canal rarely occur in dogs or cats. The route of migration of most parasites that enter the CNS is unknown, with the exception of hematogenous-borne *Dirofilaria immitis*. Parasites may cause extensive damage to neural parenchyma as a result of infarction, spinal cord compression, or granuloma formation. Parasites reported to occur in the CNS of dogs include *D. immitis*, *Toxocara canis* larvae, *Angiostrongylus cantonensis* (rat lungworm of Australia), *Ancylostoma caninum* (Australia),[274-276] *Baylisascaris* sp.,[277] and *Spirocerca lupi*.[278]

Clinical Findings

Clinical signs depend on the location of the migrating parasite, and the lesions may be focal or multifocal. Spinal nematodiasis usually is seen in immature animals, with the exception of *D. immitis*. Clinical signs often have an acute onset and usually are progressive. Clinical signs rarely occur with aberrant *Toxocara* migration in dogs; however, a single *Toxocara* larvae has been found in the cauda equina of a dog. Clinical signs reported to be associated with *A. cantonensis* infestation in the dog include paraparesis, paraplegia, urinary and fecal incontinence, paralysis of the tail, and apparent pain. *A. caninum* migration in the spinal cord has been reported to result in paraparesis, apparent neck pain, and tetraplegia.

Diagnosis

Definitive diagnosis is difficult antemortem because it requires isolation or demonstration of the parasite in the CNS.

The CSF may show an increase in the WBC count, especially in eosinophils, and/or in the protein concentration.[275] Affected animals usually have a large parasite burden, and nematode eggs or larvae may be found in the feces. Dogs with *D. immitis* infestation may have circulating microfilaria. Lesions may be located by means of myelography or advanced imaging (CT or MRI).

Treatment

The prognosis for animals with spinal nematodiasis depends on the severity of resulting neurologic deficits, and it usually is poor. Medical therapy often is ineffective at eliminating parasites in the CNS. Surgical removal of *D. immitis* adults from the spinal epidural space has been reported.

Spinal Cord Trauma

Etiology and Pathogenesis

Acute spinal cord injuries of dogs or cats result most commonly from direct physical trauma, such as missile injury or vertebral fracture or luxation. Also, spinal cord trauma is the underlying cause of neurologic signs in numerous myelopathies (e.g., intervertebral disk disease). Chronic spinal cord compression usually is seen in association with chronic progressive diseases such as neoplasia or type II disk protrusion.[279] After injury, the spinal cord may undergo sustained compression or distraction, or both. The severity of a spinal cord injury, as determined by the eventual degree and quality of recovery, is related to three factors: the velocity with which the compressive force is applied, the degree of compression (transverse deformation), and the duration of the compression. An understanding of the differences between acute and chronic spinal cord injury is essential for effective management and determination of the prognosis in cats or dogs with spinal trauma.[280]

Acute spinal cord injury Blunt traumatic injury to the spinal cord causes neurologic deficits through both direct and indirect mechanisms. The direct effects are due to immediate mechanical disruption of neural pathways, and these effects have been considered by most investigators not to be amenable to therapy. Indirect effects develop during the first few hours after injury and result in delayed secondary injury to the spinal cord. It is likely that they result in part from the release of endogenous pathophysiologic factors in response to the initial trauma and that such factors produce injury by reducing spinal cord blood flow or by altering the local metabolic environment in injured spinal cord tissue. The spinal cord remains physically intact but is functionally deranged. A common feature of acute spinal cord injury is early, often progressive hemorrhage in the central region of the injured spinal cord, especially in the gray matter. Direct mechanical disruption of vessels at the site of injury is expected; however, the loss of circulation spreads for a considerable distance cranial and caudal to the site of injury. Angiographic studies have consistently shown that the large arteries remain patent, and the major loss of microcirculation involves capillaries and venules. The secondary damage has been considered potentially reversible through the use of either physical (e.g., hypothermia) or pharmacologic interventions.

Trauma to the spinal cord triggers a series of progressive, autodestructive events that lead to varying degrees of tissue necrosis, depending on the severity of the injury.[280] Despite extensive investigation, the mechanisms responsible for the initiation and propagation of these pathophysiologic and biochemical events remain undetected. However, recent evidence suggests that the overall initiator of this autodestructive cascade of events is mechanical deformation of any type (i.e., impact or compression injury), and that the primary sites of injury are the cellular and subcellular membranes of glia, neurons, and vascular endothelial cells. Lipid peroxidation and activation of membrane lipases, with the release of fatty acids, leading to production of eicosanoids, are the earliest mechanically stimulated biochemical events described.

Within 5 minutes of spinal cord injury, postcapillary venules become congested. This is followed by opening of endothelial gap junctions there and at the capillary level, resulting in diapedesis of red blood cells and extravasation of fluid proteins and electrolytes through the "leaky" vasculature. Within 30 minutes of injury, microscopic hemorrhages appear in the central gray matter and coalesce over the following several hours (central hemorrhagic necrosis). Vacuolization develops in endothelial cells, indicating a profound ischemic or hypoxic insult, and subsequently leads to coagulative necrosis of the neuronal population. Adjacent white matter is relatively less severely affected; however, periaxonal swelling and retraction balls may be observed. These events may lead to autodissolution of the spinal cord within 24 hours, even in the absence of ongoing mechanical compression.

These phenomena would appear to have an ischemic basis, and considerable effort has been expended in characterizing the associated microcirculatory alterations. One cause of the ischemia may be direct mechanical irritation that results in vasospasm and biochemical damage due to the release of glutamate, intracellular calcium, catecholamines, and prostaglandins. Other studies point to intravascular thrombosis, possibly owing to the release of thromboxane, as an additional cause of posttraumatic ischemia. One of the most damaging biochemical alterations to the injured spinal cord is the accumulation of the excitatory amino acid neurotransmitter glutamate. Glutamate also causes an elevation of intracellular calcium that may in turn cause activation of calcium-dependent proteases or lipases, leading to further breakdown of cytoskeletal components.

A special feature of acute spinal cord injury is progressive hemorrhagic myelomalacia. This condition may occur after

spinal cord injury, and appears to be a progression of central hemorrhagic necrosis and edema to areas of the spinal cord not directly involved in the initiating injury.

Chronic spinal cord compression It has been shown experimentally that when slow compression of the spinal cord is compared with rapid compression of an equal amount, the extent of spinal cord dysfunction is determined by the contact velocity of compression. The major pathologic substrate for neural dysfunction after slow balloon compression is thought to be physical injury to the neural membranes, irrespective of blood flow changes, and the ability of that membrane to recover appears to be related to the rapidity and duration of compression. Clinical observations support the conclusion that spinal cord conduction is resistant to slow compression. Furthermore, it has been demonstrated that levels of compression that do not have an effect when applied slowly cause an immediate loss of conduction through the injured site when applied rapidly.[281]

Chronic spinal cord compression results either from a slowly developing lesion (e.g., neoplasia) or from an acute compression that is sustained. In contrast to acute spinal cord injury, chronic compression injury affects the white matter more severely than the gray matter. Hemorrhage and edema, the major findings of acute trauma, are not significant in chronic compression. Characteristic lesions are degeneration of myelin, focal areas of malacia, vacuolization, and loss of white matter axons. Mechanical deformation is likely to be the major factor in the pathogenesis of these lesions; however, ischemia and venous obstruction also may be important considerations.

Clinical Findings

Acute spinal cord injury Dogs or cats with a spinal injury frequently have serious injuries to other organ systems. A primary concern is to balance the relative urgency of non-neurologic injuries (hemorrhage, shock, airway obstruction, or limb fractures) and the need for early treatment of spinal cord injury.[279]

A complete neurologic examination is performed to localize the site or sites of injury and to determine the severity of injury. Careful palpation of the vertebral column may aid identification of a vertebral fracture or luxation. Administration of tranquilizers or analgesic drugs should be delayed until the neurologic examination has been completed, because such medications may alter an animal's responses. The neurologic examination should be performed with care to prevent further injury from excessive movement of a vertebral instability.

Several aspects of the neurologic examination are of special importance in the assessment of a dog or cat with a spinal cord injury. Recognition of the Schiff-Sherrington sign is important. After trauma, this sign must be differentiated from other postures associated with cranial injury (e.g., decerebrate rigidity or decerebellate posture). Both deep and cutaneous pain perception should be assessed, because the results of these tests are important in the determination of the prognosis. It should be remembered that vertebral column injuries may be multiple and that a neurologic examination may not detect a second lesion.

Chronic spinal cord compression Clinical signs of chronic spinal cord compression may progress over weeks or months or may be seen to occur acutely. Acute onset of neurologic signs with chronic spinal cord compression frequently is seen with such disorders as spinal neoplasia or type II disk protrusion. Sudden onset of signs may accompany pathologic fracture of a vertebra or spinal cord hemorrhage or infarction. In some cases sudden decompensation of a chronically compressed spinal cord may occur in the absence of pathologic changes. In these cases it is assumed that compensatory mechanisms in the spinal cord have been exhausted, allowing the sudden decompensation.

Diagnosis

Acute spinal cord injury The results of a neurologic examination are used to determine the site and severity of a spinal injury. Radiographs of the entire spinal column should be taken. Two radiographic views are essential only when ventrodorsal views may be accomplished by means of a horizontal beam. The objectives of radiographic examination of an animal after acute spinal trauma are to determine precisely the location and extent of a lesion; to demonstrate the presence of multiple lesions, which may not be apparent from a neurologic examination; and to assess the need for surgical therapy and determine the most appropriate surgical procedure. Accurate interpretation of radiographs depends on a knowledge of the results of a neurologic examination.

Myelography is recommended for animals that have sustained spinal trauma. The results of a myelogram may determine the extent of spinal cord swelling caused by concussion in animals without evidence of a spinal fracture or luxation and may confirm that surgical decompression through laminectomy is not necessary in animals with a fracture that is evident on plain radiographs. In the diagnosis of intervertebral disk disease, a myelogram is essential prior to surgery.

The use of advanced imaging (CT or MRI) in acute spinal cord injury may be reserved for patients in which the results of the above diagnostic techniques do not fully explain the results of a neurologic examination.

Chronic spinal cord compression The methods for diagnosing chronic spinal cord compression are the same as those used to diagnose acute spinal cord injury. A myelogram is considered essential in all such cases.

Treatment

The management of an animal with spinal trauma follows a list of priorities, and the focus of treatment is the prevention of secondary spinal cord damage that occurs after the initial injury. Immediate treatment of non-neural injuries is limited to life-threatening problems, such as shock or hemorrhage.

Acute spinal cord injury Treatment of acute spinal cord trauma should always be instituted as soon as possible after injury. The specific objectives of therapy are relief of edema, control of intramedullary or extramedullary hemorrhage, relief of spinal cord compression and, in cases of vertebral fracture/luxation, removal of bone fragments from the spinal canal and realignment and stabilization of the vertebral column. Treatment of acute spinal cord trauma may be medical or surgical or a combination of these two therapies. The goal of medical therapy is to control the chemical and vascular changes that result in secondary spinal cord injury. Numerous drugs have been described for the treatment of spinal cord injury; however, the efficacy of many of these drugs for such injuries remains undetermined.

Corticosteroids are routinely and widely used in the treatment of acute spinal cord injury. Despite a positive clinical impression that corticosteroids have beneficial effects, their use is controversial. Some studies have failed to demonstrate significant improvement of neurologic recovery with corticosteroid administration. The use of low versus high doses of corticosteroids in the treatment of spinal trauma also has yielded conflicting results. Use of corticosteroids may result in complications leading to increased morbidity and mortality (e.g., gastrointestinal bleeding, pancreatitis, colonic perforation).

The only corticosteroid with proven efficacy in the management of spinal cord injury is methylprednisolone sodium

succinate (MPSS). MPSS has been studied intensely in both the research and clinical settings for the past 10 years.[282-289] The drug must be administered as soon as possible after injury, and the effective dose range and the interval after injury when the drug may be given are narrow. Spinal cord uptake of MPSS rapidly decreases with time after injury, probably owing to secondary post-traumatic tissue loss and progressive blood flow decrease to the injury site. The molecular mechanism of action of MPSS may involve intercalation into the cell membrane and suppression of lipid peroxidation and hydrolysis. Inhibition of injury-induced lipid peroxidation results in attenuation of progressive post-traumatic ischemia and hypoxia, together with reversal of intracellular calcium accumulation. MPSS also directly retards secondary neuronal degeneration. The beneficial effects of antioxidant doses of MPSS support the contention that post-traumatic lipid peroxidation is a critical degenerative mechanism that may be interrupted with an antioxidant agent.

Current recommendations in humans are that patients with acute spinal cord injury receive MPSS (30 mg/kg given intravenously over 15 minutes) within 3 hours of injury; that they be maintained on an infusion of 5.4 mg/kg/hr for 24 hours; and that those that receive the initial bolus 3 to 8 hours after injury receive the infusion for 48 hours. Higher doses and initiation of treatment more than 8 hours after injury may exacerbate spinal cord damage. Complications include an increase in the incidence of pneumonia (2.6-fold in humans), gastrointestinal hemorrhage, and perforation. Although some experimental and clinical studies have found an improved recovery in research animals and humans treated with MPSS after spinal cord injury, a number of other studies have not found a significant improvement. One of the conclusions of the Third National Acute Spinal Cord Injury Randomized Controlled Trial[284] was that although the improvements in spinal cord injury patients after MPSS treatment were statistically significant, the actual functional differences were relatively small and benefited upper body function as opposed to actual locomotion.

The 21-aminosteroid tirilazad mesylate is a potent inhibitor of lipid peroxidation. In the Third National Acute Spinal Cord Injury Randomized Controlled Trial,[284] administration of tirilazad (2.5 mg/kg every 6 hours for 48 hours) after an initial 30 mg/kg bolus of MPSS to spinal cord injury patients resulted in motor recovery rates equivalent to those of patients who received MPSS for 24 hours. The reasons cited for failure of a 48-hour tirilazad regimen to improve neurologic recovery as much as the 48-hour MPSS regimen included the possibility that important mechanisms other than lipid peroxidation are involved in spinal cord injury and that a less than optimal dose was used. Another randomized, controlled trial of the drug in humans with spinal cord injuries is currently underway.

One of the most damaging effects of spinal cord injury is the accumulation of intracellular calcium in injured neurons, and neuronal death is closely related to the rise in intracellular calcium. Administration of a calcium channel antagonist (i.e., nimodipine or flunarizine) after spinal cord injury has had mixed results.

A decision on surgical therapy must be made as soon as non-neural injuries have been treated and medical management has been instituted. Ideally, this is within 2 hours of injury. Indications for surgery after spinal cord injury are moderate to severe paresis, or paralysis, associated with myelographic evidence of spinal cord compression; progressive worsening of neurologic signs despite adequate medical therapy; and luxation or fracture of the vertebral column in association with distraction, malalignment, instability, or myelographic evidence of spinal cord compression. Any animal with sustained compression of the spinal cord after injury, regardless of the cause, must be considered a candidate for surgical decompression of the spinal cord. In general, it is best to initiate surgical therapy in any animal in which uncertainty exists regarding the indications for surgical versus medical therapy. Neurosurgical procedures require specialized knowledge and equipment, and prompt referral to a qualified surgeon may be indicated.

The major objectives of surgical management of spinal trauma are decompression of sustained spinal cord compression and realignment and stabilization of vertebrae if necessary. Laminectomy alone is not sufficient for decompression in most cases, and the compressing mass (e.g., disk material, hematoma, bone fragments) should be removed when possible. When spinal cord swelling is the major source of compression or when discoloration of the spinal cord is present, durotomy or myelotomy may be combined with laminectomy.

No satisfactory methods of external fixation of spinal fractures exists for cats and dogs.[290] The author (RAL) favors the use of polymethyl methacrylate and Steinmann pin fixation for most spinal fractures or luxations.[291,292] Surgical management of spinal cord injuries provides the best opportunity for rapid, complete recovery in animals with sustained compression or instability and also facilitates postinjury care, because the risk of further injury from movement of an unstable vertebral column is minimized. However, conservative management, including strict confinement for 4 to 6 weeks, may be efficacious in animals with minimal neurologic deficits and without myelographic evidence of sustained spinal cord compression or vertebral displacement or instability.

Regardless of the type of stabilization used, strict confinement is recommended for 6 weeks after surgery. Potential complications encountered in dogs or cats with a spinal injury include the development of a urinary tract infection and pressure sores. Careful nursing care is essential, regardless of the type of therapy.[293]

The prognosis for an animal with an acute spinal cord injury depends on numerous factors; however, the results of the neurologic examination should be the main determinant. Assessment of pain perception is essential for an accurate prognosis. Perception of a painful stimulus must be differentiated from reflex activity mediated at the level of the spinal cord. Owners of affected animals should be made aware at the outset of therapy of factors such as the prognosis, the expense involved, the expected time from treatment to recovery, and the need for prolonged physical therapy in most cases. After a severe spinal injury, an animal may require many months to recover, and residual neurologic deficits may persist.

Chronic spinal cord compression The approach to treatment of chronic spinal cord compression is different from that for acute spinal cord injury. As previously stated, hemorrhage and edema usually are not prominent factors in chronic compression, therefore medical management with corticosteroids would not be expected to be efficacious; however, many animals with chronic spinal cord compression improve clinically with corticosteroid administration. The reason for such a response has not yet been determined; however, it may be due to the effects of corticosteroids at the membrane level, resulting in improved conduction in remaining axons. Occasionally, animals may be maintained for months or years with corticosteroid therapy alone.

Surgical decompression and stabilization should be considered in dogs or cats with neurologic deficits associated with chronic spinal cord compression. Surgical decompression in such animals should be approached cautiously, because pathologic alterations in the spinal cord may be irreversible, and the most that may be achieved is arrest of the progression of neurologic deficits. In some cases, compensation for the irreplaceable loss of neural tissue may occur. Neurologic status may be worsened by surgical decompression, even with meticulous surgical technique. Such deterioration may be the result of

reactive hyperemia that follows decompression, which in turn results in vascular protein leakage in the affected spinal cord segments.

Spinal Stenosis

Etiology and Pathogenesis

The term *spinal stenosis* indicates a narrowing of the vertebral canal, a condition that may produce a variety of neurologic syndromes.[31] The stenosis may be focal, segmental (affecting several adjacent vertebrae), or generalized (present throughout the vertebral column). Spinal stenosis may result either from bony impingement on neural elements (congenital stenosis, developmental stenosis resulting from inborn errors in skeletal growth, idiopathic developmental stenosis, or acquired stenosis) or from compression of neural tissue by nonosseous components of the walls of the vertebral canal (hypertrophy of the dorsal longitudinal ligament or ligamentum flavum or disk extrusion/protrusion).

Congenital spinal stenosis Congenital stenosis may occur as a primary lesion or may be seen in association with other congenital anomalies of the spinal cord or vertebral column.[294,295] In dogs, congenital stenosis may occur with block vertebrae or hemivertebrae.[31] Congenital spinal stenosis has been reported in association with transitional vertebrae, especially at the lumbosacral junction of dogs.[31,204] Despite the congenital origin of this stenosis, the initial manifestation of clinical signs may not occur until after an animal has reached skeletal maturity.

Thoracic vertebral canal stenosis Segmental vertebral stenosis frequently occurs in the cranial thoracic spine of several dog breeds (e.g., Doberman pinscher).[31] Vertebrae T3 through T7 are affected most frequently. A decrease in the dorsoventral diameter of the vertebral canal, compared with adjacent vertebrae, is seen, and spinal cord compression may be seen. Mild lordosis, kyphosis, or scoliosis may be seen in association with the stenosis.

Developmental stenosis resulting from inborn errors in skeletal growth This condition has been reported to occur in dogs.[168] The term *inborn errors* indicates incoordination of ossification and bone growth as a result of hereditary transmission or fresh mutation of a normal gene.[31] The errors are based on metabolic or other disturbances of cells involved in skeletal development. The disproportionate bone growth is already present at birth; however, the causative agents remain active during maturation. Therefore the term *developmental* is used to distinguish this group from the congenital stenoses. These conditions result in generalized spinal stenosis, which is more pronounced in the lumbar vertebral column. The vertebrae have a narrowed vertebral canal; however, the spinal cord and cauda equina are of normal size. This results in a disproportion between the dimensions of the vertebral canal and the volume of its contents. The relative spinal stenosis of chondrodystrophic dog breeds may contribute to the increased incidence of disk extrusion in these breeds. As with congenital stenosis, clinical signs may not develop until later in life and may be related only to a single level of the stenotic vertebral canal.

Idiopathic developmental stenosis A genetic disturbance in which pathologic effects are apparent in their entirety only when growth is complete and the vertebrae have attained full size is termed *developmental*.[31] Clinical signs of spinal stenosis may result if some additional factor (e.g., disk protrusion) compromises the available diameter of the spinal canal in adult life. Hypertrophy of the bone of the vertebral arch or of the ligamenta flava may be present in this condition, which has been reported to occur in dogs.

Hypertrophy of the nonosseous components of the vertebral canal Spinal stenosis resulting from ligamentous proliferation at C2–C3 has been reported in young rottweilers.[31,296]

Clinical Findings

Clinical signs of spinal stenosis reflect the location of the lesion, regardless of the precise cause.

Diagnosis

The diagnosis of spinal stenosis is made primarily by radiography. Myelography is essential for precise localization of the spinal stenosis. Other contrast-enhanced radiographic techniques may be used to define stenosis affecting the lumbosacral junction. Advanced imaging (CT or MRI) may aid in the determination of the location and extent of lesions associated with spinal stenosis.

Treatment

Spinal stenosis may be treated either medically or surgically. Relief of apparent pain with analgesic or anti-inflammatory drugs, combined with exercise restriction, may be adequate in dogs with mild clinical signs. In animals in which apparent pain persists or the stenotic condition worsens, decompressive surgery is indicated. Surgery is best performed early in the course of the disease. Internal spinal stabilization or fusion may be necessary when instability is evident on stress radiographs or after extensive decompressive procedures.

Spondylosis Deformans

Etiology and Pathogenesis

Spondylosis deformans is characterized by the formation of osteophytes (bony spurs) around the margins of vertebral endplates.[297] Osteophytes may form at one or more intervertebral disk spaces and may appear to bridge or almost bridge intervertebral disk spaces. The radiographic appearance of solid bony bridges may represent only an interdigitation of the adjacent osteophytes. Osteophyte production in spondylosis deformans is the noninflammatory bony response to degenerative changes in the intervertebral disks. These degenerative changes involve the anulus fibrosus and lead to the formation of intradiskal fissures.

The incidence and size of vertebral osteophytes increase with age. All dog breeds are affected, although large canine breeds may have a higher incidence of spondylosis deformans.[298] The caudal thoracic, lumbar, and lumbosacral spinal segments are affected most frequently. Because these segments are the areas of greatest spinal mobility, dynamic and mechanical factors may play a role in osteophyte formation. Spondylosis deformans is uncommon in the cervical and cranial thoracic segments in dogs. In cats, the incidence of spondylosis deformans forms a bell-shaped curve, with the highest incidence at the level of T7–T8.

The terms *ankylosing spondylosis* and *ankylosing spondylitis* have been used by some authors to describe spondylosis deformans, despite the fact that it is not an inflammatory condition and ankylosis is uncommon.

Clinical Findings

In most affected animals, spondylosis deformans is not of clinical significance. Rarely, bony spurs may project into the spinal canal or intervertebral foramina, resulting in compression of the spinal cord or spinal nerves. In such affected animals, the clinical signs, which depend on the location of the lesion, include apparent spinal pain, lameness, and signs of transverse myelopathy or peripheral neuropathy. Other causes of spinal cord disease, peripheral nerve disease, and apparent spinal pain should be investigated and ruled out before clinical signs are attributed to spondylosis deformans. Localized pain or

lameness is reported to occur in animals with fracture of vertebral osteophytes.

Diagnosis

A diagnosis of spondylosis deformans is based on the results of radiographs of the spine (Figure 193-17). Bony osteophytes associated with spondylosis deformans may be seen at one or more intervertebral disk spaces ventral to the vertebral bodies on lateral projections and lateral to the vertebral bodies on ventrodorsal views. These osteophytes have a curved, beaklike appearance with smooth ventral and lateral borders. Osteophytes range in size from small bony spurs to those that equal the dorsoventral dimensions of the vertebral body. Spurs from adjacent vertebrae may interdigitate. Osteophytes form predominantly around the ventral and lateral margins of the vertebral endplates, and those seen on lateral radiographs appear to be projecting dorsally into the spinal canal. Such osteophytes generally are located lateral to the spinal canal. Extensive osteophyte production dorsolateral to the vertebral body may compress spinal nerves at the level of the intervertebral foramina.

Bone may form in the mass of connective tissue formed between developing osteophytes and may remain unattached to the vertebral bodies. These apparently free bone fragments are usually seen ventral to the intervertebral disk and may eventually become incorporated into developing osteophytes. These bone fragments may appear radiographically to be fractured osteophytes, but in fact they are not formed as a result of trauma.

Vertebral osteophytes may occur at either normal or narrowed disk spaces. Dorsally or dorsolaterally projecting osteophytes need to be distinguished from calcified disk material on lateral radiographs. Vertebral osteophytes may also form as a result of instability between adjacent vertebrae as a result of vertebral fracture or luxation, discospondylitis, congenital vertebral malformations, and surgery (e.g., disk fenestration). However, the term *spondylosis deformans* is used specifically to define the formation of vertebral osteophytes secondary to disk degeneration. Disk protrusion may occur at the same site as spondylosis deformans, resulting in spinal cord compression. Myelography or advanced imaging (CT or MRI) is necessary to determine whether disk protrusion

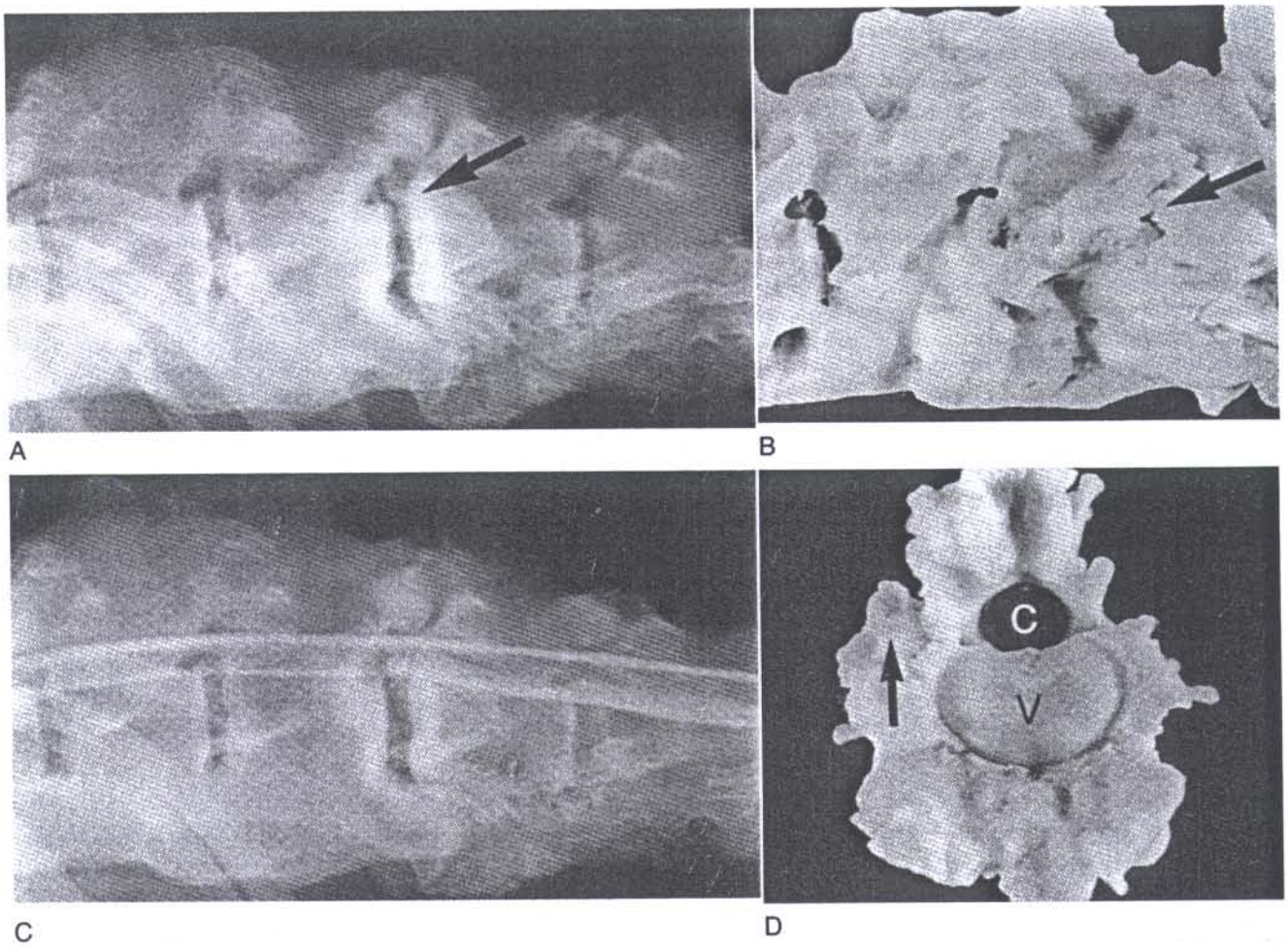


Figure 193-17 Spondylosis deformans. Lateral radiograph **(A)**, gross pathologic specimen **(B)**, and lateral myelogram **(C)** of the cranial lumbar vertebral column of a 12-year-old male golden retriever. Note the extensive spondylosis deformans present in the absence of myelographic abnormalities. Osteophytes *(arrow)* may appear to project into the vertebral canal on the lateral projection; however, these are actually dorsolateral and do not result in spinal cord compression. The typical location of osteophytes is seen in **D**, in which the spinal canal *(C)* of the L2 vertebrae *(V)* is not encroached upon by the ventrally and laterally located osteophytes. The arrow in **D** indicates osteophytes located close to the intervertebral foramen. This dog was neurologically normal.

or dorsal vertebral osteophyte formation is causing spinal cord compression.

Treatment

Spondylosis deformans rarely results in spinal cord compression. However, should spinal cord compression or nerve root entrapment be demonstrated in an animal with neurologic deficits, surgical decompression may result in clinical improvement. Analgesics may be of benefit in animals with evidence of pain suspected to be the result of spinal nerve compression by the production of vertebral osteophytes. In most animals, spondylosis deformans is not of clinical significance, and treatment is not necessary.

Synovial Cysts

Spinal synovial cysts may arise from the articular facets and surrounding connective tissues of the cervical and thoracolumbar vertebrae of dogs. These cysts may result in progressive extradural compression of the spinal cord. The etiology of synovial cysts is unknown; however, both degenerative changes and trauma have been suggested as likely causes.[299,300] Clinical signs resulting from compression of the spinal cord by a synovial cyst reflect the location of the cyst (or cysts) and are usually slowly progressive. The diagnosis of synovial cyst is made primarily by means of radiography. Myelography is essential for precise localization of the cyst or cysts. Advanced imaging techniques, particularly CT, may further delineate the location and extent of a synovial cyst. Surgical decompression of the spinal cord and excision of the cyst appear to provide long-term resolution of clinical signs.

Syringomyelia and Hydromyelia

Etiology and Pathogenesis

Syringomyelia (cavitation of the spinal cord) and hydromyelia (dilatation of the central canal) result in similar signs of spinal cord dysfunction. Syringomyelia may occur secondary to hydromyelia (communicating syringomyelia) or may not communicate with the central canal (noncommunicating syringomyelia). Syringomyelia may be associated with spinal cord tumors, myelitis, meningitis, and spinal cord trauma. The cause of syringomyelia is not known, but the condition may result from venous obstruction or distention or may be due to mechanical disruption or shearing of spinal cord tissue planes.

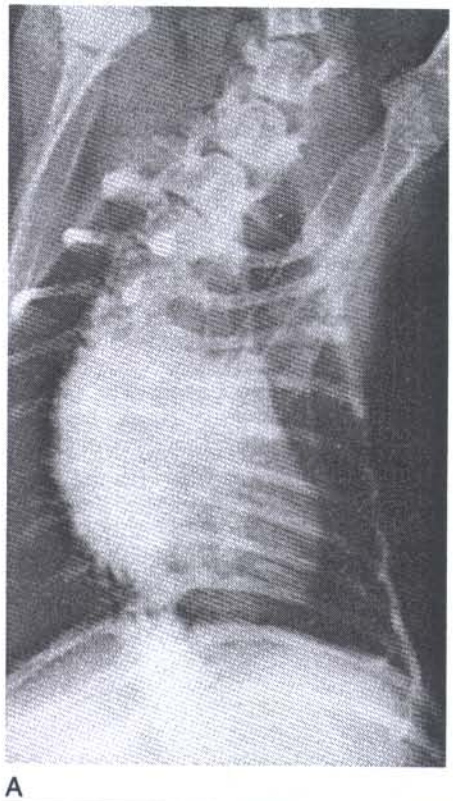
Hydromyelia with or without syringomyelia may be idiopathic or it may be associated with congenital malformations such as myelodysplasia, meningomyelocele or hydrocephalus, or lesions resulting in obstruction of CSF flow into the spinal subarachnoid space at the foramen magnum (e.g., chronic arachnoiditis, trauma, congenital malformations, and vascular malformations).[301-304] Hydromyelia and syringomyelia in these animals probably results from intracranial and spinal cord venous or arterial pressure changes and associated CSF pressure changes.

Syringomyelia in weimaraners with myelodysplasia may be the result of progressive hydromyelia, abnormalities in the central canal, or abnormal vascular patterns in local areas of the spinal cord leading to low-grade ischemia, degeneration, rarefaction, and cavitation in the spinal cord.

Regardless of the cause, cavitation may be progressive, probably along planes of structural weakness, such as the gray matter of the dorsal horns, and subsequent necrosis and edema of the spinal cord parenchyma around such a cavitation (or dilated central canal) can result in the onset and progression of clinical signs.

Clinical Findings

Clinical signs depend on the location of the lesion and whether other spinal cord lesions are present. Clinical findings include progressive spinal deformity (scoliosis, torticollis); LMN or UMN signs, depending on the location; and apparent spinal pain (Figure 193-18). Clinical signs may be acute or may be progressive over weeks to several years. In weimaraners with myelodysplasia, clinical signs do not appear to be progressive.



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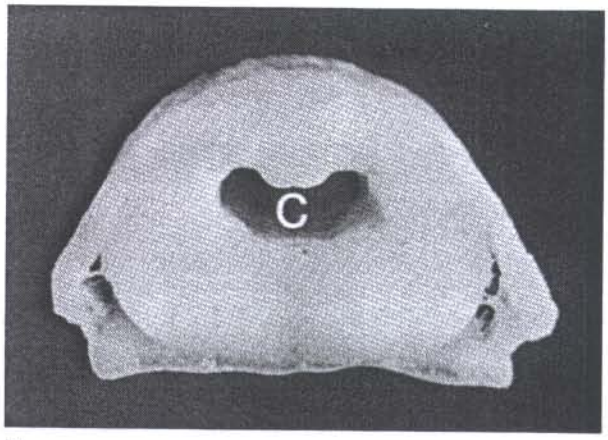

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Figure 193-18 Hydromyelia and scoliosis. Ventrodorsal radiograph **(A)** of the caudal cervical and thoracic vertebral column of a 1-year-old female beagle. Note the scoliosis of the vertebral column. The spinal cord throughout the region of scoliosis **(B)** had an enlarged central canal *(C)* consistent with a diagnosis of hydromyelia.

Diagnosis

Myelography may show obstruction of the flow of CSF at the foramen magnum if hydromyelia or syringomyelia is due to chronic arachnoiditis or arachnoid adhesions. Cisternal puncture for the collection of CSF is contraindicated in these animals, owing to likely inadvertent puncture of the spinal cord. Lumbar CSF may show evidence of chronic inflammation. Myelographic results in other cases may be normal or

may show intramedullary swelling of the spinal cord. Advanced imaging (CT or MRI) is extremely useful for identifying the location and extent of cavitary lesions of the spinal cord.[305]

Treatment

Treatment of scoliosis in a dog after drainage of an intraspinal cystic lesion has been reported.[306] Surgical drainage of cavitary lesions in humans has resulted in improvement in some cases.

Vascular Malformations and Benign Vascular Tumors

Etiology and Pathogenesis

Spinal arteriovenous malformations and benign vascular tumors (hemangioma, cavernous angioma) have been reported in dogs. Arteriovenous malformations consist of one or more anomalous arteries arising from radicular arteries that drain without a capillary bed into one or more veins communicating with veins on the surface of the spinal cord, resulting in the formation of tangles of tortuous distended vessels on or in the spinal cord. These malformations may be extramedullary or intramedullary, or both. Hemangioma is regarded as a benign neoplasm of endothelium that consists of discrete masses of tangled capillaries with or without cavernous or solid areas. Multiple hemangiomas may occur. These tumors, which arise from the meninges, are predominantly extramedullary but may be intramedullary.

Clinical Findings

Arteriovenous malformations and vascular tumors may occur anywhere in the spinal canal, and clinical signs usually reflect a progressive transverse myelopathy. An acute onset or sudden worsening of clinical signs may occur as a result of hemorrhage or thrombosis associated with abnormal vasculature of the malformation or tumor. Clinical signs may be the result of spinal cord compression or ischemia.

Diagnosis

The CSF may be normal or may have an elevated protein concentration. It may be xanthochromic, and the WBC count may be mildly elevated if subarachnoid hemorrhage has occurred or if a meningeal inflammatory response is associated with tumor growth.

Myelography may show evidence of an intradural or intramedullary mass. Advanced imaging (CT or MRI) may be used to further define the lesions. Surgical biopsy is necessary to distinguish these lesions from other neoplasms, subarachnoid cysts, and other intradural and intramedullary lesions.

Treatment

Surgical removal of a vascular malformation or vascular tumor may be possible.

CHAPTER • 194

Peripheral Nerve Disorders

Karen Dyer Inzana

The peripheral nervous system can be defined as those portions of the nervous system that reside partially or entirely outside the central nervous system (CNS) and are invested by a unique set of glial elements, Schwann cells, fibroblasts, and satellite cells. Using this definition, the peripheral nervous system includes cranial nerves II through XII, all of the spinal nerves with their roots, peripheral nerves, and the peripheral components of the autonomic nervous system.[1] Collectively they function to relay information about the environment to the CNS and in turn provide motor control of peripheral structures. Because peripheral nerves are the sole neural structure that controls skeletal muscle, they provide the most elemental level of motor control to the nervous system.

Structurally, peripheral nerves are collections of neuronal cell processes enveloped in fibrous connective tissue.[1] Three distinct supportive tissue sheaths (the endoneurium, the perineurium, and the epineurium) surround individual axons, fascicles of axons, or the entire peripheral nerve, respectively (see Figure 194-1). Neurons are the principle cells that make up the peripheral nerves.[1] Cell bodies are located in the brain stem and spinal cord (motor neurons) or in clusters of cells (ganglia; sensory and autonomic) located in the periphery. Cell bodies extend processes (axons) outside the nervous system, which either receive information from sensory receptors (sensory or afferent neurons) or transmit information regarding movement to peripheral muscles (motor or efferent neurons). All axons are invested with a Schwann cell covering. In most axons 1 μm in diameter, the Schwann cell also generates a myelin sheath that facilitates propagation of action potentials along the axon. Motor axons terminate on multiple skeletal muscle endplates, whereas sensory axons either terminate in secondary neurons, many of which form connections with the motor axons of the same or nearby peripheral nerves, or they continue uninterrupted to the brain stem as sensory spinal tracts.

Functionally, information is transmitted along axons electrically in the form of an action potential.[1] The action potential is created by ion influxes, primarily sodium, that change the electrical gradient across the axonal cell membrane. In myelinated axons, sodium ion channels are concentrated at nodes of Ranvier and action potentials are propagated along the axon from node to node (saltatory conduction), whereas ion channels are uniformly located along the entire length of nonmyelinated axons and conduction is continuous along the cellular membrane. Information is transmitted to muscles or other neurons—most commonly chemically—by the physical release of a neurotransmitter at the axon terminal, which interacts with receptors linked to additional ion channels on the receptor surface.

METHODS OF EVALUATION

There are main methods of evaluating the peripheral nervous system: (1) clinical evaluation, (2) electrophysiological evaluation, and (3) histological evaluation. Clinically, the hallmarks

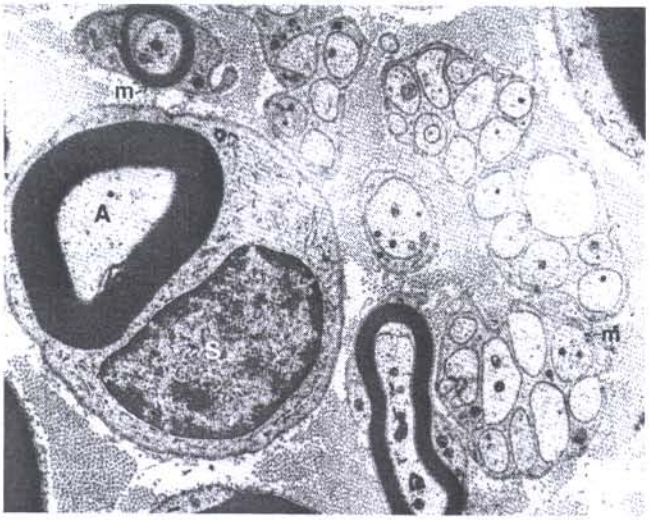

Figure 194-1 Electron micrograph of a peripheral nerve (×12000). Cross-sections of both myelinated (*A*) and unmyelinated (*a*) axons are present, surrounded by Schwann cell membranes (*m*). The section of the medium-sized myelinated axon in the center was taken through the Schwann cell nucleus (*S*).

of peripheral nerve disease are motor deficits ranging from weakness to paralysis, hypotonic muscles with rapid muscle atrophy, and diminished or absent spinal reflexes. Sensation may be altered if the disease process affects sensory nerves. These clinical signs may be diffuse or confined to one or more peripheral or cranial nerves. The clinical signs attributed to individual peripheral nerve or cranial nerve injury are outlined in Tables 194-1 and 194-2. Most peripheral neuropathies are "diffuse." Weakness is often more pronounced in the pelvic limbs. With the exception of the recurrent laryngeal, hypoglossal, and vagal nerves, cranial nerves are usually only affected in more severe cases. Clinical signs of laryngeal paralysis including stridor, inspiratory dyspnea, voice change, and exercise intolerance may be an early sign of a more diffuse peripheral neuropathy.[1] Similarly, dysphagia and megaesophagus have been associated with generalized peripheral nerve disease.[1] In rare cases where sensory nerves are affected alone, weakness is less apparent than poor coordination. Muscle atrophy is less marked, but spinal reflexes are uniformly depressed.

Measuring the electrical activity of skeletal muscle via needle electromyography (EMG) is useful to confirm suspicions of peripheral nerve or muscle disease and to map the distribution of injury.[1] A variety of spontaneous electrical potentials may be recorded from denervated or otherwise injured skeletal muscle. These spontaneous potentials have been broken down into several characteristic potentials including fibrillation potentials, positive sharp waves, and high-frequency discharges.[1]

Because nervous tissue is electrically excitable tissue, the functional integrity of specific regions can be evaluated by measuring their ability to conduct an action potential evoked by electrical stimulus or stimulation of specific receptors. Using a combination of neuroanatomic and physiologic principles, any region of the central and peripheral nervous system can be electrophysiologically evaluated. The techniques most useful for peripheral nerve disease include motor and sensory nerve conduction, brain stem auditory evoked potentials, and occasionally spinal cord evoked potentials. These have been described in detail elsewhere.[1] Briefly, in demyelinating neuropathies, motor and sensory nerve conduction is slowed but the evoked action potential remains near normal in amplitude and duration. With axonal loss, significant reduction in nerve conduction velocity is not seen but the evoked action potential is often reduced in amplitude and prolonged. The distinction between axon or myelin loss is not as readily apparent in central conduction studies. Instead, either conduction block or changes in the evoked potentials are simply an indication of disease.

Finally, the peripheral nervous system can be evaluated histologically without creating marked functional impairment. Muscle biopsies may be useful at distinguishing denervation from primary muscle disease. Denervated skeletal muscles develop characteristic changes of angular atrophy. By evaluating histologic types of muscle fibers in unfixed, frozen samples, both type grouping and large grouped atrophy can be useful indicators of chronicity of disease and regenerative attempts.[1] Fascicular biopsies of peripheral nerves can be obtained from both motor and sensory nerves. Briefly, the peripheral nerve to be sampled is surgically isolated, and a thin strip, less than one third the nerve diameter and extending 2 to 3 cm, is excised. Nerve samples should then be secured in a stretched position prior to fixation in 2.5% glutaraldehyde. Samples may then be sent to a laboratory that specializes in neuromuscular evaluation, where they will usually be osmicated and embedded in plastic for both light and electron microscopy. Postosmicated peripheral nerve biopsies can also be suspended in resin and individual fibers teased apart so that the pathology of successive internodes can be appreciated.[1]

MECHANISMS OF DISEASE

Because at least a portion of most peripheral nerves resides in the CNS, CNS diseases can affect them. However, this chapter concentrates on diseases unique to the peripheral nervous system and neuromuscular junction. Before considering individual diseases, it is useful to understand some of the complex interrelationships between neurons, axons, and Schwann cells that might contribute to disease processes.

The neuron is a specialized cell with an unusually large surface area that aids in recognition of synaptic inputs from adjacent cells. The neuron contains many of the typical cellular organelles, including a single nucleus, one or more nucleoli, Golgi, and mitochondria. Under most conditions the cytoplasm of neuronal cell bodies contains abundant rough endoplasmic reticulum or Nissl substance.[1] Unlike most cells, neurons must support cellular processes that often extend great distances from the cell body. Damage to a neuron results in degeneration of all of its cellular processes and dissolution of the myelin sheath produced by Schwann cells. Unlike damage to other peripheral nerve structures, regeneration is extremely limited in neuropathies.

Damage to the axon results in wallerian degeneration of all distal sections no longer in contact with the cell body. Histologically, this appears initially as dissolution of the myelin sheath with some clumping of the cytoskeletal elements and degenerating organelles within the axon. This is followed by progressive loss of axonal contents. Schwann cells survive, but peripheral nerve myelin degenerates with the axon. Complete severance of the axon and attendant wallerian degeneration is not difficult to identify histologically. More subtle lesions that result from metabolic alterations of the neuron or its ability to supply constitutive elements to the distal axon are more problematic.

Any disease process that injures the axon will cause secondary demyelination. However, examples of neuropathies exist that primarily target Schwann cells. In cross-section, myelin degeneration appears first as vacuolation, followed by separation of lamellae and finally removal of myelin debris by macrophages. This is usually associated with attempts at remyelination by surviving Schwann cells. Finding inappropriately thin myelin sheaths surrounding large axons or numerous

Table • 194-1

Nerves of the Brachial Plexus

NERVE	SPINAL CORD SEGMENT	MUSCLES INNERVATED	SPINAL REFLEX ALTERATIONS WITH INJURY	MOTOR FUNCTION	CUTANEOUS DISTRIBUTION	CLINICAL SIGNS OF DYSFUNCTION
Suprascapular	C6–C7	Supraspinatus, infraspinatus	None	Extension and lateral support of the shoulder	None	Little gait abnormality
Axillary	C6–C8	Deltoid	No deficits or incomplete withdrawal reflex	Flexion of shoulder	Dorsolateral brachium, behind scapular spine	Little gait abnormality
Musculo-cutaneous	C6–C8	Biceps brachii	Decreased or absent biceps tendon reflex; no elbow flexion with withdrawal reflex	Flexion of elbow	Medial forelimb, medial humeral condyle	Little gait abnormality; unable to raise paw to table top (flex elbow)
Radial	C6–T2	Triceps brachii, extensor carpi radialis, ulnaris lateralis common and lateral digital extensors	Decreased or absent triceps tendon reflex and extensor carpi radialis response	Extension of elbow, carpus, and digits	Dorsolateral forelimb, dorsal surface of paw	Loss of weight bearing; unable to fix limb in extension
Median and ulnar	C8–T2	Flexor carpi radialis, superficial digital and deep digital flexors, flexor carpi ulnaris	Decreased or absent flexion of carpus and digits during withdrawal reflex	Flexion of carpus and digits	Palmar surface of paw, caudal forelimb	Little gait abnormality
Nerves of the Pelvic Plexus						
Obturator	L4–L6	Pectineus, gracilis	None	Adduction of pelvic limb	None	Little gait abnormality; limb may slide laterally on slick floor
Femoral	L3–L6	Quadratus femoris	Decreased or absent patellar reflex	Extension of stifle	Saphenous branch supplies medial thigh and digit	Inability to extend stifle
Sciatic	L6–S3	Gluteus semimem-branosus semitendinosus, all muscles innervated by peroneal and tibial nerves	Decreased or absent withdrawal reflex	Flexion and extension of hip	Caudal and lateral surfaces of limb	Cannot flex or extend digits and hock or flex stifle
Peroneal	L6–S3	Peroneus longus, cranial tibial, lateral and long digital extensor	Decreased or absent cranial tibial response	Flexion of hock extension of digits	Dorsal aspect of paw, hock and distal limb	Cannot extend paw (therefore knuckles on dorsum), poor hock flexion
Tibial	L6–S3	Gastrocnemius, superficial and deep digital flexors	Decreased or absent gastrocnemius tendon reflex	Extension of hock, flexion of paw	Plantar surface of paw	Unable to fix hock in extension

Table • 194-2

Cranial Nerves

CRANIAL NERVE	ANATOMIC COURSE	FUNCTION	EVALUATION
CN I: olfactory	Sensory ending in nasal mucosa, enter cribriform plate to olfactory bulb of pyriform cortex	Smell	Not routinely evaluated
CN II: optic	Retinal ganglion cells form optic nerve that traverses optic foramen to optic chiasm and optic tracts in diencephalons	Vision and pupillary light reflexes (PLRs)	Menace reaction, PLRs, avoids objects
CN III: oculomotor	Cell bodies in mesencephalon send processes through the orbital fissure to extraocular eye muscles and iris	Motor to extraocular eye muscles, parasympathetic to eye	Eye movement, PLRs; damage causes ventrolateral strabismus and mydriasis
CN IV: trochlear	Cell bodies in mesencephalon; processes cross in rostral medullary velum and pass through orbital fissure to extraocular eye muscles	Motor to dorsal oblique muscle that rotates globe	Not routinely tested in dogs; damage causes rotational deviation of globe
CN V: trigeminal	Motor bodies in metencephalon; sensory cell bodies in trigeminal ganglion terminate on metencephalic neurons; axons divide in to mandibular, maxillary, and ophthalmic branches that pass through oval foramen, around foramen, and orbital fissure respectively	Motor to muscles of mastication including masseter, temporal, pterygoids, rostral digastricus, and myohyoid sensory to the face	Jaw tone, masticatory muscle mass, sensation to face
CN VI: abducent	Cell bodies in metencephalon; have a long intracranial course to exit the orbital fissure to eye	Motor to extraocular eye muscles including lateral recturs and retractor bulbi	Eye movement; damage causes ventromedial strabismus
CN VII: facial	Cell bodies in myelencephalon; pass through internal acoustic meatus and petrous temporal bone to stylomastoid foramen	Motor to muscles of facial expression; sensory to small area of pinna; parasympathetic innervation to lacrimal glands, mandibular and sublingual salivary glands	Ability to blink, retract lip, move ear, produce tears
CN VIII: vestibulocochlear	Sensory neurons arise from receptors in inner ear, traverse internal acoustic meatus to myelencephalon	Balance, linear acceleration, hearing	Body posture, eye movement, hearing; damage causes positional strabismus and nystagmus
CN XI: glossopharyngeal	Cell bodies in myelencephalon exit external jugular foramen	Sensory and motor to the pharynx; parasympathetic innervation to zygomatic and parotid salivary glands	Gag reflex, swallowing
CN X: vagus	Cell bodies in myelencephalon exit external jugular foramen	Sensory and motor to pharynx; parasympathetic to cardiac, pulmonary, and gastrointestinal (GI) systems	Gag reflex, swallowing, oculocardiac reflex
CN XI: accessory	Cell bodies in myelencephalon and rostral spinal cord exit external jugular foramen	Motor to larynx, trapezius, and sternobrachiocephalicus	Vocalization, muscle tone
CN XII: hypoglossal	Cell bodies in myelencephalon exit hypoglossal canal	Motor to tongue muscles	Tongue movement

"onion bulbs," concentric layers of Schwann cell membranes surrounding demyelinated or remyelinated axons, are indications of remyelination.[1]

Developmental and Congenital Disorders

Developmental and congenital disorders are peripheral neuropathies that occur in specific breeds with a predictable clinical course and characteristic pathology. A genetic basis is likely. The age of onset, specific clinical signs, and rate of progression varies from disease to disease. Because these disorders are, together, quite rare, the names and brief descriptions are listed in Table 194-3. More complete descriptions are available in neurology textbooks.

Metabolic and Toxic Disorders

Diabetes Mellitus Diabetic neuropathy represents one of the most significant late complications of diabetes mellitus in human beings. The reported incidence in human diabetic populations varies with diagnostic criteria but ranges from 5% to 100%.[1] Although similar incidence statistics have not been reported in animals, a casual relationship between diabetes mellitus and peripheral nerve disease has been identified in dogs and cats as well. In dogs the neuropathy is usually subclinical.[1] In cats clinical signs are much more common.[1] Diabetic cats may develop a plantigrade stance, pelvic limb weakness, muscle wasting, and depressed myotatic reflexes. Electrodiagnostic abnormalities in some cats consists of spontaneous activity in skeletal muscle and slowed nerve conduction with smaller evoked muscle responses suggestive of an axonal neuropathy. In others a relative paucity of abnormal muscle activity with slowed nerve conduction or conduction block suggests demyelination may be more prominent.[23,24]

Pathologic findings are equally mixed. Some have described a loss of axons in distal nerves similar to distal sensorimotor axonal neuropathy in human diabetic patients.[1] Others have focused on changes in Schwann cell structure and suggested that some cases of diabetic neuropathy result from primary Schwann cell injury and demyelination.[24-27] Recently, significant changes in perineural thickness caused by perineural cell hyperplasia, basement membrane thickening, and increased interlamellar space was described in dogs with diabetes mellitus, whereas another study found thickening of endoneurial capillary basement membrane along with an increase in endoneurial capillary density and luminal area.[28,29] These findings suggest that the pathogenesis of diabetic neuropathy, regardless of the primary neural target, includes compression of endoneurial structures by a nondistensible perineurium, alterations in the nerve and blood barrier, and changes in vascular perfusion.

A number of metabolic derangements are thought to be involved, including increased aldose reductase activity leading to the accumulation of sorbitol and fructose, increased production and decreased scavenging of reactive oxygen species leading to cellular oxidative stress and impaired mitochondrial function, together with activation of protein kinase C, which promotes vasoconstriction and nerve ischemia. Altered protein synthesis and delayed axonal transport of molecules necessary to maintain distal axonal segments, together with immunologic mechanisms, may also play a role.

Hypothyroidism The frequent association between hypothyroidism and a vast array of neurologic symptoms has lead to a casual association between the two conditions. Despite hypothyroidism being one of the most widely recognized causes of neuromuscular disease in both man and animals, it remains one of the least well characterized.

The most common neurologic problem described is paresis. This varied from monoparesis to hemiparesis to quadriparesis, with an equally variable onset and rate of progression. Cranial neuropathies are the second most common disorder with the facial, vestibulocochlear, and trigeminal nerves appearing most susceptible. Megaesophagus and laryngeal paralysis are also possible in dogs with hypothyroidism. Whether these are manifestations of a more generalized neuromuscular disorder or represent a unique form of the disease is unclear. Electrophysiologic evidence of a generalized neuropathy including spontaneous activity in all limb muscles and slowed nerve conduction velocities has been found. In addition, brain stem auditory evoked potentials are often reduced in amplitude and have prolonged latencies.[1]

In human patients and experimental models, hypothyroidism has been associated with both Schwann cell and primary axonal injury, with glycogen aggregates occurring in the cytoplasm of both cells.[1] Remaining axons often appear to have shrunken axons with inappropriately thick myelin sheaths, suggesting that axonal atrophy may be a feature of the neuropathy in some cases.

Botulism

Botulism in an acute, rapidly progressive, generalized lower motor neuron (LMN) paralysis that results from ingestion of the exotoxin produced by *Clostridium botulinum*.[1] *C. botulinum* is a saprophytic soil organism with a worldwide distribution. Under anaerobic conditions the toxin is elaborated from both vegetative cells and, to a lesser extent, spores. Although eight antigentically different types of botulinum neurotoxins have been identified; most cases of botulism in dogs are caused by type C.[1]

Clinical signs may begin within hours of toxin ingestion or may be delayed for up to 6 days. The severity of signs varies with both the amount and potency of toxin ingested, as well the susceptibility of the individual animal. Most often, clinical signs begin as an ascending paralysis in the rear limbs preceding forelimb involvement. In severe cases, complete flaccid paralysis is accompanied by weakness of facial, pharyngeal, and esophageal musculature.

Electrophysical changes characteristic of botulism include a marked reduction in the amplitude of the muscle action potential evoked by electrical stimulation of a motor nerve, whereas motor conduction velocities are normal or only mildly reduced. EMG is usually normal. The diagnosis of botulism is confirmed by identifying toxin in the food, serum, stomach contents, or feces. A mouse neutralization is available. By injecting toxin alone and in combination with specific antitoxins, both the type and potency of the botulinum toxin can be identified. Radioimmunoassay, enzyme-linked immunosorbent assay (ELISA), and passive hemagglutinations tests have been developed that will evaluate the toxin and type but do not evaluate potency. Recovery of *C. botulinum* from fecal culture is also presumptive evidence of intoxication because the organism rarely colonizes the normal canine intestine.

Pathophysically, ingested toxin is absorbed from the gastrointestinal (GI) tract and is transported to cholinergic nerve terminals. The toxin binds to presynaptic terminals, is internalized, and then blocks acetylcholine release, presumably by inhibition of calcium ion increases necessary for transmitter release. Recovery usually occurs in 2 to 3 weeks, after regrowth of terminal motor branches. Because most animals recover within weeks, treatment is largely supportive. Antibiotics should only be used to treat secondary infections because they may facilitate intestinal colonization of *C. botulinum* by altering the normal GI flora. An antitoxin is available and should either be a polyvalent antitoxin or specific for type C. Antitoxin is not effective after the toxin has entered nerve terminals; therefore it will only halt the progression of the disease and not reverse clinical signs. Recommended antitoxin dose is 10,000 to 15,000 U, intravenously or intramuscularly administered twice at 4-hour intervals. Anaphylaxis is possible, so a

Table • 194-3

Developmental/Congenital Disorders in Dogs and Cats Involving the Peripheral Nervous System

SPECIFIC NEUROPATHY, BREED AFFECTED, AND REFERENCE(S) CITED	INITIAL SIGNS	HISTOLOGY
Loss of Motor Neurons		
Progressive neuropathy in Cairn terriers[1]	Rear limb weakness	Central and peripheral chromatolysis
Focal spinal muscular atrophy in German shepherd dogs[1]	Forelimb weakness	Asymmetrical degeneration of somatic motor neurons
Hereditary progressive spinal muscle atrophy in English pointers[1]	Generalized weakness	Chronic denervation
Spinal muscular atrophy in rottweilers[1]	Regurgitation and generalized weakness	Central chromatolysis and marked cell body swelling
Neuronal abiotrophy in Swedish Lapland dogs[1]	Weakness to tetraplegia	Neuronal degeneration and central and peripheral chromatolysis
Spinal muscle atrophy in Brittany spaniels[2,3]	Weakness to tetraplegia	Neuronal chromatolysis and proximal axonal swelling
Loss of Peripheral Axons		
Giant axonal neuropathy in Alsatians[1]	Rear limb weakness	Swelling in axons
Peripheral neuropathy in aged German shepherds[1]	Rear limb weakness	Endoneural fibrosis
Hereditary polyneuropathy in Alaskan malamutes[1]	Rear limb weakness	Demyelination of axons
Idiopathic polyneuropathy in Alaskan malamutes[1]	Rear limb weakness and hyperesthesia	Axonal degeneration
Neuropathy in Birman cats[1]	Rear limb weakness and hypermetria	Loss of myelinated fibers
Polyneuropathy in rottweiler dogs[1]	Paraparesis then tetraparesis	Degeneration of peripheral nerves
Progressive axonopathy in boxer dogs[1]	Rear limb weakness	Mild axonal swellings
Laryngeal paralysis-polyneuropathy in dalmatians and rottweilers[1,4]	Respiratory distress and syncope	Peripheral neuronal degeneration
Schwann Cell Dysfunction		
Hypomyelinating neuropathy in golden retrievers[1]	Rear limb weakness	Hypomyelination and elevated Schwann cell cytoplasm
Hypertrophic neuropathy in Tibetan mastiffs[1]	Tetraparesis	Extensive demyelination
Loss of Sensory Neuron or Axon and Laryngeal Nerves		
Sensory neuropathy in long-haired dachshunds[1]	Abnormal rear limb abduction	Distal loss of sensory nerve fibers
Acryl mutilation in English pointers and shorthaired pointers[1]	Biting paws to severe self-damage	Lowered number of ganglionic cell bodies
Laryngeal paralysis in Bouvier des Flanders[1]	Inspiratory stridor and dyspnea	Axonal degeneration
Laryngeal paralysis in Siberian huskies[1]	Inspiratory stridor and dyspnea	Neuronal loss
Inborn Errors in Metabolism		
Hyperchylomicronemia in cats[1,5-8]	Horner's syndrome and tibial/radial nerve compression	–
Hyperoxaluria type 2 in domestic shorthaired cats[1,9-11]	Acute renal failure	–
α-L-fucosidosis in English springer spaniels[1,12-18]	Behavior changes and generalized ataxia	Neuronal infiltration with macrophages
Atypical GM2 gangliosidosis in cats[1]	CNS dysfunction	Wallerian degeneration of peripheral axons, lamellar inclusions of Schwann cells
Globoid cell leukodystrophy[1,19,20]	Paraparesis and/or cerebellar signs	Axonal degeneration
Neiman-Pick disease in Siamese cats[1]	Tetraparesis and hypotonia	Marked demyelination; vacuolated and granular nerve distention
Glycogen storage disease IV in Norwegian forest cats[1,21,22]	Hyperthermia, tremors, ataxia	Peripheral asymmetrical Schwann cell accumulations throughout nervous tissue

test injection of 0.1 mL interdermally 20 minutes prior to antitoxin administration is advisable.

Tick Paralysis

Tick paralysis is an acute, rapidly progressive generalized LMN paralysis caused by a salivary neurotoxin produced by ticks.[1] Adult female *Dermacentor andersoni* (the Rocky Mountain wood tick) and *D. variabilis* (the American dog tick) are most often incriminated in North America, whereas *Ixodes holocyclus* is most often incriminated in Australia. Adult females, nymphs, and larvae of *Ixodes* ticks may produce the neurotoxin. Although additional sites of neuronal dysfunction may result from intoxication, the predominate clinical signs are produced by inhibition of acetylcholine release from motor nerve terminals.

In the United States, clinical signs are restricted to dogs. Cats are also susceptible to the effects of *Ixodes* neurotoxin in Australia and have similar clinical signs. In most cases, rear limb weakness begins 5 to 7 days after tick attachment. This is rapidly followed by generalized weakness and eventually complete flaccid paralysis and areflexia within 24 to 72 hours. Cranial nerves, especially the facial nerve, may be mildly affected by the *Dermacentor* neurotoxin, but pain sensation is preserved and the animals do not appear hyperpathic. In contrast, *Ixodes* neurotoxin causes more profound signs of facial paralysis, dysphagia, and megaesophagus. Autonomic signs include mydriasis with loss of pupillary light reflex (PLR), peripheral vasoconstriction and arterial hypertension, pulmonary hypertension and edema, and either tachycardia or bradycardia. Failure to diagnose tick paralysis can result in death from respiratory paralysis within days.

Electrodiagnostic changes are similar in both forms of tick paralysis. EMG is usually normal. The evoked muscle action potential is reduced in amplitude or nonexistent, and mild slowing of both motor and sensory nerve conduction velocities occurs.[1] The diagnosis is made by exclusion of other causes of rapidly progressive generalized LMN paralysis (i.e., botulism, acute polyradiculoneuritis, myasthenia gravis [MG]) and response to tick removal. Clinical signs improve within 24 hours after *Dermacentor* tick removal, and the animals are usually normal within 48 hours. In Australia, clinical signs may progress for 24 to 48 hours after tick removal.

Administration of canine hyperimmune serum at 0.5 to 1 mL/kg intravenously has been recommended to bind circulating neurotoxin and prevent further progression. Because the only available hyperimmune serum is derived from dogs, cats should be pretreated with 30 mg/kg hydrocortisone, and epinephrine (1 mL of a 1:10,000 solution) should be available to counteract anaphylaxis. Autonomic dysfunction may be improved by administration of a combination of phenoxybenzamine hydrochloride 1 mg/kg as a 0.1% solution administered intravenously over 15 minutes every 12 to 24 hours and acepromazine 0.05 to 0.10 mg/kg intravenously every 6 to 12 hours. Oxygen therapy and respiratory support may be necessary for severely affected cases. Dogs are susceptible to repeat bouts of tick paralysis. Even though an immune response develops against *Ixodes* neurotoxin, it has only a limited duration. Vaccines are currently unavailable, so minimizing tick infestation is the best method of prevention.

Miscellaneous Toxins

The nervous system is the target of a tremendous number of toxic compounds. The list of drugs, metals, and other environmental chemicals that have been associated with peripheral neuropathy in humans is lengthy.[1] Unfortunately the clinical significance of most of these agents in veterinary medicine is uncertain. Far fewer documented toxic peripheral neuropathies exist in dogs and cats than in human beings. Potential explanations for this observation include difficulty in identifying toxin exposure without critical historical information and difficulty in identifying subtle signs of sensory deficits, weakness, or both in veterinary patients. Without overt clinical signs, a cause-and-effect relationship between chemical exposure and disease may be difficult to ascertain. Finally, clear differences exist in species susceptibility to recognized toxins. Toxin exposure should be considered for any animal with an undiagnosed peripheral nerve disease. The National Animal Poison Control Center (1-900-680-0000) can provide valuable information regarding any suspicious exposure. Some of the recognized neurotoxicants that affect the peripheral nervous system in dogs and cats are listed in Table 194-4.

Table • 194-4

Toxic Neuropathies Recognized in Dogs and Cats

COMPOUND	SUCCEPTABLE SPECIES	PATHOLOGY
Vincristine	Dogs and cats	Distal axonopathy, loss of neurotubules with neurofilamentous accumulations in axons
Pyridoxine	Dogs	Neuronal loss in sensory, dorsal root ganglia, and trigeminal ganglia
Mercury	Dogs and cats	Neuronal loss in sensory, dorsal root ganglia, and trigeminal ganglia
Thallium	Dogs and cats	Gastrointestinal (GI) irritation, skin lesions, neuronal loss in cerebrum, cerebellum, and sensory ganglia
Lead	Dogs and cats	Central nervous system (CNS) signs predominate, rare megaesophagus; Schwann cell pathology in other species
Organophosphates	Cats (experimental)	Distal axonopathy with tubovesicular profiles in axons
Acrylamide	Cats and dogs (experimental)	Distal axonopathy with neurofilament accumulation in axons
Hexacarbons	Cats (experimental)	Distal axonopathy with giant neurofilamentous axonal swellings
Lasalocid	Dogs	Pathology not described; dogs recovered in 2-50 days.

Inflammatory and Immune-Mediated Neuropathies

Acute Polyradiculoneuritis (Coonhound Paralysis)

Acute polyradiculoneuritis is a common neuropathy affecting primarily dogs and occasionally cats.[1] The syndrome was first described in 1954 as an acute, rapidly progressive paralysis that occurred in dogs 7 to 10 days after contact with a raccoon.[1] An identical syndrome has subsequently been described in dogs and cats with no known exposure to raccoons.[1] The syndrome was originally named *coonhound paralysis* to reflect the association between raccoons and paralysis. However, the recognition of additional cases suggests the broader term *acute polyradiculoneuritis* better reflects the full spectrum of the disease.

Clinical signs of generalized weakness typically begin in the pelvic limbs and progress in an ascending fashion to involve thoracic limbs. In severe cases, cranial nerves and respiratory muscles may be affected as well. Even animals severely affected often retain voluntary tail movement and voluntary control of urination and defecation. Sensory function is likewise preserved, and many animals seem unusually sensitive to mild stimulation indicating generalized hyperpathia. In rare cases, the thoracic limbs may be affected first or preferentially. Clinical signs may progressively worsen for up to 10 days after the onset of signs and then plateau. The severity of motor deficits once the plateau is reached varies from mild weakness to complete flaccid paralysis, areflexia, and respiratory paralysis. Remission may begin as early as 1 week after the onset of clinical signs or may be delayed for several months. Complete recovery may take several months and is often incomplete. Some animals do not improve within the period that supportive care is tenable. Unfortunately no reliable prognostic criteria exist by which clinicians can gauge the probable speed or degree of functional recovery of individual cases.

Despite the fact that polyradiculoneuritis is a well-recognized syndrome, definitive diagnosis is not always straightforward. History of raccoon exposure shortly before the onset of clinical signs is helpful, but as previously mentioned, not present in all cases. Abnormal spontaneous activity is usually detected with needle EMG 5 to 7 days after the onset of clinical signs. Motor nerve conduction is typically slowed at about the same time that EMG changes are present, and the muscle action potential is often dispersed, indicating both demyelination and axonal injury. Small motor potentials produced by orthodromic conduction of evoked motor action potentials to the cell body and then back to the muscle (F wave) are often delayed or absent, reflecting injury to ventral nerve roots.[1] Increased protein without an increase in white blood cells (WBCs) (albuminocytologic dissociation) is typically found in lumbar cerebrospinal fluid (CSF) but not fluid collected from the cisterna magna. This protein appears to be albumin rather than immunoglobulins and probably arises from transudation across the blood-brain barrier.[30]

Histologically, all regions of peripheral nerves have signs of injury, but lesions are usually concentrated in ventral roots. Demyelination and inflammatory cell infiltration is the predominant finding, with more variable degrees of axonal degeneration accompanying the inflammation. The pathogenesis of the diseases is uncertain. However, an antigenic stimulus in raccoon saliva is thought to stimulate an immune reaction against peripheral nerve myelin. The source of antigenic stimulation in animals without raccoon exposure is unknown but may be viral, toxic, or infections in origin. In an attempt to find potential triggers, serum from affected dogs was evaluated for antibody titers to a number of infectious agents. Affected dogs did have significantly higher titers to *Toxoplasma gondii* than controls, but a causal relationship is not clear.[31] Similarly, antibody titers to *Campylobacter jejuni* were not significantly different between affected and control animals. Therefore the inciting agent in cases without raccoon exposure remains to be identified. An immune basis for this syndrome is supported by several factors. Epidemiologic evidence indicates that not all dogs bitten by the same raccoon are affected. Once affected, repeated episodes can be precipitated in the same animal by raccoon exposure or injections of raccoon saliva. These two observations indicate that disease is associated with an idiosyncratic response in some dogs. Dogs with an acute onset of clinical signs shortly after a known raccoon exposure have antibodies against an antigen in raccoon saliva.[1] Histologically, demyelination can occur in regions without inflammatory cells suggesting antibody-mediated damage in some instances. Finally, the disease shares many clinical and histopathologic features with human Guillain-Barre syndrome, an immune-mediated radicuoneuropathy.

Therapy for this disease is largely supportive. Despite the probable immune-mediated cause, immunosuppressive therapy usually increases the incidence of secondary infections and muscle atrophy. Plasmapheresis has become standard in human beings with Guillain-Barré syndrome. Unfortunately, this is not widely available for animals.

Chronic (Relapsing) Demyelinating Neuropathy and Acquired Demyelinating Neuropathy

A generalized polyneuropathy that follows a remitting and relapsing clinical course has been identified in male and female dogs and cats of various breeds.[1] Clinical signs may be acute or chronic in onset and are often asymmetrical in distribution. In most cases, an overall progressive course of generalized weakness, areflexia, and diffuse muscle atrophy is interrupted by spontaneous periods of partial remission. Cranial nerves may be affected as well.

Electrophysiologic changes consist of variable degrees of spontaneous activity in limb muscles and marked slowing of nerve conduction velocities with more variable degrees of attenuation of the evoked response. These findings are most suggestive of a demyelinating neuropathy. Cerebrospinal analysis reveals increased protein concentrations without concomitant pleocytosis (albuminocytologic dissociation). Muscle biopsies contain changes characteristic of denervation, whereas primary demyelination with remyelination is seen in peripheral nerves. Variable degrees of mononuclear cell infiltrates are found in both peripheral nerves and nerve roots. The inflammatory response varies markedly between nerves and probably varies with stage of the disease process. Macrophages, monocytes, and lymphocytes are associated with prominent primary demyelination and remyelination. Redundant Schwann cell membranes form concentric layers around nerve fibers (onion bulbs are prominent in some cases, indicating repetitive cycles of demyelination and remyelination). Lesser degrees of axonal necrosis are also present in peripheral nerves, suggesting that axonal injury occurred as a consequence of the inflammatory reaction against peripheral nerve myelin. Immunosuppressive doses of prednisolone (2 mg/kg orally every 12 hours) resulted in reversal of clinical signs in some cases within weeks of therapy.[1,32] Prednisolone may be tapered after 6 or 8 months, but some cases require additional cycles of therapy. Rare cases are resistant to therapy and follow a progressive course.[1] The pathogenesis of the neuropathy in all cases remains unknown. Based on histologic appearance of an inflammatory response against peripheral nerve myelin and the response to immunosuppressive therapy, an immune-mediated cause is likely.

Brachial Plexus Neuritis Brachial plexus neuritis is an inflammatory neuritis involving primarily the ventral branches of spinal nerves that give rise to the brachial plexus. This rare condition has been reported in two unrelated dogs and a single cat.[1] Clinical signs consisted of an acute onset of flaccid paralysis in the thoracic limbs only, with diminished or absent

spinal reflexes. Sensory nerves may be affected as well, causing anesthesia of the distal limb. Electrophysiologic changes were confined to the affected limbs. Spontaneous activity suggested denervation in limb muscles, whereas nerve conduction studies were mildly slowed with a reduced or small nerve action potential. CSF was evaluated only in the dogs and was normal. Clinical recovery occurred in the cat and one dog between 4 days and 4 months respectively.[1] No improvement was noted in the remaining dog 45 days after the onset of clinical signs.[1] In the dog that was euthanized, axonal degeneration appeared concentrated in ventral branches of spinal nerves with wallerian degeneration and mast cell infiltration present in most peripheral nerves in the thoracic limbs. More proximal portions of axons in ventral nerve roots were spared, and the disease process appeared mildly asymmetrical between left and right brachial plexi. Retrograde sensory degeneration and chromatolysis in motor and sensory neurons was the only change noted in the CNS. The cause of the condition is unknown.

Sensory Ganglioneuritis

Sensory ganglioneuritis is a poorly defined sensory neuropathy that has been reported in young adult dogs of various breeds.[1,33] The onset of clinical signs maybe subacute, acute, or chronic, with an equally variable rate of progression. Initial signs consist of rear limb ataxia that progresses over weeks or months to generalized ataxia. Facial hypalgesia, dysphagia, and regurgitation secondary to megaesophagus have been seen in some cases. A characteristic feature of the syndrome is preservation of limb muscle mass, strength, and tone, but diminished to absent proprioception and tendon reflexes. Withdrawal reflex is usually intact and most have some preservation of nocioception. Less frequent findings in some of these dogs include self-mutilation and masticatory muscle atrophy.

Electrophysiologically, needle EMG and motor conduction velocity is either normal or only mildly abnormal. However, sensory nerve conduction is usually not recordable. CSF is typically normal or may show mild increases in protein and WBC count. Axonal atrophy of large-diameter fibers is found in biopsy material from a mixed or sensory nerve.

The pathology of this syndrome is characterized by a nonsuppurative inflammation of dorsal root ganglia and cranial sensory ganglia with loss of sensory neuronal cell bodies. A concomitant loss occurs of larger-diameter fibers corresponding to sensory axons involved in proprioception and stretch reflexes in both peripheral nerves and sensory tracts in the spinal cord. The masticatory muscle atrophy reported in a few dogs was attributed to the loss of motor fibers as they coursed through the trigeminal ganglion. The cause is unknown, but immune-mediated, toxic, and viral causes have been considered. Similar clinical and pathologic changes can be produced by number of toxins including mercury intoxication, pyridoxine (vitamin B_6) excess, and doxorubicin. No treatment exists for the condition, and recovery has not been reported.

Myasthenia Gravis

MG is a disorder characterized by inefficient neuromuscular transmission secondary to a reduction in acetylcholine receptors on the postsynaptic muscle membrane. Two forms of the disease are recognized in dogs and cats: (1) congenital and (2) acquired. In congenital MG, the deficiency in acetylcholine receptors has been attributed to reduced or imperfect synthesis, probably secondary to a genetic defect. In acquired myasthenia, antibodies, usually immunoglobulin G (IgG), are generated against acetylcholine receptors. These autoantibodies block neuromuscular transmission either by directly interfering with the actions of acetylcholine on receptors, accelerating the normal turnover rate of receptors, or activation of compliment-mediated lysis of the postsynaptic membrane.[1]

Acquired MG is the most common form of the disease. An increased risk has been identified in Akitas, various terriers, German shorthaired pointers, and Chihuahuas, whereas rottweilers, Doberman pinschers, dalmatians, and Jack Russell terriers have lower relative risks compared with mixed-breed dogs. Despite these statistics, German shepherds, and Labrador and golden retrievers are the breeds most commonly diagnosed with the disease.[1] Abyssinians and Somalis appear overrepresented in cats.[34] Two age groups appear most susceptible in dogs (2 to 3 years of age; >9 years of age). Cats can be affected at any age.

Myasthenia involves a spectrum of clinical signs that vary in both distribution and severity of muscle involvement. Three major categories have been identified in dogs: (1) focal, (2) chronic generalized, and (3) acute fulminant generalized.[1] The focal form occurs in approximately 36% of recognized cases and consists of variable degrees of facial, pharyngeal, laryngeal, and esophageal dysfunction. Subclinical evidence of appendicular muscle involvement has been demonstrated in some focal myasthenics. The two generalized forms are distinguished primarily by the rate with which clinical signs develop. Twenty-five percent of dogs with generalized neuromuscular weakness have acute, fulminate clinical signs that result in nonambulatory tetraparesis and severe dyspnea within 72 hours, whereas the remaining 39% will exhibit a more chronic onset and gradual progression of clinical signs. Studies indicate that not all dogs with generalized weakness worsen with exercise, and weakness may appear concentrated in pelvic limbs. It is important to note that about 90% of dogs with generalized myasthenia also have megaesophagus.[1] Chronic regurgitation and aspiration pneumonia is a common complication. The incidence of megaesophagus is lower in cats, most likely because of the different distributions of skeletal muscle in the feline versus the canine esophagus. However, both generalized and focal forms are present in cats.[34] Thymomas are much more common in feline myasthenics, and methimazole treatment appears to be a predisposing factor.

Currently the primary criteria for diagnosis of all forms of acquired myasthenia in both dogs and cats is demonstrating serum antibodies that react with α-bungarotoxin extracted acetylcholine receptors.[35] This test is readily available and appears to be specific for MG. Sensitivity of this test is difficult to evaluate; however, approximately 15% of suspected myasthenics are seronegative for acetylcholine receptor antibodies, yet they have immune complexes localized to endplates in their muscle biopsy samples or antibodies in the serum that bind the postsynaptic membrane of normal muscle.[1] Explanations for these apparent false-negative serum tests are speculative but may be caused by the production of high-affinity antibodies that are largely bound and not free in serum. Alternatively, antibodies may be directed to additional antigens on muscle membranes other than those recognized by α-bungarotoxin. Antibodies to the muscle protein titin and a calcium channel receptor ryanodine (RyR) have recently been identified in myasthenic dogs, and these may also play a significant role in the severity of muscle weakness seen in some cases.[36]

Additional supportive evidence for the diagnosis of myasthenia can be made by the demonstration of increased muscle strength after administration of the short-acting acetylcholinesterase agent edrophonium chloride (Tensilon) or by finding a decrementing evoked muscle response after repetitive nerve stimulation. Recommended doses of Tensilon are 0.1 to 0.2 mg/kg intravenously and should cause temporary improvement in clinical signs within minutes. Esophageal musculature does not respond to Tensilon, limiting the usefulness of this test in focal myasthenics. Similarly, a large percentage of myasthenics will have a decrementing response after repetitive motor nerve stimulation that will be blocked by Tensilon administration. Both false-positive and false-negative results

occur with both of these tests, so they should be used for supportive evidence only. Recently the canine nicotinic acetylcholine receptor alpha subunit gene has been cloned and an ELISA developed to identify dogs with circulating antibodies to this receptor.[37] Sensitivity and specificity of this test is not yet known.

Treatment is directed toward amelioration of generalized muscle weakness with longer-acting anticholinesterase agents that prolong the interaction of acetylcholine with any available receptors. Pyridostigmine bromide (Mesthinon, Roche Laboratories) may be given at 1 to 3 mg/kg every 8 to 12 hours in dogs and cats. Therapy should begin at the low end of the scale and gradually increase to desired effect. Alternatively, injectable neostigmine (Prostigmin, Roche Laboratories) has been recommended at a dose of 0.04 mg/kg every 6 hours intramuscularly to bypass the problem of oral administration of medication in regurgitating pets. Esophageal motility is minimally affected by anticholinesterase therapy. Immunosuppressive therapy is controversial. Many animals can be adequately controlled with anticholinesterases, lessening potential complications of immunosuppression in pets with aspiration pneumonia. In a recent review, 47 of 53 dogs treated only with anticholinesterase therapy developed spontaneous remissions within an average of 6.4 months.[38] However, immunosuppressive therapy increased the probability of patient survival in one study and has been used successfully to shorten the course of disease in others.[1] The best advice is to tailor drug therapy to each individual patient while providing supportive care. If corticosteroids are used, current recommendations are to begin with an anti-inflammatory dose and gradually increase to an immunosuppressive dose over 3 to 4 weeks.

Most myasthenics die from aspiration pneumonia. Clinicians and owners can reduce the risk of aspiration pneumonia by feeding in an upright position and holding the animals in an elevated position for 5 to 10 minutes after feeding. Percutaneous gastrostomy has been recommended for alimentary support but will not prevent the occurrence of aspiration pneumonia. Pneumonia may require additional therapy such as antibiotics and oxygen supplementation. Several drugs (e.g., aminoglycoside antibiotics, antiarrhythmic agents, phenothiazines, methoxyflurane, and magnesium) may reduce the efficiency of neuromuscular transmission and worsen clinical signs in myasthenics. Therefore additional drugs should be used with caution.

A simple correlation between acetylcholine receptor antibody and severity and distribution of clinical signs does not exist in dogs with MG. However, clinicians can monitor the course of the disease by evaluating serum acetylcholine receptor antibodies. Spontaneous remission occurs and the antibody titer will decrease as the animal goes into remission. Duration of the disease varies from months to years, and recurrence is possible.[35] One of the most important, yet unanswered questions about myasthenia is what initiates the immune response to acetylcholine receptors. An association has been made between the occurrence of thymomas and myasthenia in both dogs and cats.[1] This is probably related to antigenic similarity between neoplastic thymocytes and acetylcholine receptors. A less direct association has been made between myasthenia and other forms of neoplasia.[1] More recent association with immune-mediated endocrinopathies such as hypothyroidism and hypoadrenocorticism, myocarditis with third-degree atrioventicular (AV) block, myositis, and other immune-mediated diseases suggests that a generalized immune dysfunction may occur in many patients.[1]

A congenital form of MG has been reported as an autosomal recessive condition in Jack Russell terriers, smooth-haired fox terriers, and English Springer spaniels.[1] It has also been reported in Siamese and domestic shorthaired cats.[1] Clinical signs are similar to generalized acquired MG, with the exception that megaesophagus has only been infrequently reported in smooth-haired fox terriers. Remissions have not been reported. Instead, clinical signs are chronically progressive usually resulting in paralysis despite treatment with pyridostigmine bromide. Circulating autoantibodies are not present in congenital MG. Instead the diagnosis is based on response to anticholinesterase agents, decrementing response on repetitive stimulation, and demonstration of reduced concentrations of acetylcholine receptors in skeletal muscle.

Neoplastic Neuropathies

Neoplastic processes can affect the peripheral nervous system in at least three different ways. The most common clinical manifestation is the development of primary neural tumors that arise from the neoplastic transformation of cells intrinsic to the peripheral nervous system. Less commonly, secondary peripheral nerve tumors develop as peripheral nerves are invaded by neoplastic hemolymphatic cells or entrapped by nearby carcinomas or sarcomas. Finally, the peripheral nervous system can be the target of paraneoplastic processes. Both clinical and subclinical neuropathies have been attributed to the remote effects of a wide number of neoplastic process.

Primary Peripheral Nerve Tumors

The peripheral nervous system is composed of neurons and their cell processes surrounded by fibroblasts, Schwann cells, and perineural cells. Each of these cell types is capable of becoming neoplastically transformed.

Neuroblastomas, ganglioneuroblastomas, and ganglioneuromas are primary neural tumors that develop in the peripheral nervous system. These are rare tumors that arise from neural crest cells, usually in adrenal medulla or sympathetic ganglia, and are distinguished primarily by the degree of differentiation of the neoplastic cells. These tumors typically occur in young dogs in retroperitoneal or mediastinal locations.[1] Occasionally, tumors are reported in the GI tract, olfactory mucosa, and peripheral sympathetic ganglia.[1] A single case of a kitten with an intestinal ganglioneuroma has been reported.[1] Clinical signs vary with location of the tumor, with vomiting, diarrhea, and dyspnea being most common. Neurologic signs occur after metastasis to the brain or spinal cord.[1]

Primary tumors that develop from the neoplastic transformation of supporting cells in the peripheral nervous system are more common. Considerable controversy exists over the nomenclature of these tumors. They have been referred to as *schwannomas*, *neurinomas*, *neurilemmomas*, *neurofibromas*, and *neurofibrosarcomas*. Much of the controversy stems from difficulty in determining the primary cell of origin. Most canine primary nerve sheath tumors are poorly differentiated, pleomorphic neoplasms in which the cell of origin is difficult to identify.[1] Therefore the term *malignant nerve sheath tumor* is preferred by most authors. Malignant nerve sheath tumors may arise along the course of any peripheral nerve, including cranial nerves and spinal nerve roots. They typically are slow-growing tumors that extend by local invasion along the peripheral nerve and its branches. They rarely invade surrounding tissue, and metastasis is rare.[1] Neurologic signs are created by compression of peripheral axons, spinal cord, or brain stem by the expanding neoplastic mass. Although any peripheral nerve may be affected, over 80% of the reported cases have occurred in the brachial plexus or its nerve roots. The remaining 20% of cases occur in the pelvic plexus, thoracolumbar nerve roots, and cranial nerves.[1] Of the cranial nerves, the trigeminal nerve is most commonly affected.

Clinical signs typically begin in mature dogs with only rare examples of the disease in cats. No breed or sex predisposition has been identified. Clinical signs vary with area affected, but they begin as a chronic, progressive forelimb lameness. Muscle atrophy, pain in the axillary area, and a palpable mass

may be present. Horner's syndrome and loss of the ipsilateral panniculus response reflects loss of the first two thoracic nerve roots that contain preganglionic sympathetic fibers that supply the face and give rise to the lateral thoracic nerve. Ipsilateral hemiparesis that progresses to paraparesis occurs with extension of neoplastic tissue and secondary spinal cord compression. In cases that involve the cranial nerves, multiple cranial nerve deficits are accompanied by ipsilateral hemiparesis secondary to brain stem compression.

Diagnostically, EMG reveals denervation in muscles innervated by affected nerves. Survey radiographs may show enlarged intervertebral foramen, and myelography may show an intradural extramedullary mass if neoplastic cells have invaded nerve roots. Computed tomography (CT) has been helpful at identifying tumors in peripheral nerves.[1] Surgical exploration and biopsy of nerve or plexus may be necessary to confirm the diagnosis.

Surgical excision has been curative in a few cases.[1] Unfortunately, inability to completely resect all neoplastic tissue usually results in tumor recurrence. In one study, median survival interval after diagnosis in dogs with tumors of the brachial plexus or nerve roots was 12 and 5 months respectively.[1] Radiation therapy has been proposed as a potential treatment for malignant nerve sheath tumors, but results have not been reported.

Secondary Peripheral Nerve Tumors

Peripheral nerve involvement by non-neural tumors is rare. However, infiltration of cranial and spinal nerves by neoplastic lymphocytes has been reported in cats and dogs with lymphosarcoma.[1,39] More recently, two dogs with myelomonocytic neoplasia and infiltration of multiple cranial nerves and spinal nerve roots has been reported.[1] Both dogs had an acute onset of "dropped jaw" and facial hyperesthesia secondary to bilateral trigeminal neuropathy. One dog also had Horner's syndrome, whereas the other had clinical signs of optic nerve and hypoglossal nerve involvement. Antemortem diagnosis was made in one dog by identification of blast cells in lymph nodes and peripheral blood. In both cases neoplastic myeloid cells were found infiltrating cranial nerves and spinal nerve roots on postmortem examination.

Paraneoplastic Neuropathies

Although paraneoplastic diseases can affect a variety of tissues, neurologic involvement can be quite disabling. The incidence of paraneoplastic peripheral neuropathy in veterinary patients is uncertain but probably varies with tumor type. Most cases with clinically significant neuropathies have been associated with insulinomas.[1,40] A total of 6 dogs with histologically confirmed insulinomas have been described that had tetraparesis. All had generalized muscle atrophy, diminished spinal reflexes, and electrophysiologic changes compatible with diffuse axonal degeneration. Angular atrophy of both type I and type II myofibers seen in muscle biopsy suggested denervation and axonal degeneration was apparent in peripheral nerve sections. The association between clinically significant neuropathies and other tumor types in animals is more tenuous.

In an effort to identify the subclinical incidence of peripheral nerve changes in dogs with cancer, Braund and colleagues evaluated peripheral nerves from a series of 21 dogs with malignant tumors.[1] All of the dogs examined with bronchogenic carcinoma, insulinoma, malignant melanoma, osteosarcoma, thyroid adenocarcinoma, mammary adenocarcinoma, and one dog with a mast cell tumor had significantly more degenerative changes than age-matched controls. A combination of demyelination, remyelination, and axonal necrosis was present in every case. The number of dogs with each tumor type was relatively small, and no correlation between duration of the tumor and degree of neuropathic change was attempted. Additional studies are needed to better define the true incidence of peripheral nerve changes in animals with cancer.

Several hypotheses have been proposed regarding the pathogenesis of paraneoplastic diseases. The most widely investigated include elaboration of a neurotoxic substance by the neoplastic cells, secondary nutritional deficiencies caused by competition between the tumor and the host for an essential metabolite, cancer-associated immunosuppression may predispose affected individuals to opportunistic infections, and finally an immune-mediated disorder in which autoantibodies are produced against antigens shared by the tumor and the nervous system. To date, most evidence supports an immune-mediated disorder. Antibodies that recognize specific neuronal populations have been found in humans with a variety of paraneoplastic neurologic syndromes including Eaton-Lambert myasthenic syndrome, cerebellar degeneration, subacute sensory neuropathy, retinal degeneration, and others.[1] Although probably responsible for the neurologic signs, identification of these antibodies has also proven useful as a serologic marker for neoplasia. In many instances neurologic signs may antedate the diagnosis of cancer, and identification of these specific antibodies in serum provides presumptive evidence of occult neoplasia.

Treatment for paraneoplastic neuropathies has been unrewarding in animals. A single case with insulinoma-associated neuropathy improved with corticosteroid therapy, whereas another case regained motor function after removal of mammary carcinomas.[1,40]

Traumatic Neuropathies

Research into peripheral nerve trauma suggests that at least five different classifications exist for the types of injury that can occur.[1] Class 1 is referred to as *neurapraxia* and describes the response to mild or moderated focal compression. Nerve conduction is reversibly blocked. Histologically, either no lesions or mild segmental demyelination occurs. Complete recovery may occur within hours; however, with more severe compression, it may be delayed for up to 6 weeks. Class 2 injuries or axonotmesis usually occur with crush or percussion injuries. Axons are interrupted, but the supporting connective tissue remains intact. Wallerian degeneration usually occurs distal to the site of injury, but regeneration is usually effective because regenerating axons can be guided back to the appropriate targets. Class 3, 4, and 5 injuries refer to varying degrees of neurotmesis. Class 3 injuries result in disruption of axons and endoneurium, but fascicular orientation is preserved by an intact perineurium. Class 4 injuries also disrupt the perineurium, whereas the entire peripheral nerve is severed in class 5 injuries. With increasing degrees of damage to supporting structures, the ability of regenerating axons to successfully bridge the gap and reinnervate original structures is lessened.

All five classes of injury exist in animals, and more than one class can occur simultaneously. Unless the peripheral nerve is completely severed, most surgeons wait several weeks before attempting repair to assess how much functional return will occur. Surgical repair of transected nerves has been attempted either using direct end-to-end anastomosis or using a nerve graft to bridge the defect. Autologous sensory nerves may be harvested to be used as a graft, or a non-neural conduit can be used. Experimentally, application of nerve growth factors to synthetic conduits has aided peripheral nerve regeneration after complete resection and may be clinically useful in the future.[1] Axonal regrowth occurs at a rate of approximately 1 to 2 mm/day. Therefore the prognosis for functional return depends not only on class of injury or precision of surgical repair but also on the distance the axon must travel to reach its end organ.

Individual peripheral nerves can be injured in a number of ways. Injection injuries, trauma from bone fracture and repair,

lacerations from dog fights, and automobile accidents are some of the more common sources in dogs and cats. Motor and sensory deficits associated with individual peripheral and cranial nerves are outlined in Tables 194-1 and 194-2. Diagnosis is usually based on clinical signs of motor and sensory deficits. EMG will reveal denervation, and peripheral nerve conduction should fail 5 to 7 days after the injury. Recently, ultrasonography has shown promise at imaging transected nerve stumps.[1]

Brachial Plexus Avulsion

The brachial plexus is typically formed from the sixth cervical through the second thoracic spinal nerve roots. Because nerve roots lack a perineurium, traction of the forelimb or severe abduction of the scapula frequently results in avulsion of these nerve roots, usually within the dura. Depending on the direction and extent of forelimb traction, all or only part of the brachial plexus may be involved. The caudal portion of the plexus is more commonly involved in partial injuries.[1]

Clinical signs are characterized by an acute, nonprogressive monoparesis usually precipitated by an automobile accident or a fall. The resulting motor and sensory dysfunction in the limb varies with the extent of the avulsion. Avulsion of C8, T1, and T2 nerve roots injures the radial, median, and ulnar nerves. The limb may be carried in a flexed position because the musculocutaneous, axillary, and suprascapular nerves are intact, but weight bearing is impossible without the ability to extend the elbow and carpus. Injury to C8, T1, and T2 spinal nerve roots also results in Horner's syndrome and loss of the ipsilateral cutaneous trunci (panniculus) reflex due to damage to the origins of the presynaptic sympathetic innervation to the face and lateral thoracic nerve respectively. More rostral nerve root injuries also involve the musculocutaneous nerve and prevent flexion of the elbow. Limb movement is generated by advancement of the shoulder. Injury of only proximal portions of the brachial plexus is rare. Useful limb function depends on the radial nerve; in a review of 30 cases, the radial nerve was involved in 92% of dogs with brachial plexus avulsion.[1] Like motor function, sensory deficits depend on the number and distribution of nerve roots avulsed. In some instances, dorsal roots may be spared, resulting in some preservation of sensation even though motor function was lost with avulsion of the ventral roots. Despite the potential variability in sensory deficits, most cases are analgesic distal to the elbow.[1]

Diagnosis of brachial plexus avulsion depends on history, clinical signs, and electrophysiologic evidence of denervation in limb muscles. Motor nerve conduction is usually abolished in affected nerves. A sensory nerve evoked potential may be present even in the absence of conscious perception of pain, if the dorsal nerve root is avulsed proximal to the dorsal root ganglion. Somatosensory evoked potentials produced by stimulation of a peripheral nerve and measuring the response of afferent neurons in the spinal cord and brain will be abolished if all nerve roots are avulsed. Unfortunately, somatosensory evoked potentials are less useful with partial lesions.[1]

Prognosis for functional return is hopeless if the radial nerve has been avulsed. Several salvage procedures have been described for distal radial nerve deficits, but triceps innervation is required for any useful limb movement. Neurapraxia is certainly a feature of any traumatic peripheral nerve injury. Therefore a hopeless prognosis should not be given before a minimum of 4 to 6 weeks after the injury. Unfortunately less than 12% of reported cases regained radial nerve function.[1] Limb amputation should be considered if self-mutilation or other continuous trauma occurs in desensitized areas.

Vascular Neuropathies

Acute obstruction of blood vessels supplying peripheral nerves is rare except in cats with aortic thromboembolism. Reports in dogs usually involve heartworm disease. Although thromboembolism of any major artery could produce clinical signs, the most common site is the terminal aorta obstructing the internal and external iliac arteries and the median sacral artery. Both physical restriction of blood flow by the embolus and the production of vasoactive substances, including serotonin and thromboxane that limit collateral blood flow, combine to produce ischemia of the sciatic nerve and adjacent muscles. Axonal necrosis occurs in the center of nerve fascicles in the distal sciatic nerve and its branches, whereas paranodal demyelination is evident in peripheral areas.[1] Muscle damage consists of focal necrosis, with inflammatory cell infiltrates and myophagia.

Clinical signs typically consist of an acute onset of pelvic limb paralysis. The femoral pulse is usually weak or absent, the rear limbs are cold, and nail beds are ischemic and fail to bleed if cut. Rear limb musculature often feels stiff because of ischemic muscle contracture, and the cats often are painful on muscle palpation. Evidence of cardiac disease is usually present either in physical examination findings, thoracic radiographs, or echocardiography. Most cats have hypertrophic cardiomyopathy; however, other forms of cardiac disease are possible. Therapeutically, in addition to specific treatment for the cardiac disease, most cats benefit from warming the limbs and administering acepromazine 0.2 to 0.4 mg/kg subcutaneously every 8 hours to encourage vasodilatation and collateral blood flow. Heparin sodium (100 to 200 IU/kg intravenously initially, followed by 50 to 100 IU/kg every 6 to 8 hours) is recommended to prevent further thrombus formation, and analgesics such as butorphanol (02. to 0.4 mg/kg every 6 to 12 hours) should be used to control pain. Specific therapy to remove the clot has been attempted both surgically and medically using thrombolytic agents.

Idiopathic Neuropathies

Distal Denervating Disease Distal denervating disease is considered the most common neuropathy in dogs in the United Kingdom.[1] Dogs of all ages, breeds, and both sexes are affected. The onset of clinical signs is variable, ranging from days to a month or more. Quadriparesis to quadriplegia is accompanied by neck weakness, loss of bark, diminished spinal reflexes, and muscle atrophy (especially prominent in proximal limb muscles). Voluntary control of tail movement, urination, and defecation is maintained, and pain sensation is preserved. EMG reveals diffuse spontaneous activity in all muscles. Motor nerve conduction velocity is modestly reduced, but the evoked muscle action potential is usually small and dispersed. These electrophysiologic changes are most compatible with primary axonal loss with little demyelination. Sensory nerve conduction is normal. Muscle and nerve biopsy confirms a distal axonopathy with denervation atrophy of muscle. Most cases spontaneously resolve without treatment, with complete recovery occurring 4 to 6 weeks after clinical signs plateau.[1] Pathologic changes are restricted to the distal motor axon. No changes have been reported in the CNS, nerve roots, or main portions of peripheral nerves. Intramuscular branches are reported to show extensive collateral axonal sprouting, with early cases also exhibiting modest degrees of terminal axonal degeneration. The cause is unknown, but an unidentified toxin is considered likely.

Distal Symmetrical Polyneuropathy

Numerous adult, large breeds of dogs have been described with a distal sensorimotor polyneuropathy, which have been collectively referred to as *distal symmetrical polyneuropathy*.[1] A remarkable similarity exists to the developmental and congenital axonopathy "polyneuropathy in rottweiler dogs." Clinical signs are insidious in onset and gradually progressive over 1 to 2 months. Pelvic limb paresis is the initial presenting sign, but tetraparesis with atrophy of distal limb muscles and muscles

of mastication eventually develops. Diffuse spontaneous activity is prominent with needle EMG. Motor nerve conduction velocities are usually normal or slightly slowed, but the amplitude and duration of the evoked muscle action potential is small and prolonged, suggesting axonal injury. Muscle and nerve biopsy confirms a distal axonopathy with denervation atrophy of skeletal muscles. No other abnormalities have been reported in peripheral blood or CSF. Histologically, lesions are confined to the distal regions of motor nerves. Degeneration of large-diameter motor axons is prominent in distal limb nerves and the recurrent laryngeal nerve. Variable degrees of demyelination are present as well but appear secondary to axonal loss. Sensory and autonomic nerves may be affected as well but to a lesser degree. No lesions are found in the CNS. The cause is obscure, but metabolic, toxic, and paraneoplastic neuropathies may appear similarly. Prognosis is poor because the disease is chronic and progressive in nature and has not previously responded to treatment. However, preliminary results from a multicenter trial involving the use of Prosaptide™ TX14(A), a neurotropic peptide, in large breed dogs with idiopathic distal symmetrical peripheral neuropathy showed promising results.[41] Of the seven dogs that completed the trial, three showed improvement in neurologic function.

Dancing Doberman Disease

Dancing Doberman disease is an unusual neuromuscular disorder that presently appears restricted to adult Doberman pinschers of both sexes.[1] Clinical signs begin between 6 months and 7 years of age and are gradually progressive over several years. Affected dogs have a characteristic habit of holding one or both pelvic limbs flexed while standing. The condition may begin in one limb and then spread to the alternate limb within 3 to 6 months. When both pelvic limbs are affected, the condition may appear as shifting rear limb lameness with an increased tendency for the dogs to sit rather than stand. Conscious proprioceptive deficits have been reported in two dogs 5 and 6 years respectively after the disease was diagnosed. Exaggerated pelvic limb reflexes and atrophy of the gastrocnemius muscle are also common.

Electrophysiologic abnormalities suggest a mixture of mild myopathic and neuropathic changes. EMG shows spontaneous activity in affected muscles, but motor and sensory nerve conduction velocities are usually normal. Pathologic changes are confusing. Some dogs have multifocal pelvic limb muscular atrophy and hypertrophy, fibertype grouping, focal necrosis, and endomysial and perimysial fibrosis suggestive of a form of myotonic myopathy.[1] Other dogs have peripheral nerve changes suggestive of a primary axonopathy. Evidence of axonal degeneration in sensory and autonomic fibers has been reported, suggesting that dysesthesias caused by pressure on the feet may be responsible for the unusual clinical signs.[42]

No treatment has proven beneficial to date. Although the syndrome is slowly progressive, affected animals remain functional pets for many years. Without definitive diagnostic criteria, the syndrome can only be diagnosed by ruling out other diseases such as lumbosacral stenosis, intervertebral disk disease, or nerve root tumors that might initially appear with rear limb paraesthesias without obvious motor impairment.

Dysautonomia

Dysautonomia is a general term for dysfunction of the autonomic nervous system. A syndrome characterized by diffuse autonomic dysfunction was first reported in cats in 1982 by Key and Gaskell.[1] Over the next 2 years this previously undiagnosed disease was reported in epidemic proportions throughout the United Kingdom and later in Europe and the United States. The incidence of the disease has since markedly declined in cats. The first case of dysautonomia was reported in dogs in 1983, again in the United Kingdom.[1] Only sporadic reports of canine cases appeared until recently when 11 dogs were identified in Missouri over a 7-year period.[1] Although additional dogs have subsequently been described, all cases appear confined to the Midwest.[43,44]

Animals between 6 weeks and 11 years have developed dysautonomia, but both dogs and cats less than 3 years of age appear to be more susceptible. Both males and females are equally affected. The onset is acute in most cases, with clinical signs developing over 2 to 3 days. Rarely the onset is more insidious, lasting a week or more. Initial clinical signs are usually nonspecific and consist of lethargy, anorexia, and depression. GI signs including regurgitation and vomiting, constipation or diarrhea follow. Dysuria with a distended urinary bladder, myasis with depressed PLRs, dry mucus membranes, prolapsed third eyelids, dysphagia, and weight loss are also commonly seen. More inconsistent features include loss of anal tone and mild postural reaction deficits. Many pets also have bradycardia with heart rates less than 120 beats per minute that do not change with stress or exercise.

No consistent abnormalities have been detected in peripheral blood or CSF. Radiographically most animals have evidence of decreased peristaltic activity throughout the GI tract including megaesophagus, delayed gastric emptying, and generalized ileus. Electrodiagnostic testing is usually normal, with the exception of occasional spontaneous activity in limb muscles. Pharmacologic testing has been used to confirm parasympathetic and sympathetic nervous system dysfunction. Specifically, denervation of the iris muscle results in supersensitivity to cholinergic drugs. Instillation of 0.05% pilocarpine ophthalmic solution should cause rapid constriction of the pupils. It usually takes at least 30 minutes for miosis to occur in normal dogs, and no effect should be seen in cases where parasympathetic signs are due to atropine or a similar toxin.[44]

Histologically, sympathetic and parasympathetic ganglia are affected. Because the degree of involvement of any one ganglia can be quite variable, multiple samples are recommended. Depletion of neuronal cell bodies is the more prominent change, with many remaining neurons containing atypical homogenous cytoplasm, dissolution of Nissl substance, and an eccentric pyknotic nucleus. Axonal degeneration is present in autonomic nerves. Peripheral nerves are relatively spared, although occasionally smaller neurons in dorsal root ganglia and cranial nerve ganglia may show chromatoylitic changes. A percentage of neurons in cranial nerve nuclei, ventral horn cells, and cells in the intermediolateral gray matter of the spinal cord may also show characteristic changes. Unusual ultrastructural changes consist of derangement of rough endoplasmic reticulum with existing cisternae denuded of ribosomes and distended with electron-dense flocculent material.[1] No normal Golgi bodies are found, but instead stacks of smooth membranous profiles are seen. Membranous dense bodies and autophagic vacuoles are common in some neurons.

Treatment is largely supportive. Pilocarpine (1%) eye drops may improve mydriasis and stimulate lacrimation and salivation. Bethanechol (2.5 to 7.5 mg every 8 hours) should facilitate evacuation of the bladder at least temporarily. Metoclopramide will enhance the actions of any available acetylcholine on muscarinic receptors in the GI tract and enhance gastric emptying. Unfortunately the prognosis is poor. Less than 25% of affected cats survive, and recovery often takes over a year. The cause of the disease remains a mystery, despite numerous efforts identify an infectious or toxic agent. The clustering of cases in the United Kingdom and more recently Missouri suggests an environmental agent; however, none have been identified. Recently, autoantibodies against ganglionic acetylcholine receptors were demonstrated in dogs with dysautonomia.[45] It is not yet clear whether this represents a cause or an effect of the disease process.

Idiopathic Trigeminal Neuritis

The trigeminal nerve is most commonly injured by inflammatory or neoplastic intracranial diseases. Rarely, the trigeminal nerve is directly infiltrated by neoplastic cells (as previously described with peripheral nerve neoplasia). The trigeminal nerves are also the target of an idiopathic, inflammatory condition referred to as *trigeminal neuritis*. Clinical signs are characterized by an acute onset of bilateral trigeminal motor paralysis causing inability to close the mouth ("jaw drop").[1,46] Facial sensation is usually preserved. Occasionally, Horner's syndrome may accompany trigeminal neuritis, presumably because the postganglionic sympathetic axons course with the ophthalmic branch of the trigeminal nerve.[46,47]

Biopsy of the muscles of mastication reveals denervation atrophy. CSF may be normal or may have mild increases in protein concentration. Rarely, a lymphocytic pleocytosis is described.[46] Histology has been limited, but nonsuppurative neuritis in all portions of the trigeminal nerve and ganglion has been described.[1,47] The brain stem is spared. Spontaneous recovery usually occurs within 2 to 3 weeks but may take months to completely resolve. Steroid therapy does not appear to alter the course of the disease.[46] Maintenance of hydration and alimentation is critical during this time. Percutaneous gastrostomy has been helpful in this regard.

Idiopathic Facial Neuritis

Because of its anatomic proximity to the inner and middle ear, the facial nerve is commonly injured in otitis media and interna. The facial nerve also has a superficial location after emerging from the stylomastoid foramen and is therefore easily susceptible to traumatic injury. The facial nerve is often affected in generalized peripheral nerve diseases including polyradiculoneuritis, tick paralysis, and botulism. Less frequently, facial nerve paralysis results from no identifiable cause and has been referred to as *idiopathic facial neuritis*.[1]

Clinical signs of facial paralysis are characterized by inability to move the lip, ear, and eyelids. Ptyalism and inability to blink are the most common admitting complaints. The facial nerve also provides parasympathetic innervation to lacrimal glands, and proximal injury may result in keratoconjunctivitis sicca. Xerostomia, focal hypalgesia to the pinna, and partial loss of taste may also occur with facial nerve paralysis, but these are difficult to appreciate clinically. Both dogs and cats have been reported with idiopathic facial neuritis.[1] The syndrome tends to occur in mature animals, and Cocker Spaniels have been identified in two studies as being predisposed.[1] Clinical signs typically appear acutely and in the absence of any other systemic illness. One or both facial nerves may be initially affected. In cases with unilateral facial neuritis, the other side may become affected later. Electrophysiologically, spontaneous activity suggestive of denervation appears in superficial facial muscles. Stimulation of the facial nerve failed to evoke an action potential in one report.[1] Fascicular biopsy of the ventral buccal branch of the facial nerve in two dogs showed axonal degeneration.[1]

The cause of this condition is unknown. A casual link has been made, with hypothyroidism. Statistically the relationship with hypothyroidism has been difficult to prove.[1] However, numerous cases have concurrent hypothyroidism and clinically improve with thyroid supplementation.[1] Other theories that are also unproved include herpes viral neuritis or swelling of the facial nerve causing compression in the bony facial canal traversing the petrous temporal bone.

The prognosis for idiopathic facial neuritis is poor. Steroid therapy has been recommended, but its efficacy is uncertain. Cases may improve within weeks or months. However, the facial nerve remains permanently paralyzed in a significant number of cases. Exposure keratitis, especially if compounded by decreased lacrimation, is the most significant complication.

Idiopathic Peripheral Vestibular Disease

An idiopathic vestibular dysfunction has been identified in old dogs and cats of all ages.[1] Clinical signs are acute in onset and consist of head tilt, nystagmus, falling, rolling, and ataxia. Postural reactions remain intact, and spinal reflexes are normal. Facial nerve deficits and Horner's syndrome are common features of otitis media and interna are conspicuously absent in idiopathic vestibular disease. In cats an unusually high frequency of cases occurs in July and August.[1] The reason for this seasonal incidence is unknown. The diagnosis is based on clinical signs and failure to identify other causes of vestibular dysfunction including trauma, otitis media and interna, or toxins. Aminoglycoside antibiotics, especially streptomycin in cats, can damage vestibular and auditory receptors and result in vestibular dysfunction. The prognosis for idiopathic vestibular dysfunction is excellent. Most cases spontaneously improve within weeks. Some cases have a residual head tilt. An association between idiopathic peripheral vestibular disease and hypothyroidism has been noted.[1] Other inner and middle ear diseases are covered more thoroughly in Chapter 209.

CHAPTER 195

Disorders of the Skeletal Muscles—Canine*

Stéphane Blot

Striated muscle, which accounts for approximately 50% of the body mass, is an intricate machine designed to convert chemical energy into mechanical energy. The component processes include excitation-contraction coupling, the contractile mechanism itself, various structural components, and the energy system that supports the activity and integrity of the other systems. Proper function of striated muscle, therefore, depends on the integrity of all organs of the body. This chapter focuses on primary defects involved in skeletal muscle diseases (primary myopathies), but numerous secondary myopathies are encountered as a result of defects in other organs. Disorders of the neuromuscular junction are discussed elsewhere.

ANATOMY AND PHYSIOLOGY

Skeletal muscles are composed of fusiform, multinucleated cells, called *myofibers*, as well as connective tissue, vessels, and nerves.[1-3] During myogenesis, myofibers are produced by the fusion of *myogenic cells*, the myoblasts that stem from the same mesodermal embryonic tissue that provides bone, cartilage, and connective tissue. However, all muscles do not derive from the same origin, which explains the immunologic differences between groups of muscles and therefore may account for specific topographic muscle lesions. Some multinucleated myogenic cells, called *satellite cells*, do not merge, but rather lie beneath the basement membrane of mature muscle fibers. When a muscle is damaged and necrosis occurs, the satellite cells develop and merge to form new muscle fibers.

On transverse section of normal muscle, myofibers are all polygonal, roughly of equal size with peripheral nuclei; however, different types of myofibers are identified based on physiologic and histochemical criteria (Table 195-1). *Slow contraction fibers (type 1)* withstand fatigue and use oxidative metabolism, whereas *fast contraction fibers* extract energy from the glycolytic pathway. Most skeletal muscles are made up of a mixture of these functional types, the proportion of each type being stable for a given muscle in each species.[4] In specific muscles, one type appears largely predominant. The functional type of each myofiber is actually determined by the neuronal cell body innervating the cell.[5,6] All myofibers innervated by the same motor neuron define a motor unit, the size of which varies; muscles with fine movement are composed of small motor units (e.g., extraocular muscles), and antigravity muscles are composed of large units.

Perimysial connective tissue defines fascicles that enclose several motor units. All motor units are closely intermingled, producing a particular mosaic-like or checkerboard pattern. Each muscle fiber is surrounded by a thin layer of connective tissue (the *endomysium*), and the entire muscle is encased in epimysial connective tissue. Each myofiber is composed of hundreds of myofibrils made of thin and thick contractile filaments separated by an intermyofibrillar network containing aqueous sarcoplasm, mitochondria, glycogen, and the sarcoplasmic reticulum (calcium reservoir) with the associated transverse tubular system. The protein myosin is the main component of the thick filaments, and actin, troponin, and tropomyosin constitute the thin contractile filaments.

Ultrastructurally, the regular spatial distribution of the contractile filaments presents a characteristic striated appearance that is the result of the repetition of a transverse pattern. This repetitive pattern, called the *sarcomere*, contains an electron-dense area (the *A band*), which is produced by the overlapping of thick and thin filaments, and an electron-lucent area (the *I band*), which contains thin filaments alone. In the middle of the A band is an area in which the absence of thin filament produces an additional electron-lucent band, the *H zone*. The *transverse M line* in the H zone is composed of cross-linked thick filaments, and the *transverse Z line* in the I band is made up of protein-anchoring adjacent thin filament. The sarcomere thus is the structural unit defined by two successive Z lines.

Molecular studies yield constant enlightenment about the components of the cytoskeletal, sarcolemmal, or contractile apparatus, leading to the discovery of molecular defects involved in degenerative myopathies. The muscle fiber converts a biochemical signal (i.e., the release of acetylcholine from the nerve terminal after arrival of a nerve action potential at the neuromuscular junction) into a mechanical force produced by the coordinated contraction of several thousand sarcomeric units. To achieve this complex process, known as *excitation-contraction coupling*, several elementary phases are required, comprising depolarization of the sarcolemma, transverse tubules, and sarcoplasmic reticulum. Depolarization leads to the release of calcium into the sarcoplasm. At rest, tropomyosin (a regulating protein) blocks the active site of actin and prevents the myosin-actin interaction. Binding of the calcium to troponin moves tropomyosin, which then promotes formation of several cross-bridges between actin and myosin molecules. With the availability of energy (adenosine triphosphatase [ATPase] from myosin catalyzes hydrolysis of adenosine triphosphate [ATP], which comes from the phosphocreatine stock—the myofiber's battery—or from oxidative phosphorylation metabolism or glycogenolysis), the thin filaments move on the thick myofilaments, leading to the shortening of the myofibrils. Dissociation of the cross-bridges, which produces relaxation time, also requires energy.

GENERAL CLINICAL FEATURES

The main sign of a disease affecting the appendicular musculature is weakness. Weakness induced by skeletal muscle disorders usually is persistent but may become more pronounced after exercise (increased fatigability). In rare cases weakness disappears with exercise, and the signs are exacerbated by rest (myotonia). Weakness may be discrete, manifesting as a stiff gait; tremors; an abnormal posture, such as neck ventroflexion

*At the author's request, this chapter (with feline referencing deleted) has been reprinted from the last edition.

Table 195-1

Characteristics of Mammalian Myofiber Types

PROPERTIES	TYPE 1	TYPE 2m*	TYPE 2a	TYPE 2b†	TYPE 2c‡
Histochemistry Staining Intensity					
ATPases pH 10,4/9,4	Low	Low	High	High	High
ATPases pH 4,63/4,53	High	Moderate	Low	Moderate	Moderate
ATPases pH 4,35 Oxidative	High	Low	Low	Low	Moderate
NADH-TR, SDH	High		Moderate	Low	Moderate
Menadione	Low		Moderate	High	
Phosphorylase	Low		Moderate	High	
Periodic acid—Schiff	Low		High	Moderate	High
Physiologic/Morphologic Features					
Contraction speed	Slow		Intermediate/fast	Fast	—
Fatigue resistance	High		Intermediate	Low	—
Size	Small	—	Intermediate	Large	—
Myoglobin	High	—	High	Low	—
Energy metabolism	Oxidative	—	Oxidative/glycolytic	Glycolytic	—
Mitochondria	Many	—	Many	Few	—
Glycogen content	Low	—	High	Intermediate	—
Lipid content	High	—	Intermediate	Low	—

From Guy PS, Snow DH: Skeletal muscle fibre composition in the dog and its relationship to athletic ability. *Res Vet Sci* 31:244, 1981.
*Masticatory myofiber type.
†Type 2B myofiber does not exist in the canine.82
‡Type 2C myofiber is a primitive myofiber that may be a precursor of types 2A and 2B.

(more pronounced in cats owing to the absence of a nuchal ligament); palmigrade or plantigrade stance; splaying of digits; bunny hopping gait; or difficulty negotiating simple motions, such as jumping over steps or climbing into the car. Weakness may also be extreme, mimicking a neurogenic disease. Muscle atrophy is common; however, hypertrophy can occur in some instances. In most cases hypotony with normal tendon reflexes is encountered, although hypertonic muscles are also observed (polymyositis, myotonia). Absent tendon reflexes are sometimes observed in congenital myopathies or later in the course of degenerative myopathies. Muscular fibrosis and contracture, causing reduced range of articular movement, is a frequent feature in severe inflammatory or degenerative myopathies. Muscle pain *(myalgia)* occasionally may be identified in inflammatory conditions. The normal muscular response to percussion is a barely visible transient contraction of the myofibers. It disappears prematurely in primary muscle diseases, in contrast to the conservation of tendon reflexes. However, mechanical excitability is exaggerated in neurogenic muscular atrophies. In the myotonic syndrome, the myotonic dimple persists for several seconds. Signs affect the appendicular musculature and several other striated muscles, such as the masticatory, extraocular, cardiac, digestive, and respiratory musculature. Therefore disorders of striated muscle should be suspected as one cause of the condition in dogs with regurgitation, vomiting, dysphagia, dysphonia, or ophthalmoplegia.

Because weakness is a nonspecific sign frequently encountered in other nonmuscular diseases, ancillary tools must be used to confirm the presence of a myopathy.

GENERAL DIAGNOSTIC FEATURES

Several serum enzymes, such as creatine kinase (CK), lactate dehydrogenase, aldolase, and aspartate aminotransferase, may be elevated in muscle diseases.[3] In particular, owing to the short half-life of creatine kinase (about 6 hours), the level of serum CK is the best indication of a recent muscle lesion.[7] However, tremendous variability occurs, based on age (the younger the animal, the higher the value), breed (the smaller the dog, the higher the value), motor activity (exercise produces a higher value), recent intramuscular injections, and sampling methods. Although some myopathies are associated with dramatic persistent elevations (i.e., muscular dystrophies, polymyositis), numerous myopathies cause little, transient, or no elevation at all. Therefore a normal CK level should not exclude a muscle disease from the differential diagnosis.

Electrophysiologic tests (electromyography, nerve conduction studies, and repetitive stimulation) are more valuable in the evaluation of peripheral neuropathies than in myopathies.[8] If contractile activity is recorded, myopathies are classically associated with smaller, shorter, and sometimes polyphasic motor unit potentials. Spontaneous abnormal activity (fibrillation potentials, positive waves, high-frequency discharges, and complex repetitive discharges) may be recorded in numerous myopathies, but no activities are specific for certain myopathies except the myotonic burst that is pathognomonic for myotonia. If a muscle biopsy is planned, that muscle site should not be electrophysiologically tested, to avoid iatrogenic changes.

When muscle disease is suspected, a muscle biopsy is indicated to confirm the diagnosis. The sampling is a relatively innocuous procedure, but certain guidelines must be followed if maximum information is to be gained.[9] Blood for serum muscle enzyme analysis should be collected before the biopsy is performed. Selection of the muscle for biopsy is guided by electromyography or, failing that, atrophic or hypertrophic muscles are chosen. Although a single muscle biopsy is usually satisfactory, the chances of identifying characteristic lesions are considerably enhanced if several muscles are sampled (generally at least one muscle biopsy each from the pelvic and

thoracic limbs). The biopsy specimen is taken at the center of the muscle belly by parallel incisions along the longitudinal axis of the myofibers. A section 4 to 5 mm wide and 2 cm long is satisfactory for routine light microscopic evaluation. Tools for reducing the shortening of the muscle sample may be used (muscle biopsy clamp or a sterile applicator stick).

The muscle sample should be divided into two fragments; one is fixed in 10% buffered formalin, and the other is submitted prior to fixation, in a refrigerated gauze sponge, within 24 hours, so that histochemical stains can be applied. Such stains are the only satisfactory method for analyzing degenerative myopathies. When muscle atrophy is of nervous origin, it is characterized by variability in fiber diameter, the presence of angular, atrophied fibers, and alteration of the normal checkerboard pattern.

Myopathies can be categorized as inflammatory or degenerative (Box 195-1). The inflammatory conditions are either infectious or immune mediated, whereas degenerative myopathies are acquired or inherited. This discussion focuses on the main myopathies in dogs.

Box • 195-1

Classification of Myopathies

Inflammatory
Infectious
Bacterial
Leptospirosis
Toxoplasmosis/neosporosis
Parasitic

Immune mediated
Masticatory muscle myositis
Polymyositis
Dermatomyositis

Degenerative
Acquired
Endocrine
- Hyperadrenocorticism
- Hypothyroidism
- Hypokalemic polymyopathy (cats)

Fibrotic/ossifying myopathies
Ischemic
Nutritional
Neoplastic
Toxic

Inherited
Muscular dystrophy
- X-linked muscular dystrophy (dystrophin deficient)
- Other muscular dystrophies (dystrophin positive)

Myotonia
Metabolic
- Glycogen storage disease
- Mitochondrial myopathy
- Lipidic myopathy
- Malignant hyperthermia

Centronuclear myopathy (Labrador retriever)

INFLAMMATORY MYOPATHIES

A classic distinction is made between infectious myositis conditions and those that are immune mediated. In cases of infectious myositis, bacteria (*Leptospira* or *Clostridium* spp.) or parasites (*Toxoplasma* or *Neospora* spp.) are directly responsible. Some agents are capable of triggering noninfectious myositis by modifying muscle immunogenicity (leishmaniasis or ehrlichiosis).

Infectious Bacterial Myositis

Bacterial myositis is a rare disorder in carnivores; it occurs more frequently in food animals.[10] A distinction can be made between polymyositis and focal myositis. The manifestation of the latter disorder is lameness accompanied by pain and muscle enlargement. This type of myopathy occurs with bacterial spread from a distant site of infection via the blood or after bacterial inoculation through external trauma, such as a bite, a sting, or contamination of surgical wounds.[11-14] Staphylococci and streptococci are often involved in canine traumatic infectious myositis. Clostridial myositis (caused by *Clostridium perfringens*) is rarely found in domestic carnivores. *Leptospira icterohaemorrhagiae* is responsible for serious myositis. However, the severe nature of the general signs masks the muscle damage. The treatment consists of lancing the wounds and draining any abscesses. In the case of secondary bacterial myositis, the first step consists of identifying the primary site. The antibiotic is selected by the results of sensitivity testing. Clindamycin (5 mg/lb given orally twice a day) is the antibiotic of choice for anaerobic bacterial myositis.[12,15,16]

Parasitic Myositis

Toxoplasmosis (Toxoplasma gondii)

Toxoplasmosis develops clinically only in young animals (less than 1 year old) and often arises when another disease occurs. The muscular signs are characterized by abnormal gait, muscle pain, and muscle atrophy. In some cases myositis with subsequent fibrosis evolves quickly.[17]

Neosporosis (Neospora caninum)

Neurologic damage dominates the clinical presentation of neosporosis, and pups that are affected rapidly show hyperextension of the hindlimbs. Transplacental transmission mimics a hereditary disease. Clindamycin (5 mg/lb twice daily) or trimethoprim combined with sulfadiazine (7 mg/lb twice per day) is the drug of choice; however, pelvic limb extensor rigidity does not respond to therapy.[18-20]

Other Parasites

Trichinella spiralis, *Ancylostoma caninum*, and *Sarcocystis* spp. may infect the muscle and only rarely produce clinical signs. Generally, they are discovered purely by chance.[17,18,21,22]

Immune-Mediated Myositis

Myositis of the Masticatory Muscles

The muscle fibers of the masticator muscles have a distinct embryologic origin, which explains the presence of a particular type of fiber called *type 2M*. These fibers enclose a specific myosin, which is specifically involved in this immune-mediated reaction. Type 1 fibers are spared. This myopathy affects all dogs regardless of age, gender, or breed, but the German shepherd seems to have a predisposition.[23-26]

In the acute form, hypertrophy of the temporal and masseter muscles is observed with myalgia. The animal is reluctant to open its mouth. It has difficulty eating and may dribble saliva. Sometimes the jaws remain open because complete closing is impossible. Fever, inflammation of the tonsils, and local adenitis may also be found. In most cases myositis of the masticatory muscles is a chronic condition with severe,

progressive muscular atrophy accompanied by fibrosis, resulting in a reduced ability to open the mouth and trismus (lockjaw).

The disorder generally is bilateral. Exophthalmos linked to enlargement of the temporal muscles sometimes can be the cause of an optic neuritis and can result in vision disorders. Biochemical examinations are not specific, but the serum CK level may be increased, and leukocytosis is sometimes found. Electromyography (EMG) reveals abnormal spontaneous activity. Muscle biopsy shows sites of necrosis and phagocytosis of type 2M fibers, with perivascular infiltration of mononucleate cells. In the serum of affected dogs, type 2M antitype antibodies are identified.

Administration of immunosuppressive doses of corticosteroids is the only advisable therapy. Clinical recovery is usually rapid and complete if treatment is begun early. A dosage of 0.5 to 1 mg/lb twice a day is maintained for 15 days, after which the dose is gradually reduced. Should a relapse occur, the maximum dose should be administered again. Sometimes a prolonged course of treatment is required, with small doses administered on alternate days. Therapy is ineffective if administered to an animal that has already experienced several inflammatory episodes that have resulted in extensive fibrosis.

Polymyositis

Polymyositis is an inflammatory polymyopathy with an immune-mediated etiology. It is sometimes associated with other immune-mediated diseases, such as systemic lupus erythematosus. Polymyositis may also be caused by parasitic disorders (toxoplasmosis and ehrlichiosis) or various forms of cancer (paraneoplastic syndrome).[26] In most cases the etiology is unknown. Polymyositis affects all skeletal muscles of the limbs, although occasionally there are reports of focal damage, such as the extraocular muscles.[27]

Large adult dogs are most commonly affected. Signs include muscle weakness, which is sometimes exacerbated by exercise, and myalgia, pyrexia, amyotrophy, and muscle stiffness are sometimes noted. Dysphagia and regurgitation caused by megaesophagus are less common. Pneumonia is a frequent complication. Generally, an increase in the CK level is observed. EMG abnormalities are similar to those seen in myopathy of the masticator muscles. The muscle biopsy reveals perivascular infiltrations of mononucleate cells, and necrosis and regeneration are also noted. Therapy is based on immunosuppressive doses of corticosteroids. The prognosis is guarded, especially when pneumonias arise. The combination of prednisolone and azathioprine is effective in certain cases that prove refractory to the administration of corticosteroids only.

Dermatomyositis is an inherited disorder in which myositis is associated with dermatitis. It has been reported in the collie, the Shetland sheepdog, and the Welsh corgi.[28-34] The manifestations of the nonpruritic cutaneous disorder are erythema, alopecia, and ulceration. The signs appear in 3- to 11-week-old pups, and the disease appears to wax and wane. The myopathic signs of weakness are usually observed within a few months. Myositis, especially involving the temporal muscles, is seen histologically.

DEGENERATIVE MYOPATHIES

Endocrine Myopathy

Both myopathy and peripheral neuropathy have been associated with hypothyroidism.[35] These conditions may occur simultaneously. The EMG examination may record high-frequency discharges. In most cases the muscle biopsy result is normal, and if any lesions are present, they are not specific (glycogenic inclusions, type 2 atrophy, necrotic fibers, and centralized nuclei). Moderate signs can be resolved through hormone supplementation. Abnormal serum electrolytes, particularly with regard to potassium, can cause a myopathic syndrome.[35]

Myopathy has been reported in spontaneous and iatrogenic hypercorticism in dogs.[36] Clinical forms vary from muscle weakness to a myotonic form. Myotonia causes limb stiffness and seems to affect the poodle in particular. In some cases, it is even associated with muscular hypertrophy. EMG shows bursts of pseudomyotonic potentials. Muscle biopsy demonstrates disorganized muscle fibers with an abnormal accumulation of mitochondria (ragged red fibers). Treatment of the underlying disease leads to improvement of the neuromuscular signs, except in the pseudomyotonic form.

Hyperkalemia

Hyperkalemic periodic paralysis is an inherited myopathy characterized by frequent episodes of weakness, during which serum potassium is elevated. A myotonic syndrome may often accompany this myopathy, and the fits of weakness can be triggered by oral administration of potassium. Only one report of this has been documented, in a 7-month-old female American pit bull. Administration of acetazolamide and fludrocortisone led to clinical improvement in the patient's condition.

FIBROTIC AND OSSIFYING MYOPATHIES

Ossifying myopathy is generally described as a progressive ossifying myositis. It may occur in both localized and generalized forms. Clinically, the animal refuses to move. Upon radiographic investigation, intramuscular zones can be seen, and their density is close to that of bone. Histologically, a progressive ossification of the connecting intramuscular tissue is seen in which isolated patches of trabecular bone and cartilage are found, in addition to perivascular lymphocytic infiltrates, which gave rise to the term, myositis, used for this disorder. However, the term *fibrodysplasia* is preferable, because neither the optical microscope nor the electron microscope shows any lesions confirming primary damage to the muscle fibers.[37,38]

The appearance of a permanent focal contracture with muscle fibrosis (infraspinous, femoral quadriceps) causes lameness. The cause is often obscure; congenital malformation, *Neospora caninum* infection, and trauma have been proposed.[18,39,40]

INHERITED MYOPATHIES

Muscular Dystrophies

Muscular dystrophies are a group of inherited myopathies clinically defined by a muscular weakness and histologically characterized by chronic degeneration and regeneration of muscle fibers accompanied by progressive fibrosis. Among these conditions, the best known is X-linked muscular dystrophy.

X-Linked Muscular Dystrophy

X-linked muscular dystrophy results from an alteration of the gene dystrophin, as is the case in Duchenne muscular dystrophy in humans. The absence of dystrophin or production of abnormal dystrophin leads to degeneration of the muscle fibers. The gene is carried by the X chromosome, and in a natural environment, only males are affected. The canine disease was initially identified in the golden retriever,[41,42] in which the mutation was cloned.[43] Since then, the disease has been detected in the rottweiler, Samoyed,[44] Groenendaeler shepherd,[45] and miniature schnauzer.[46] The clinical signs appear at about 8 weeks of age and manifest as muscular weakness, stiffness in gait, and reduced opening of the mouth. Within a few weeks, exercise intolerance appears and the muscles become atrophic. Hypertrophy of the esophageal muscle, the tongue,

and the diaphragm can lead to severe digestive signs. The dog's gait becomes peculiar; abduction of the elbows, adduction of the hocks, and lordosis occurs in older animals. The signs usually stabilize by about 6 months of age, and movement becomes restricted with the onset of muscular fibrosis. There is no neurologic deficiency. Life expectancy depends on the severity of the signs. Death may occur within the first few days, caused by severe diaphragmatic necrosis,[47] or the animal may survive for several years and die after progressive deterioration of its general condition and because of difficulty eating. The onset of dilated cardiomyopathy is gradual, and this condition is considered a major cause of mortality.[48] The CK levels vary (10,000 to 30,000 IU/L). EMG reveals high-frequency and pseudomyotonic discharges.

Muscle biopsy reveals necrosis with an influx of macrophages and phagocytosis, muscle regeneration, and sites of intracellular calcification.[49] Some muscles, such as the sartorius, the extensor carpi radialis, the deltoid, and the cranial tibial muscle, are affected earlier and more severely. Fiber size varies with the centralized nuclei.

OTHER MUSCULAR DYSTROPHIES

Several cases of canine muscular dystrophies without dystrophin deficiency have been reported.[50,51]

Labrador Retriever Myopathy

Labrador retriever myopathy is an autosomal recessive myopathy that has been reported in the United States, Australia, Great Britain, and France. It has been initially described as a dystrophic disease affecting type 2 muscle fibers.[28] The cause of the disease remains unknown. Muscle biopsy specimens display a mixture of denervation and primary myopathies.

Clinical signs appear by 8 weeks to 11 months of age, the peak being around 4 months.[52,53] General weakness is seen with muscle atrophy, most visibly in the temporal muscles. Neck ventroflexion and a bunny hopping gait are also noted. Fatigability is variable. The animal has a very slender profile, in contrast to the muscular stature of a healthy Labrador. Tendon reflexes are absent or reduced. Some dogs have kyphosis or megaesophagus. Clinical signs stabilize after 8 months of age, and the disease is not lethal. The CK level is normal, and EMG revēals early fibrillation potentials, slow positive waves, and repetitive complex discharges that disappear in aged dogs. Muscle biopsy shows a marked diameter difference, with small angular or round fibers and large fibers with centralized nuclei. Later in the course of the disease, most fibers display centrally placed nuclei.[54] Necrosis is visible on rare occasions.[28]

Myotonia

Nondystrophic myotonia is caused by dysfunction of one or several ionic sarcolemmal channels, mainly the chloride and sodium channels. Myotonic or pseudomyotonic syndrome may be continuous or transient and can be drug induced.

In the chow chow, myotonia is inherited with an autosomal recessive trait. Nonetheless, certain descendants may exhibit autosomal dominant transmission with incomplete penetrance. Clinical signs are visible at 10 to 12 weeks of age.[55,56] These dogs have excess muscle mass. Immediately after rest the gait is stiff, and animals may frequently fall forward with the forelimbs spread out. Dyspnea and hypoxia are common because the respiratory muscles are unable to respond to the rise in metabolic requirements. A myotonic dimple persists several seconds after percussion on the surface of a muscle. Myopathy stabilizes after a few months, but because myotonia occurs in young animals, bone or articular deformations may appear. The CK level is normal or only moderately increased, and myotonic discharges are seen on EMG. Muscle biopsy is not specific; it displays mild abnormalities, mainly hypertrophy of the muscle fibers with some centralized nuclei. No satisfactory therapy is available, although the disease itself is not life-threatening. A possible dystrophic myotonia in boxers was recently described.[57]

Metabolic Myopathy

Glycogenoses are storage diseases caused by an enzymatic deficiency in glycolytic metabolism that leads to the accumulation of glycogen in cells. Signs are nonspecific. Muscular weakness, fatigability, syncope, rhabdomyolysis, and convulsions caused by hypoglycemia after a period of fasting or moderate exercise are clinical hallmarks. Seven types have been identified in humans, but only three have been identified in dogs. Type II glycogenosis, or Pompe's disease, is caused by a deficiency in alpha-glucosidase (acid maltase). This disease has been described in the spitz.[41] The mode of transmission is autosomal recessive. Clinical signs are usually observed by 6 months of age, and the animal usually dies in its second year.[58-60] Type III glycogenosis, or Cori's disease, is caused by a deficiency in amylo-1,6-glucosidase. In the German shepherd, clinical signs appear during the second month, and the disease is rapidly fatal.[61] Type VII glycogenosis, which is caused by a phosphofructokinase deficiency, has been identified in a colony of springer spaniels[62] and in an American cocker spaniel.[63] The animals show exercise intolerance and suffer from muscle cramps and hemolytic anemia. Mitochondrial myopathies are characterized by a functional abnormality (an enzymatic deficiency) or a structural abnormality of the mitochondria (membrane transporter deficiency). An enzymatic deficiency in pyruvate dehydrogenase has been identified in the clumber spaniel and the Sussex spaniel.[35] In these dogs, exercise leads to collapse and severe metabolic acidosis. Another mitochondrial myopathy is suspected in the Old English sheepdog, but the biochemical substrate remains unknown.[64]

Lipid storage has been noted in muscle in dogs with myopathies.[35,65] Clinically, once the dogs reach adulthood, they show muscle weakness and muscle pain. Tremors, stiffness, and fatigability may well be encountered.

CHAPTER • 196

Feline Myopathies

Frédéric P. Gaschen
Boyd R. Jones

Although muscle and neuromuscular junction diseases occur relatively rarely in cats, a number of congenital and acquired feline myopathies have been described over the last 20 years.[1] Muscle weakness is a common clinical sign and may cause a stiff, stilted gait. Weak cats are more prone to show cervical ventroflexion than other species with muscle disease because they lack a nuchal ligament (Figure 196-1). Other clinical signs include mild lower motor neuron (LMN) deficits, tiredness, and changes in muscle size (swelling, hypertrophy, atrophy), possibly accompanied by pain in some diseases. Cats with acquired myopathies may additionally show clinical signs involving other organ systems.

The clinical investigation of cats with suspected muscle diseases is similar to that described for muscle disease in the dog. The special techniques for investigation, including electromyography (EMG), muscle biopsy, and histologic and histochemical analysis, are described elsewhere in this text. Specific feline serologic tests such as testing for the retroviruses, feline immunodeficiency virus (FIV) or feline leukemia virus (FeLV), and for the protozoan *Toxoplasma gondii* may be required.

In spite of the relative rarity of muscle diseases in cats, it is important for clinicians who regularly examine feline patients to recognize and identify the specific feline disorders in a timely way. A good knowledge of these diseases and their features is necessary to enable a diagnosis to be made and prognosis to be given. Treatment of individual cats and advice to breeders that may help them to eliminate an hereditary trait from their breeding lines both depend on an accurate diagnosis. The congenital myopathies described in the cat are shown in Table 196-1.

Figure 196-1 Adult cat with severe weakness and cervical ventroflexion.

CONGENITAL MYOTONIA

Primary congenital myotonia has been reported in a variety of species but only recently in the cat.[2,3] The clinical features of myotonia in cats described by Hickford and colleagues[2] and Toll and colleagues[3] are very similar. The affected cats walk with a stiff, awkward gait. The limbs are abducted when walking due to poor flexion of proximal appendicular joints. Widespread hypertrophy of muscle groups occurs. The stiffness is worse on awakening and in cold weather, but it improves with exercise. When affected kittens are startled, they may stiffen and fall into lateral recumbency with legs extended. Spasm of the eyelids and facial muscles frequently occur when the cats are startled (Figure 196-2). Their jaws cannot be opened fully, and mild dysphagia sometimes occurs. Clinical chemistry, including serum (CK) activity is normal.

The presence of a dimple on percussion of muscle (tongue or skeletal muscle) and the occurrence of spontaneous high-frequency discharges that wax and wane on EMG after insertion of a needle electrode and the "dive bomber" sound are features of all affected cats (Figure 196-3).

Histologic section of muscle shows a variation in fiber size, central nuclei, and proliferation of sarcolemmal nuclei.[2,3] The reports of myotonia in cats neither described treatment nor emphasized that medical treatment was required.

DYSTROPHIN-DEFICIENT MYOPATHY

Feline dystrophin deficiency, like that in other species, is due to a mutation in the dystrophin gene—a very large gene located on the X chromosome—and is transmitted according to an X-linked recessive inheritance pattern.[4] In cats the most prominent sign is severe hypertrophy of the axial and proximal appendicular skeletal muscles (Figure 196-4). The tongue and diaphragm also show massive hypertrophy in some individuals, and this can result in potentially lethal complications, such as esophageal compression, insufficient water intake, and severe hyperosmolality due to dehydration.[4]

Dystrophin-deficient kittens cannot be differentiated from normal kittens at birth, although they are slow to grow. Appendicular muscular hypertrophy is first seen around 10 weeks of age, followed by axial muscle hypertrophy, especially of the cervical muscles. Dystrophin deficiency causes a disease often called *hypertrophic feline muscular dystrophy* (HFMD). These animals have a stilted gait, and they tend to "bunny hop" when they run. Occasionally, they show marked stiffness and reluctance to move.

Dystrophin-deficient cats develop a subclinical cardiomyopathy with myocardial hypertrophy from 6 to 9 months of age.[5] Fractional shortening of the left ventricle is usually normal, suggesting normal left ventricular contractility. These cats infrequently develop clinical signs of heart failure, but some older

Table • 196-1

Congenital Myopathies

DISEASE	AFFECTED BREEDS AND GEOGRAPHIC PROVENIENCE	MODE OF INHERITANCE	UNDERLYING DEFECT	CLINICAL SIGNS	PROGNOSIS
Congenital myotonia	DSH (NZ, USA)	Autosomal recessive	Probable defect in chloride channels	Stiff gait; hyperactivity of selected muscle groups when startled; percussion dimple	Fair to good (nonprogressive condition, cats enjoy a normal quality of life)
Devon Rex myopathy	Devon Rex (AUS, GB)	Autosomal recessive	Unknown	Cervical ventroflexion; generalized muscle weakness; abnormal gait; megaloesophagus	Poor (many cats die of asphyxiation)
Dystrophin-deficient myopathy	DSH (USA, NL, CH)	X-linked recessive	Dystrophin deficiency	Skeletal muscle hypertrophy with possible complications; sensitivity to stress; stiff gait	Guarded to fair (cats can have almost normal quality of life but may require more frequent veterinary visits)
Glycogen storage disease type IV	Norwegian forest cats (USA, Europe)	Autosomal recessive	Glycogen branching enzyme (GBE) deficiency	Stillbirth; muscle tremor; muscle atrophy; cardiomyopathy	Poor (all cats eventually die)
Hypokalemic myopathy	Burmese (AUS, NZ, GB, NL)	Probably autosomal recessive	Unknown	Transient, paroxysmal clinical signs with generalized muscle weakness, cervical ventroflexion	Good response to potassium supplementation
Malignant hyperthermia	DSH	Unknown	Unknown	Severe hyperthermia during anesthesia (halothane)	Poor (the two reported cats died)
Merosin-deficient myopathy	DSH, Siamese (USA)	Unknown	Merosin (laminin α2) deficiency	Hindlimb weakness from 6 months old, worsening to muscle atrophy and contractures at 1 year old	Poor (both cats were euthanized before 2 years of age)
Myasthenia gravis (MG)	DSH	Unknown	Lack of acetylcholine receptors	Generalized muscle weakness	Fair, generally good response to therapy
Nemaline myopathy	DSH (USA)	Possibly autosomal recessive	Unknown	Progressive weakness (6-18 months); rapid, choppy, hypermetric gait; tremor, exercise intolerance	Poor (all five reported cats died or were euthanized)

AUS, Australia; *CH*, Switzerland; *GB*, Great Britain; *NL*, Netherlands; *NZ*, New Zealand; *USA*, United States of America.
From Gaschen F et al: Congenital diseases of feline muscle and neuromuscular junction, *J Feline Med Surg*, 2003 (in press).

cats have died from cardiomyopathy (Gaschen, unpublished observations).

EMG findings include myotonic discharges, fibrillation potentials, prolonged insertional activities, complex repetitive discharges, and positive sharp waves.

In young and adult cats, serum (CK) activity is increased, but serum CK concentrations do not allow a differentiation of dystrophin-deficient kittens from normal littermates at birth. Serum aspartate transaminase (AST) and alanine aminotransferase (ALT) are also increased.

Histopathologic changes in dystrophin-deficient skeletal muscle include variation in myofiber diameter, with large myofibers showing splitting, foci of degeneration and regeneration, with minimal mononuclear infiltration and absence of endomysial or perimysial fibrosis. Severe dystrophic calcification can be present. A definitive diagnosis is made when immunohistochemistry (IHC) staining confirms a lack of dystrophin at the sarcolemma.

The prognosis for HFMD is fair; no specific treatment is available. Many cats enjoy a nearly normal quality of life.

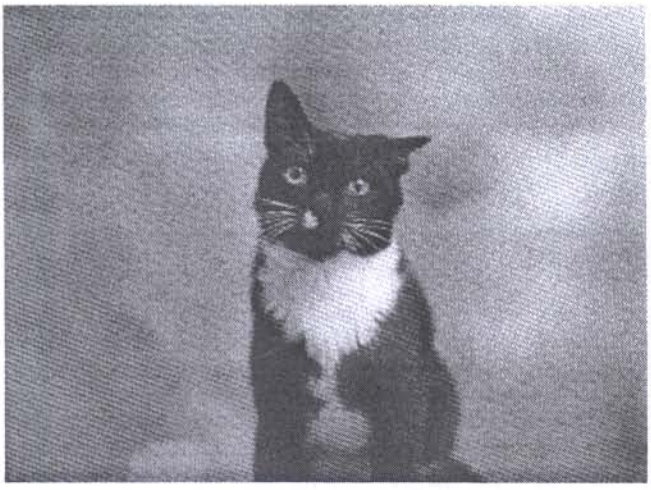

Figure 196-2 An affected kitten showing flattening of the ears and retraction of the lip after receiving a fright. (From Hickford FH et al: Congenital myotonia in related kittens, *J Small Anim Prac* 39:281, 1998, with permission.)

Figure 196-4 Adult dystrophin–deficient cat with appendicular muscle hypertrophy and hypertrophy of the tongue.

However, stress, intense physical activity, and inhalant anesthesia should be avoided if possible because they may elicit acute rhabdomyolysis.[6]

MYOPATHY OF DEVON REX CATS

This myopathy has been reported in many countries: Australia, New Zealand, the United Kingdom, and the United States.[7]

The most obvious and consistent clinical sign is passive ventroflexion of the head and neck. Ventroflexion is frequently accentuated when walking, during micturition and defecation. Typically the animal has a high-stepping forelimb gait, head bobbing, and dorsal protrusion of the scapulae. Due to weakness of the shoulder girdle musculature with exertion, they tire easily and eventually collapse in sternal recumbency.

Myopathic Devon Rex cats frequently rest in a characteristic "dog-begging" position, with their front paws on a supporting object (Figure 196-5). One of the significant features of the disease is the difficulty affected cats have prehending food and swallowing. They can choke and asphyxiate due to the accumulation of ingesta in the pharynx. The severity of signs often fluctuate from day to day. Stress, concurrent illness, exertion, and cold all tend to accentuate weakness.

The age of onset is variable, and less seriously affected kittens may go unnoticed for several months. Breeders normally recognize the affected kittens at about the time they start to walk. The disease is inherited as an autosomal recessive trait.

In the one detailed study by Malik and colleagues[7] of four cats with this muscle disorder, esophageal hypomotility and megaesophagus were identified in all animals. Hematologic and serum biochemistry values including electrolytes and CK are within reference ranges.[7] Sparse fibrillation potentials and positive sharp wave activity may be detected on EMG of the upper limb and cervical muscles.

Skeletal muscles appear grossly normal, but histologic changes are best identified in dorsal cervical and proximal forelimb muscles. The severity of the changes correlates with both the severity of signs and the age of the cat.[7] In muscle biopsies, the significant lesions are variation in cross-sectional area, more

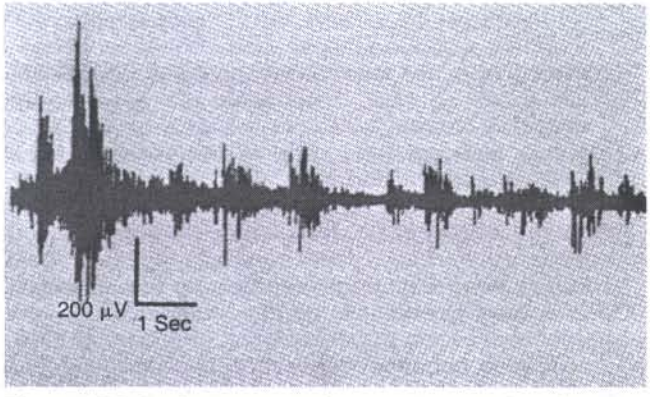

Figure 196-3 Electromyography (EMG) recording from the biceps muscle of an affected kitten showing waxing and waning, high-frequency discharges after needle insertion. (From Hickford FH et al: Congenital myotonia in related kittens, *J Small Anim Prac* 39:281, 1998, with permission.)

Figure 196-5 Young Devon Rex kitten showing the characteristic posture when resting. (Published with permission of Manon publishing.)

rounded fibers, occasional degenerating fibers, some fiber segmentation, and increased subsarcolemmal nuclei. Lesions do not affect one fiber type in particular, and dystrophin is present. No specific treatment is available, but feeding from a raised platform can help ingestion of food and prevent choking.

NEMALINE ROD MYOPATHY

Affected cats are normal until 6 to 18 months of age; then they develop muscle atrophy and weakness, and their gait becomes wobbly. They show a fast, jerky, and hypermetric gait and a crouched stance with an exaggerated hip and tarsal flexion. These cats become quickly exhausted and pant after exertion. The clinical course is slowly progressive. CK activity in serum is increased, but no changes are seen on EMG examination. Myofibers contain nemaline rods. The prognosis is poor, and most affected cats are euthanized for humane reasons.[1]

LAMININ α2 (MEROSIN) DEFICIENCY

Laminin 2, also called *merosin*, is a glycoprotein indirectly anchoring the cell membrane and the basal lamina and is present in skeletal muscle and Schwann cells. O'Brien and colleagues have described two merosin-deficient cats.[8] Hindlimb weakness starts at 6 months of age and is followed by generalized muscle atrophy by 12 months of age. Hindlimb muscle contractures are present. Serum CK is increased, and the motor nerve conduction velocity is markedly decreased. Myofiber necrosis, variation in fiber size, and lipid accumulation are present in muscle, and axonal demyelination is present in peripheral nerves. IHC stains show a lack or decrease of laminin α2 in skeletal muscle.

GLYCOGEN STORAGE DISEASE TYPE IV

A myopathy associated with glycogen storage disease type IV has been reported in Norwegian forest cats.[9] Many affected cats are stillborn or die within the first few days of life. The surviving cats are often normal until they reach 5 to 7 months of age. They may show clinical signs of persistently increased body temperature, generalized muscle tremors, intermittent listlessness and a "bunny hopping" gait, muscle weakness, atrophy, and contracture. Most affected cats die by 10 to 14 months of age.

The disease is due to a lack of the glycogen branching enzyme (GBE) and is characterized by accumulation of abnormal glycogen in several tissues including skeletal muscle. Hereditary transmission occurs according to an autosomal recessive pattern. Affected cats are homozygous for a deletion in the GBE gene causing instability of mRNA.

Serum CK and ALT are increased. Fibrillation potentials and bizarre high-frequency discharges are present in the EMG. Cytoplasmic inclusions containing periodic acid-Schiff (PAS) and toluidine blue–positive material are present in many organs.

Diagnosis of the disease in an affected kitten unequivocally identifies the parents as carriers of the mutation, which should have direct implications for their use in any breeding program. A DNA-based carrier test is available in selected laboratories to screen problem breeding families.

MYASTHENIA GRAVIS

Acquired myasthenia gravis (MG) is a rare disease, but sporadic reports and a published series of 20 cases exist.[10] Congenital MG has been described in two cats.[11] Acquired feline MG is an immune-mediated disease as evidenced by the presence of serum acetylcholine receptor antibodies. The main clinical sign is muscle weakness. Ducote and colleagues described three distinct forms.[10] Cats with focal MG have signs isolated to the esophageal, pharyngeal, laryngeal, or facial muscles. Generalized MG is characterized by appendicular muscle weakness with or without esophageal, pharyngeal, laryngeal, or facial muscle involvement. Acute fulminating MG is a severe acute onset form of generalized MG with a rapid progression of muscle weakness often associated with respiratory muscle paresis or paralysis.

The diagnosis of MG in the cat is similar to the dog and includes an increase in muscle strength after intravenous edrophonium hydrochloride administration, decremental evoked muscle action potential response to repetitive nerve stimulation, and an increase in serum ach-receptor antibody concentration. MG in cats may be associated with a thymic mass (thymoma) and concurrent immune-mediated myositis. Thoracic radiography and muscle biopsy may be indicated in selected cases. Treatment of feline MG patients includes administration of anticholinergics (pyridostigmine 0.25 to 1 mg/kg every 12 hours) with the dose titered to the clinical response. An immunosuppressive dose of prednisone (2 to 4 mg/kg every 24 hours) is indicated if aspiration pneumonia is absent.

HYPOKALEMIC POLYMYOPATHY

A polymyopathy associated with total body potassium depletion has been recognized in cats of all breeds, ages, and both sexes.[12] Some cats with chronic renal failure and cats eating acidifying diets are affected. Cats with polyuria or polydipsia secondary to hyperthyroidism and cats with anorexia from any cause may also be at risk. Severe total body depletion of potassium occurs secondary to decreased dietary intake or increased urinary excretion of potassium.[12]

Burmese kittens develop hypokalemia associated with disturbances of the intracellular and extracellular balance of potassium.[12] The condition has a familial and inherited basis (putative autosomal recessive), with affected kittens being produced in specific lines of this breed.[12,13]

The significant clinical sign in these cats is weakness characterized by persistent ventroflexion of the neck; a stiff, stilted gait; and reluctance to move. Muscle pain may be elicited on palpation, but the neurologic examination is normal. Clinical signs may have an acute onset and may be episodic. Serum CK activity is often high (>50,000) and the serum potassium concentration is decreased (<3.0 nmol/L), and increased fractional urinary excretion of potassium can be measured (>10% to 15%). No evidence exists for reduced potassium intake or urinary potassium loss in affected Burmese kittens. Many affected cats have renal disease; urea and creatinine concentrations are elevated. Hypokalemia can result in decreased glomerular filtration, which can alter urine-concentrating mechanisms; therefore a low urine specific gravity is not a good guide to renal function.

Mild diffuse EMG changes, including increased insertional activity, positive sharp waves, fibrillation potentials, and high-frequency discharges have been recorded in affected cats. Muscle biopsies show mild myonecrosis or are normal.[13]

Signs of hypokalemic polymyopathy usually resolve after parenteral or oral supplementation of potassium. Oral treatment with potassium gluconate is recommended for mildly affected cats (Kaon Elixir, Adria Laboratories, Columbus, OH; Tumil K, Daniels Pharmaceuticals) at a dose of 2 to 4 nmol/cat twice a day for 2 days, then once daily. The dose administered is adjusted based on the response and the serum potassium concentration. Cats with more dramatic hypokalemia

(<2.5 nmol/L) or those with severe muscular weakness will initially require parenteral administration of intravenous saline or lactated ringers with supplemented potassium chloride. Intravenous infusion of potassium should not exceed 0.5 nmol/kg/hour. Oral supplementation with potassium gluconate should be continued and potassium concentration measured at regular intervals.

HYPERTHYROIDISM

Hyperthyroidism is one of the most common endocrinopathies affecting older cats. Mild muscle weakness is a relatively frequent accompanying sign. However, severe muscle disease only affects a low percentage of hyperthyroid cats.[15] The pathogenesis of hyperthyroid myopathy is unknown. In humans, depletion of energy-rich molecules in the striated muscle and intracellular displacements of potassium have been suspected.[15] In cats, hyperthyroidism may be associated with hypokalemia and hypokalemic myopathy.[16] Increased renal losses of potassium may occur without evidence of azotemia because hyperthyroidism generally leads to an increase in renal plasma flow and may mask the presence of renal insufficiency. In such cats, renal disease may only become obvious after onset of treatment.

Generalized muscle weakness with abnormal gait and exercise intolerance occur relatively frequently. Sometimes, cervical ventroflexion can occur before hyperthyroidism is diagnosed. In addition to the typical laboratory finding observed in hyperthyroidism, serum activity of CK can be increased. The prognosis is good: signs of muscle weakness usually disappear after hyperthyroidism has been successfully treated. In treated cats developing overt renal failure, regular monitoring of serum potassium concentration and oral potassium supplementation (see previous discussion) are essential for a successful outcome in addition to adequate management of chronic renal failure.

PARASITIC POLYMYOSITIS

The cat is the definitive host of the protozoal parasite *Toxoplasma gondii*. Although the parasite mainly undergoes an enteroepithelial cycle in this species, it can also occasionally lead to the formation of tissue cysts and cause clinical signs. The prevalence of antibodies against *Toxoplasma* spp. in cats varies from 30% to more than 65%, depending on the geographic area. Prevalence increases with age due to the higher risk of contact with *Toxoplasma*. However, only a small fraction of seropositive cats develop clinical toxoplasmosis.[17]

Typical clinical signs include poor general condition with anorexia, lethargy, and fever. Toxoplasmosis affects different organs such as the lungs, CNS (brain, spinal cord), liver, pancreas, heart, and eyes. In contrast to dogs, myositis is only rarely observed in cats.[17] However, if muscle weakness, exercise intolerance, and myalgia are present, toxoplasmosis should be considered as a differential diagnosis. Positive immunoglobulin M (IgM) titers and increasing immunoglobulin G (IgG) titers can help confirm the diagnosis. Immunodeficiency (e.g., after retroviral infections) can increase the risk of new infections or reactivate chronic *Toxoplasma* infections.[17] (Treatment and prognosis of feline toxoplasmosis are described in detail in the section on infectious diseases.)

OTHER FORMS OF POLYMYOSITIS

Polymyositis may occur in association with various diseases. Adult cats experimentally infected with FIV show histologic and occasionally EMG changes in skeletal muscle in the absence of clinical signs of muscle disease.[18] Some cats with thymoma can develop a paraneoplastic polymyositis that is sometimes associated with dysphagia.[19] Idiopathic polymyositis is an inflammatory muscle disease for which no specific cause can be found, and an immune-mediated pathogenesis is suspected.[19-21]

The clinical signs are muscle weakness of varying severity; cervical ventroflexion is occasionally observed. Affected cats may show dysphagia, especially with paraneoplastic or idiopathic polymyositis. The serum concentration of CK is significantly increased. Nonspecific EMG changes are present with normal nerve conduction velocities. Multifocal inflammatory infiltrates with mononuclear cells[18,19] are observed histologically.

Idiopathic polymyositis is treated with immunosuppressive doses of glucocorticoids (prednisolone 2 mg/kg twice a day). The prognosis is guarded to good for idiopathic polymyositis, but dysphagia or the presence of megaesophagus are poor prognostic signs.[20,21]

ISCHEMIC NEUROMYOPATHIES

Arterial Thromboembolism Associated with Cardiomyopathy

Arterial thromboembolism is a significant complication of feline cardiomyopathies and occurs most frequently in the distal aorta. It may also rarely occur secondary to neoplasia in cats without cardiovascular disease.[22] Recently, 271 cats with feline arterial thromboembolism (FATE) were described in three large retrospective studies.[22-24] The main features of these cases are summarized in Table 196-2.

The high proportion of male cats may reflect the high prevalence of hypertrophic cardiomyopathy in male cats.[20] Frequently, cats with FATE have no previous history of cardiac disease. Affected animals most often experience acute to peracute onset of bilateral hind limb paralysis. However, unilateral hind limb or front limb involvement can be observed. Paralysis or paresis is often accompanied by painful swelling of all involved muscles. In the affected hind limbs, the femoral pulse is absent or, with partial embolism, it is weaker. Cyanosis of the unpigmented nail beds and foot pads is observed when compared with the unaffected limbs. The cardiovascular signs of cats with FATE are discussed elsewhere in this text.

In the published case studies, laboratory changes included increases in serum activities of CK, ALT, and AST in most cats and azotemia in up to one half of the cases.[22] Bilateral embolism of the hind limbs and absence of motor function in the affected limbs were negative prognostic factors.[22] Cats that survived the FATE episodes had higher body temperature (mean 99° F [37.7° C] versus 96.5° F [35.8° C] and higher heart rates (median 210 versus 188 beats per minute). The diagnosis of congestive heart failure (CHF) did not appear to significantly influence the prognosis.[22]

Management of FATE includes supportive treatment, including intravenous fluids and oxygen supplementation. Analgesia with opiates (buprenorphine, oxymorphone, or fentanyl) is essential, because most signs of distress are due to pain and abate once the pain is controlled. The use of anticoagulant and antithrombogenic drugs is controversial. Aspirin is often administered as an antithrombogenic drug, but efficacy data is lacking. No differences in outcome were noticed between cats with FATE receiving anti-inflammatory (81 mg/cat every 72 hours) and low (5 mg/cat every 72 hours) doses of aspirin.[22] Thrombolytic therapy with streptokinase, an activator of fibrinolysis, was studied in 46 cats with FATE. The survival rate did not significantly differ from that of cats receiving no streptokinase in other retrospective studies; however, the authors claim that their study population was more severely affected than cats in other studies.[26] The underlying cardiomyopathy

Table • 196-2

Diagnostic Features of Feline Arterial Thromboembolism

PARAMETER	LASTE ET AL, 1995	SHOEMAN, 1999	SMITH ET AL, 2003
Number of cats	100	44	127
Prevalence in hospital population	N/A	N/A	0.57%
Signalment:			
Mean age (years)	7.7	8.7	8.6
Gender distribution in % (M:F)	67:33	75:25	67:33
History:			
No previous diagnosis of cardiac disease	89%	77%	93.0%
Vomiting shortly before thromboembolic episode	N/A	6.8%	15.7%
Physical examination:			
One limb affected	N/A	N/A	24.8%
Two or more limbs affected	N/A	N/A	75.2%
Partial thromboembolism	20%	31%	N/A
Hypothermia	35%	N/A	65.5%
Tachypnea	26%	N/A	90.8%
Cardiac parameters:			
Cardiac murmur	35%	N/A	30.7%
Gallop rhythm	20%	N/A	24.4%
Arrhythmia	19%	N/A	15.7%
Mod to severe LA enlargement	71.2% (n=63)	66% (n=9)	91.0% (n=78)
Congestive heart failure (CHF)	66.3% (n=80)	51% (n=25)	44% (n=125)
Laboratory parameters:			
Increased CK	N/A	80% (n=5)	100% (n=87)
Increased ALT	88.7% (n=53)	N/A	72.8% (n=87)
Increased AST	84.9% (n=53)	N/A	98.6% (n=87)
Increased BUN	54.7% (n=53)	N/A	41.3% (n=87)
Increased creatinine	56.6% (n=53)	N/A	26.3% (n=87)

must be treated according to the recommendations given elsewhere in this text.

In recent retrospective studies, 35% to 39% of cats survived episodes of FATE, 28% died during the initial hospitalization, and 33% to 35% were euthanized.[22-24] In one study, survival rate was better during the last 10 months of the study (up to 75% survivors) than during the 9 earlier years (less than 30% survivors).[22] Among cats for which treatment was initiated, 45% survived to be discharged.[22] Depending on the study, median survival time (MST) was between 117 days and 6 months. Re-embolization occurred in 24% to 50% of discharged cats. These results confirm that FATE is associated with a poor prognosis. The underlying cardiomyopathy represents a clear risk for new thromboembolic events and contributes to the unfavorable prognosis. Rapid identification of cats with more favorable prognosis is important to allow owners to make an informed decision to treat or not. Cats that recover may have permanent ischemic muscle or nerve damage.

Traumatic Ischemic Neuromyopathy Associated with Bottom-Hung Pivot Windows and Garage Doors

In Europe, bottom-hung pivot windows are common. Cats try to get in or out through these windows and get themselves wedged in between the costal arch and the pelvis (see Figure 196-6). After unsuccessful efforts to free themselves, the cats become wedged with pressure on their abdomen and in a position that can lead to traumatic lesions to muscle, internal organs, blood vessels, spine, and spinal cord. A recent report reviewed the clinical features and outcome of 30 cats trapped in bottom-hung pivot windows.[27]

The signs shown were hypothermia (19 cats); pain in the hind limbs, lumbar area, and abdomen (21 cats); swelling of the hind limb muscles (7 cats); cold hind limbs (6 cats); weak femoral pulse (10 cats); absent femoral pulse (9 cats); and paraparesis or paraplegia (17 cats), often associated with decreased spinal reflexes in the hind limbs (see Figure 196-6). Deep pain perception was decreased in two cats and absent in four.

Moderate hyperkalemia may be have been due to reperfusion injury after the cats had been freed from the window.

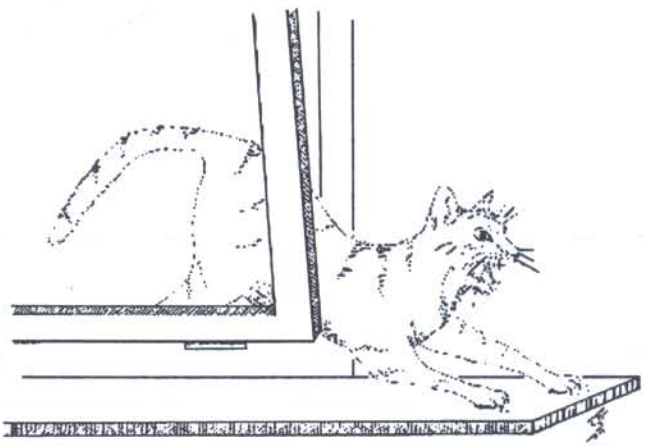

Figure 196-6 A cat trapped in a bottom-hung pivot window.

Serum activities of CK and AST were massively increased, with a moderate increase in ALT. Hematuria was present in some cats. Abdominal radiographs showed soft tissue density underneath the lumbar spine or in the retroperitoneal area, with a loss of contrast in the caudal abdomen. Occasionally, fractured vertebrae were present.

Medical treatment included fluid therapy, management of pain, and administration of antibiotics and high dose of corticosteroids. Physical therapy consisting of massage of the involved muscles and gentle manipulation of the hind limbs was performed once the limbs were less painful.

The prognosis was good. Eighty percent of the cats were discharged, and all but one recovered fully within 1 month.[26] The duration of the hospital stay was between 1 and 12 days.

INDEX

Page numbers followed by f indicate figures; t, tables; b, boxes.

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IND

IN

IND

IND

IND