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Michael D. Willard and David C. Twedt

Gastrointestinal, Pancreatic, and Hepatic Disorders

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- **Weight Loss or Anorexia of Unknown Cause**
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Gastrointestinal (GI) problems (e.g., vomiting, diarrhea, weight loss, anorexia, icterus, hepatomegaly, abnormal behavior associated with eating, abdominal pain) typically necessitate laboratory testing. Dysphagia, regurgitation, ptyalism, halitosis, constipation, mucoid stools, hematochezia, and melena are best approached initially by other means (e.g., physical examination, radiology, endoscopy, surgical biopsy).

DIFFERENTIATION OF EXPECTORATION, REGURGITATION, AND VOMITING

Whenever fluid, mucus, foam, food, or blood is expelled from the mouth, one must determine whether vomiting, regurgitation, gagging, or expectoration is occurring. The history sometimes allows differentiation.

Expectoration

Expectoration is the coughing up of material from the lungs or major airways. The material typically is frothy mucus or red blood; bile is absent. The characteristic sequence of coughing followed by oral expulsion must be determined from the history. Regurgitation and vomiting typically occur without simultaneous coughing, although regurgitation is often accompanied by tracheitis and aspiration pneumonia. Of the three, expectoration should be the easiest to identify.

Regurgitation

Regurgitation is due to oral, pharyngeal, or esophageal dysfunction and is typically characterized as a relatively passive expulsion of esophageal contents. Gagging is the expulsion of oral or pharyngeal material and may be associated with disorders causing dysphagia (i.e., difficult swallowing) or regurgitation. The relatively minor abdominal contractions associated with gagging can often be differentiated from the vigorous abdominal contractions that occur with vomiting. Regurgitation may follow seconds to hours after eating or drinking. If only saliva is regurgitated, eating may not have occurred for hours or even days before the act. Regurgitated food material is undigested and sometimes has a tubular form conforming to the shape of the esophageal lumen. Most clients cannot reliably distinguish undigested from digested food. Regurgitated material that has remained in the esophagus for long time periods often becomes macerated and odoriferous and is mixed with saliva and mucus. If blood is present it is usually undigested (i.e., bright red), whereas blood originating from the stomach is usually partially digested by gastric acid and has a "coffee ground" appearance readily distinguishing it from the undigested form.

It is sometimes difficult to differentiate vomiting from regurgitation via history, and in some patients the processes are concurrent. Vomiting may cause secondary esophagitis and subsequent regurgitation, or a patient with longstanding esophageal disease may develop another concurrent disorder causing vomiting. It is therefore important to clarify the chronologic order of specific signs. Finally, some patients with signs suggesting regurgitation are vomiting. To aid in differentiation, one may attempt to observe the act of expulsion by feeding the patient, although this is very unreliable ("watched" regurgitating patients often do not regurgitate). Watching the patient eat may be helpful, because pharyngeal dysphagia is usually obvious and suggests oropharyngeal disease. Some patients with pharyngeal dysphagia also have concurrent esophageal dysfunction. Contrast radiographs of the pharynx and esophagus usually differentiate the two disorders.

Regurgitation is usually best evaluated by history, physical examination, plain and contrast radiographs, or esophagoscopy (Figure 9-1). Contrast radiographs should use barium instead of iodide contrast agents unless esophageal rupture is strongly suspected. The main purpose of a contrast esophagram is to distinguish esophageal motility abnormalities from lesions such as an obstruction, diverticulum, or fistula. Some drugs (e.g., xylazine) commonly used for restraint cause esophageal paralysis, making the radiographs potentially misleading. Esophagoscopy may not diagnose esophageal muscular weakness but is effective for sampling mass lesions, differentiating intramural from extramural obstruction, identifying esophagitis, detecting diverticula, and removing foreign objects. Patients with acquired esophageal weakness (i.e., megaesophagus) should be evaluated for myopathies, neuropathies, and myasthenia gravis (generalized or localized to the esophagus). Occasionally, hypoadrenocorticism, hyperkalemia, lead poisoning, *Spirocerca lupi*, and selected central nervous system (CNS) disorders (e.g., distemper, hydrocephalus) may be responsible. Generalized or localized

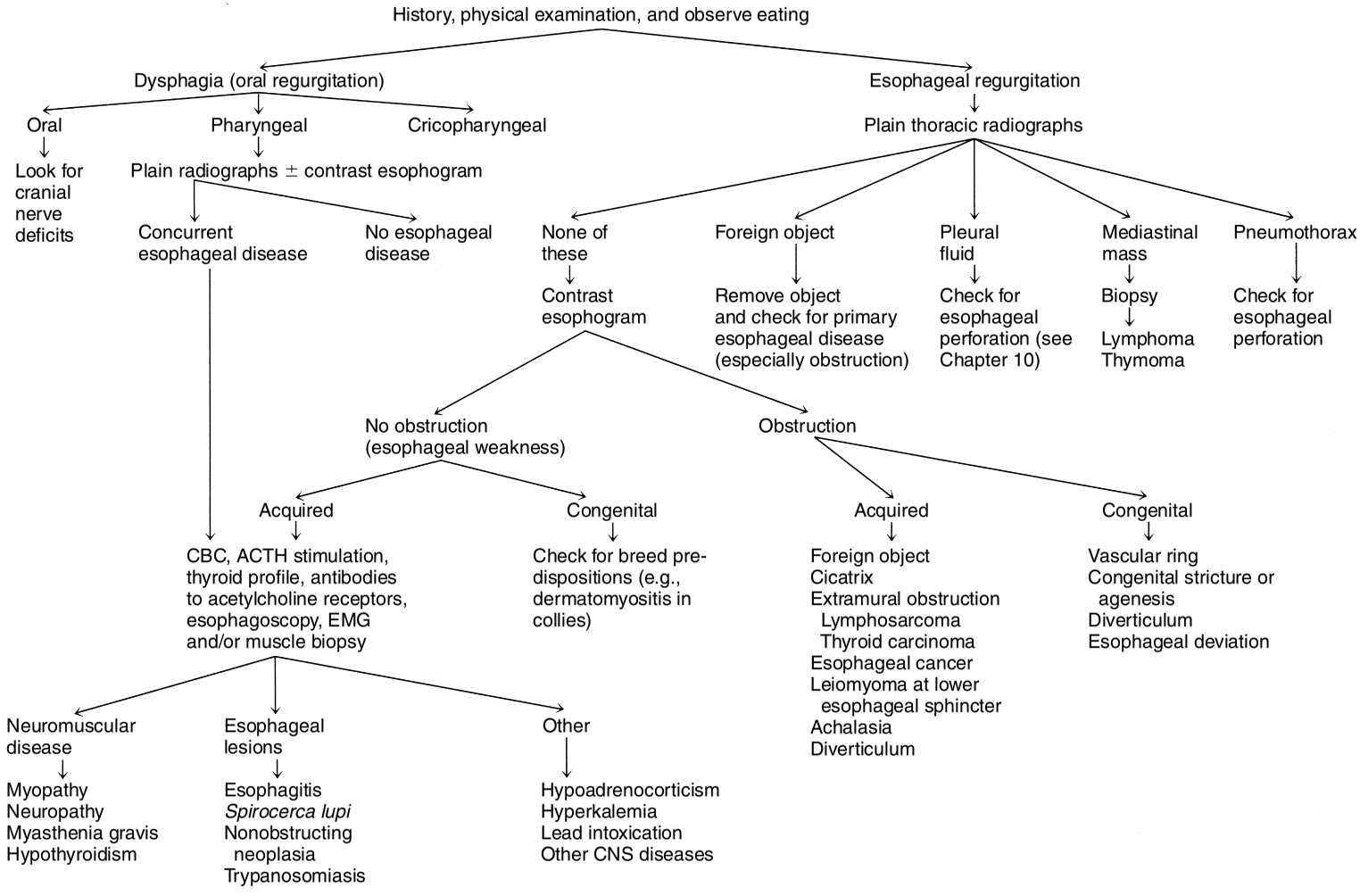

FIGURE 9-1. Diagnostic approach to chronic regurgitation in dogs and cats. *ACTH,* Adrenocorticotropic hormone; *CBC,* complete blood count; *EMG,* electromyogram; *CNS,* central nervous system.

myopathies and neuropathies have several causes, such as trauma, dermatomyositis, thymoma, botulism, tick paralysis, hypothyroidism, hyperadrenocorticism, systemic lupus erythematosus, nutritional factors, toxoplasmosis, and trypanosomiasis. Dysautonomia has been recognized in dogs and cats and causes generalized dysfunction of the autonomic nervous system, including regulation of esophageal motility. Hypothyroidism and systemic lupus erythematosus may exist without obvious clinical signs. It is important to detect these underlying disorders so that one may treat the cause rather than just the symptoms. It is also wise to evaluate patients with unexpected esophageal foreign objects (e.g., a relatively small bolus of food) for partial obstructions (e.g., subclinical vascular ring anomaly, stricture).

Vomiting

Vomiting is a reflex act originating in the CNS that can be stimulated by various conditions. One must consider primary GI disease and non-GI disorders as causes of vomiting. Examples of non-GI disorders include metabolic, inflammatory, and toxic conditions. Many vomiting patients are probably vomiting from non-GI instead of primary GI problems.

Vomiting is classically characterized by prodromal nausea (i.e., salivation, licking of lips) followed by retching or forceful abdominal contractions. Vomiting may occur any time after eating or drinking (seconds to hours). A patient may vomit food, water, fresh blood, or mucus that is indistinguishable from regurgitated material. Bile, partially digested blood (i.e., "coffee grounds"), or expelled material with a pH of five or less confirms that vomiting is occurring. Vomited duodenal contents may have a pH greater than or equal to six and are usually positive for bile. A urine dipstick with a pH indicator is useful in making pH determinations.

Clinically, vomiting patients are best divided into those with acute (<2 weeks) versus those with chronic (>2 weeks) vomiting. The most common categories of causes for each are listed in Tables 9-1 and 9-2. Acute vomiting often spontaneously resolves if the patient is supported by fluid, electrolyte, and acid-base therapy. A thorough history and physical examination are indicated first. Laboratory evaluation (including electrolytes and acid-base evaluations) or imaging should be considered next if the disease is severe. If vomiting persists, is progressive, or is attended by other clinical signs (e.g., polyuria-polydipsia [pupd], weight loss, icterus, painful abdomen, ascites, weakness, hematemesis), additional testing is also indicated (Figure 9-2).

TABLE 9-1. Major Causes of Acute Vomiting in Dogs and Cats

Eating Inappropriate or Spoiled Foods
Motion Sickness
Postoperative Nausea
Acute Gastritis-Enteritis (various viral or bacterial agents or toxins)
Parvoviral enteritis (dogs and cats)
Hemorrhagic gastroenteritis
Parasites
Gastrointestinal (GI) Obstruction
Obstructing foreign body
Linear foreign body
Intussusception
Dietary Indiscretion
Overeating
Eating inappropriate or spoiled foods
Acute Pancreatitis
Drug Administration
Adriamycin
Chloramphenicol
Cisplatin
Cyclophosphamide
Digitalis
Erythromycin
Narcotics
Nitrofurantoin
Tetracycline
Theophylline
Xylazine
Intoxications
Ethylene glycol
Herbicides
Organophosphates
Strychnine

Diet and Parasites

Diet and parasites commonly cause acute and chronic vomiting; hence, dietary change (to a bland or hypoallergenic diet), fecal examination, and broad-spectrum anthelmintic therapy (e.g., fenbendazole, pyrantel) are reasonable initial choices in nonobstructed patients. Continued vomiting is an indication for laboratory tests or imaging.

Obstruction

Gastric or intestinal obstruction does not require clinicopathologic testing for diagnosis. A complete blood count (CBC) may suggest sepsis, disseminated intravascular coagulation (DIC), or severe blood loss. Renal function,

TABLE 9-2. Major Causes of Chronic Vomiting in Dogs and Cats

Obstructive Disease
Foreign objects *(especially common)*
Intussusception
Neoplasia (gastric or intestinal)
Pyloric stenosis
Gastric antral mucosal hyperplasia
Inflammatory infiltrates (gastric or intestinal)
Chronic partial gastric volvulus
Idiopathic hypomotility of stomach/intestines (physiologic obstruction) *(rare)*
Congenital structural abnormalities *(rare)*
Inflammatory Disease
Inflammatory bowel disease *(common)*
Pancreatitis *(common)*
Chronic gastritis
Gastrointestinal (GI) ulceration/erosion
Peritonitis (sterile or septic)
Pharyngitis (caused by upper respiratory virus in cats)
Parasites (e.g., *Physaloptera*)
Systemic (extraalimentary tract diseases stimulating the chemoreceptor trigger zone and/or vagal afferents) (*common*)
Hepatic disease/insufficiency
Hypoadrenocorticism
Diabetic ketoacidosis
Uremia
Hypercalcemia
Cholecystitis
Pyometra
Miscellaneous Causes
Feline hyperthyroidism *(common)*
Feline heartworm disease *(questionable)*
Central nervous system (CNS) disease (e.g., limbic epilepsy, tumor, encephalitis, or increased intracranial pressure) *(rare)*
Psychotic or behavioral changes *(rare)*
Early congestive heart failure *(questionable)*

electrolyte, and acid-base evaluations are recommended before anesthesia. One cannot reliably predict changes in these parameters even when the site of obstruction is known. Gastric vomiting sometimes causes hypokalemic, hypochloremic metabolic alkalosis with aciduria. These changes generally occur secondary to persistent and profuse vomiting, gastric outflow obstruction, or high duodenal obstruction. Most patients with gastric vomiting are not alkalotic. Insignificant acid-base changes or metabolic acidosis due to dehydration with resultant lactic acidosis is perhaps more common. Intestinal obstruction may cause acidosis as the result of loss of pancreatic bicarbonate, although some patients have a normal blood pH or a metabolic alkalosis if the obstruction is high.

Abdominal palpation and imaging are the best initial diagnostic tests. In otherwise occult cases, contrast radiographs may be necessary. Barium is preferred over iodide compounds unless intestinal rupture is strongly suspected. Barium leakage causes peritonitis and requires vigorous abdominal lavage at the time of surgery (see Chapter 10).

Extraalimentary Tract Disease

A serum chemistry profile should be obtained to help rule out hepatic disease (alanine aminotransferase [ALT], serum alkaline phosphatase [SAP], blood urea nitrogen [BUN], and albumin), hypoadrenocorticism (sodium and potassium), hypercalcemia (calcium and albumin), uremia (creatinine, BUN, and urinalysis), and diabetic ketoacidosis (glucose and urinalysis). Very young patients (those < 12 to 14 weeks of age) should undergo blood glucose monitoring to avoid secondary hypoglycemia. More precise testing is occasionally required to diagnose these disorders (e.g., serum bile acids for hepatic insufficiency, adrenocorticotropic hormone [ACTH]-stimulation test for hypocortisolemia). Other tests to consider are serum gastrin for gastrinoma, and serum thyroxine for feline hyperthyroidism.

Pancreatitis

Acute pancreatitis is recognized commonly. Predisposing causes in dogs include hyperlipidemia, fatty meals, or obesity. Pancreatitis can occur in any dog, but middle-aged obese female dogs, schnauzers, and Yorkshire terriers seem to be most commonly affected. Vomiting may or may not be associated with eating, abdominal pain, fasting hyperlipidemia, bloody diarrhea, and rarely, diffuse subcutaneous fat necrosis. On radiographic examination, a mass or indistinctness (as the result of localized peritonitis) may be visible in the cranial right abdominal quadrant. Serum amylase and lipase activities can be measured, but false-negative and false-positive results are common, necessitating reliance on other findings. Leukocytosis with or without a left shift and with or without WBC toxicity (as the result of the sterile inflammation) and increased ALT and SAP concentrations (as the result of the proximity of the pancreas to the liver and obstruction of the biliary duct) are common. The latter occasionally causes extrahepatic biliary tract obstruction and subsequent icterus. Mild to moderate hypocalcemia may occur. Abdominal ultrasonography seems to be an excellent test for canine pancreatitis, and it usually reveals abnormalities in the

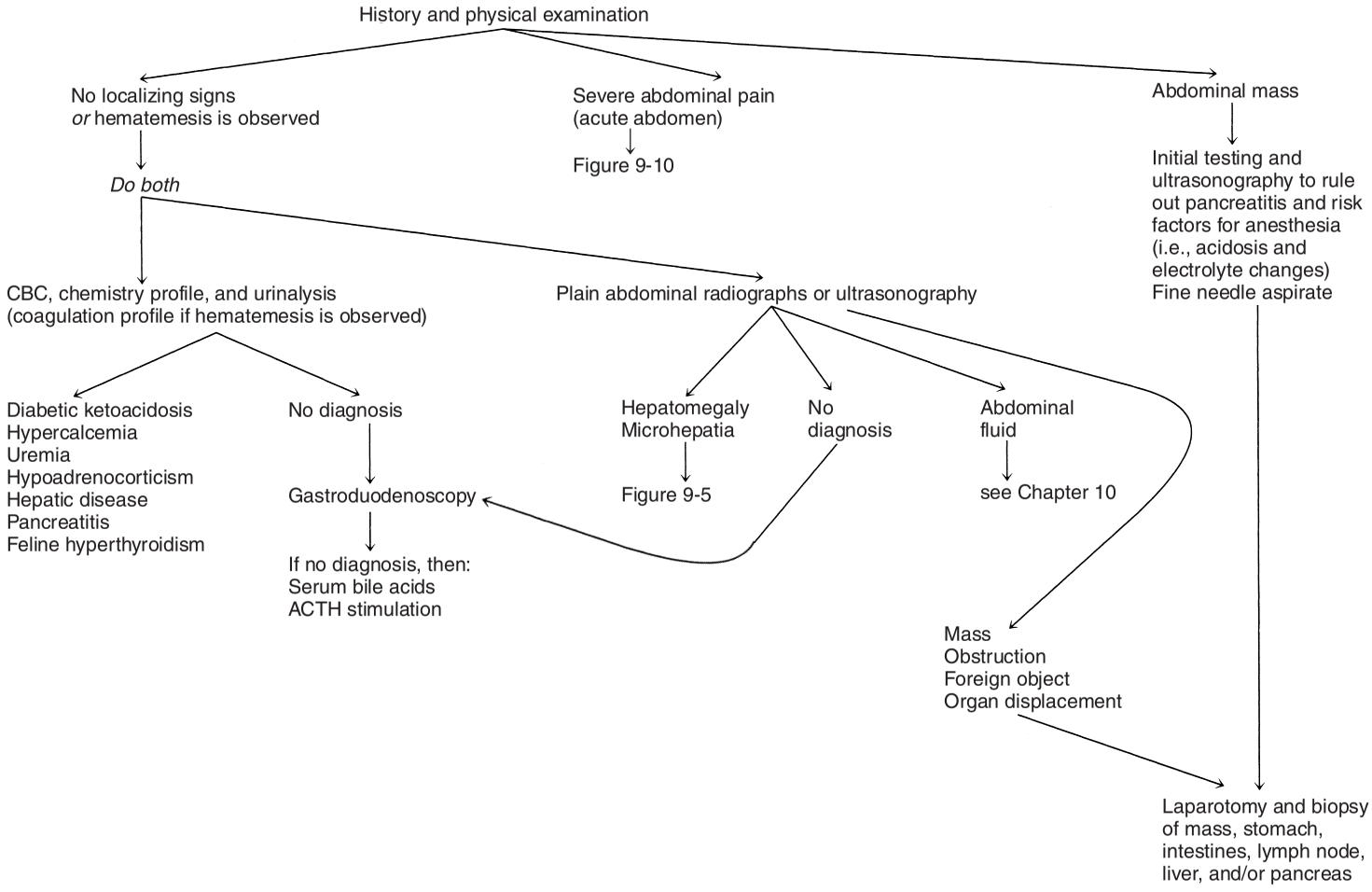

FIGURE 9-2. Diagnostic approach to chronic vomiting in a dog or cat that has been unresponsive to dietary change and anthelmintic therapy. *ACTH,* Adrenocorticotropic hormone; *CBC,* complete blood count.

pancreatic region. If a pancreatic mass is discovered during surgery, it must be biopsied; this is because chronic pancreatitis is grossly indistinguishable from pancreatic neoplasia, and both may be associated with normal or increased serum amylase and lipase values. Recently an assay for immunoreactive canine pancreatic lipase has been developed and validated (GI Laboratory at Texas A&M University); this test seems to hold promise for being a sensitive, specific test for acute pancreatitis.

Once considered rare in cats, pancreatitis is being recognized with increasing frequency in cats. Feline pancreatitis is more difficult to diagnose. Chronic pancreatitis is not uncommon in older cats, occurring in conjunction with cholangiohepatitis and sometimes with inflammatory bowel disease. The presence of the three diseases together has been referred to as "triaditis syndrome." Vomiting is not as prominent as in dogs. Amylase and lipase values are usually in the normal reference range; feline trypsin-like immunoreactivity (fTLI) concentrations are increased in some patients. Abdominal ultrasonography may be useful if an obvious abnormality is found, but the sensitivity of ultrasonography is uncertain. A pancreatic biopsy may be required for a definitive diagnosis. Feline pancreatitis occasionally is due to toxoplasmosis or to feline infectious peritonitis (FIP) (see Chapter 15).

Gastritis, Enteritis, and Colitis

Chronic enteritis, colitis, or gastritis can cause various degrees of vomiting and may require mucosal biopsy for diagnosis. Abdominal imaging may delineate infiltrative or inflammatory intestinal patterns. If gastritis or enteritis is suspected or if the other major causes of chronic vomiting have been ruled out, gastric and intestinal mucosal biopsies via endoscopy or laparotomy are indicated. Inflammatory bowel disease is a significant cause of feline chronic vomiting. Duodenitis is also a significant cause of vomiting without diarrhea in dogs; therefore, both gastric and intestinal biopsies should be performed. Finally, because 10% to 20% of patients with colitis vomit, it is useful to perform endoscopy routinely on both the upper and lower intestinal tracts in patients (especially cats) with chronic vomiting. It is critical that mucosal tissue samples be taken and handled properly to avoid artifacts, which can render them nondiagnostic.

Hematemesis

Hematemesis is the vomiting of blood. It suggests gastric ulceration. The character of the vomitus may be either bright-red blood or digested blood that resembles coffee grounds. Administration of nonsteroidal anti-inflammatory drugs (especially concurrently with corticosteroids) is a major reason for canine ulceration. Renal and hepatic failure, mast cell tumor, shock with poor mucosal perfusion, and coagulopathy must be considered. After these have been ruled out, endoscopy is indicated and allows diagnosis of ulceration (especially because of a foreign object, inflammatory disease, or neoplasia). Alternatively, one may treat symptomatically for ulceration; however, such treatment may allow progression of underlying disease.

Abdominal Inflammation

Septic or nonseptic peritonitis (or inflammation of any abdominal organ) may cause vomiting. Abdominocentesis or abdominal lavage (see Chapter 10) may be needed, especially if physical examination or abdominal imaging suggests abdominal fluid. Occult cases may require exploratory surgery for diagnosis.

Gastrinoma

Gastrinoma (e.g., Zollinger-Ellison syndrome) is a gastrin-secreting tumor of the pancreatic islet cells; it increases gastric acid production and produces duodenal ulceration. Gastrinoma is rare but has been diagnosed more commonly since the advent of reliable serum gastrin assays. No other typical, unique clinicopathologic tests exist that suggest this disease. Any chronically vomiting middle-aged or older dog with weight loss or diarrhea is a reasonable suspect. Duodenal ulceration and reflux esophagitis are common. Resting gastrin concentrations are usually increased, but in rare cases one must measure gastrin concentrations after administering food or secretin.

AMYLASE

Controversial Indications • Patients (especially obese) with vomiting, abdominal pain, nonseptic inflammatory abdominal exudate, icterus, or a prior history of pancreatitis.

Disadvantages • Poor sensitivity and poor specificity. Serum amylase activity does not correlate with the severity of pancreatitis.

Analysis • Measured in serum, heparinized plasma, or body fluid by spectrophotometric methods via amyloclastic, saccharogenic, and chromogenic techniques. Turbidimetric, nephelometric, and "dry reagent" methods may also be used.

NOTE: Different methods can give substantially different values. Some saccharogenic methods are affected by normal canine serum maltase concentrations and should not be used in dogs. Serum amylase activity is stable at room temperature for up to 7 days and at 4° C for as long as 1 month.

Normal Values • As with other enzymes, these vary among laboratories, depending on the technique and units used.

Danger Values • None.

Artifacts • See Introduction to Serum Chemistries.

Drug Therapy That May Cause Hyperamylasemia • Some drugs may occasionally cause pancreatitis (Table 9-3). Corticosteroids do not reliably increase serum amylase concentrations.

Causes of Hypoamylasemia • Insignificant. This finding does not support a diagnosis of pancreatic insufficiency.

TABLE 9-3. Drugs That May Cause Acute Pancreatitis

Asparaginase
Azathioprine
Calcium
Estrogens
Furosemide
Glucocorticoids (especially dexamethasone)
Isoniazid
Metronidazole
Potassium bromide (this is a reported but unproven association)
Salicylazosulfapyridine (Azulfidine)
Sulfonamides
Tetracycline
Thiazide diuretics

NOTE: These drugs do not reliably cause pancreatitis, and a history of administration of one of these drugs plus signs of pancreatitis cannot be assumed to be cause and effect. A patient with acute pancreatitis that is receiving one of these drugs, however, should undergo drug withdrawal, if possible.

Causes of Hyperamylasemia • Decreased glomerular filtration (i.e., azotemia) and pancreatitis are two causes. Hyperamylasemia as the result of renal dysfunction usually is less than two to three times the upper limit of normal. Patients with pancreatitis may have normal to markedly increased values. Intestinal disease, ruptured intestines, and hepatic disease *have been suspected* of causing increased serum amylase because of amylase present in these tissues. Serum amylase level is an unreliable indicator of pancreatitis in cats. Hyperamylasemia in a vomiting or anorexic animal is an indication to search for pancreatitis by CBC, serum chemistry profile (including ALT and SAP), abdominal imaging, serum trypsin-like immunoreactivity (TLI), or a combination thereof.

Causes of Increased Fluid Amylase • When abdominal fluid amylase is greater than serum amylase, a nonseptic exudate caused by pancreatic disease is possible. Bowel rupture may also be possible.

LIPASE

Controversial Indications • Same as for amylase.

Disadvantages • Questionable sensitivity and specificity; some dogs with duodenal foreign objects, chronic gastritis, and abdominal carcinomas have very increased serum lipase activity without evidence of pancreatitis. Serum lipase activity does not correlate with the severity of pancreatitis.

Analysis • Measured in serum or body fluids via dry reagent analysis. Turbidimetric and titrimetric techniques are rarely used.

Normal Values • As for other enzymes, these vary from laboratory to laboratory, depending on the technique and units used.

Danger Values • None.

Artifacts • See Introduction to Serum Chemistries.

Drug Therapy That May Cause Hyperlipasemia • Same as for amylase (see Table 9-3) plus heparin. Corticosteroids (dexamethasone) may increase serum lipase activity up to fivefold over baseline without

histologic evidence of acute pancreatitis; however, the lipase activity is usually only slightly greater than the reference range.

Causes of Hypolipasemia • Not significant. This finding does not support a diagnosis of pancreatic insufficiency.

Causes of Hyperlipasemia • These are similar to the causes of hyperamylasemia. Renal dysfunction increases serum lipase, usually less than two to three times normal, although it may rarely be more than four times normal. Not all patients with acute pancreatitis have increased serum lipase, and the increase in serum lipase activity is not proportional to the severity of the pancreatitis. Extremely increased lipase values have been associated with pancreatic carcinomas. Abdominal ultrasonography and increases in serum fTLI appear to be more useful than serum amylase or lipase in the diagnosis of feline pancreatitis. In addition to serum TLI, trypsin-activating peptide (TAP) and phospholipase A_2 have been investigated as tests for pancreatitis in dogs; however, none have become accepted as valued clinical tests.

CANINE IMMUNOREACTIVE PANCREATIC LIPASE

Common Indications • Patients (especially obese) with vomiting, abdominal pain, nonseptic inflammatory abdominal exudate, icterus, or a prior history of pancreatitis.

Advantages • Appears to be sensitive and specific and only requires a serum sample.

Disadvantages • Currently the only laboratory offering this test for dogs is GI Laboratory, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843-4474.

Analysis • Measured in serum by enzyme-linked immunosorbent assay (ELISA). See Appendix I for availability.

Normal Values • 2.2 to 102.1 µg/L.

Artifacts • Uncertain.

Causes of Decreased Values • Exocrine pancreatic insufficiency (EPI) or isolated pancreatic lipase deficiency. However, slightly more overlap exists between normal dogs and dogs with EPI than for serum TLI concentration. Thus serum TLI remains the test of choice for EPI.

Causes of Increased Values • Pancreatic inflammation is currently the only recognized cause of an increase. Further experience with this test may change the indications and interpretation of this test.

GASTRIN

Occasional Indications • Chronic vomiting, diarrhea, weight loss, suspected gastrinoma, or gastric or duodenal ulceration of unknown cause. This test is usually not requested until more common diseases have been ruled out.

Advantages • Detects otherwise occult gastrinomas.

Disadvantages • Requires radioimmunoassay (RIA) method (long turnaround time).

Analysis • Measured in serum by RIA. Serum should be frozen until assayed. See Appendix I for availability.

Normal Values • Dogs, depends on laboratory (the assay must be validated for dogs); cats, not established.

Conversion of pg/ml to ng/L: multiply pg/ml × 1.0 = ng/L.

Artifacts • Falsely decreased: hormone degradation as the result of storage for several days at temperatures above freezing.

Drug Therapy That May Increase Gastrin • Antacids including H_2 receptor antagonist drugs, and proton pump inhibitors.

Causes of Hypogastrinemia • Not significant.

Causes of Hypergastrinemia • Atrophic gastritis (uncommon), antral G-cell hyperplasia (rare), short bowel syndrome, hyperparathyroidism, ulcers, gastric outlet obstruction, renal failure, and gastrinoma are the main causes. The last four are the most common. Hepatic insufficiency does not appear to directly increase serum gastrin concentrations. If gastrinoma is suspected in a patient that has a normal or equivocal serum gastrin concentration, secretin or calcium stimulation tests

may be performed. A rise in the serum gastrin concentration after giving either of these drugs suggests a gastrinoma.

ACUTE DIARRHEA

Patients with diarrhea are best classified into those with acute (<2 to 3 weeks) versus those with chronic (>2 to 3 weeks) diarrhea. Acute diarrhea (Table 9-4) is usually self-limiting, although some conditions may be severe and cause mortality, such as acute hemorrhagic gastroenteritis, parvoviral disease, parasites (e.g., hookworms), or intoxication. History should explore the possibility of recent dietary change or exposure to infectious agents. Diet, bacteria, viruses, and parasites are the major identifiable causes of acute diarrhea in dogs and cats. Because intestinal parasites may contribute to any diarrheic state, multiple fecal examinations (direct and flotation) are warranted in all diarrheic patients. Giardiasis may be particularly occult and require special diagnostic techniques (see Fecal *Giardia* Detection).

Feeding with bland or hypoallergenic diets may be diagnostic and therapeutic. Depressed, weak, and dehydrated patients should undergo electrolyte and acid-base evaluations to aid in selecting fluid replacement therapy. All patients less than 12 to 14 weeks of age and those that are emaciated or weighing less than 5 pounds should undergo blood glucose monitoring to detect secondary hypoglycemia. Febrile or depressed patients should undergo CBC analysis so that sepsis or transmural inflammation can be detected. To identify the cause of acute diarrhea that is not the result of diet or parasites (such as that occurring in kennels, pet stores, shelters, and households where more than one member has diarrhea), fecal cultures for *Salmonella* spp., *Campylobacter jejuni*, *Yersinia enterocolitica*, verotoxin-positive *Escherichia coli*, and other pathogens plus viral identification methods (i.e., ELISA, electron microscopy) or toxin identification methods (i.e., ELISA for *Clostridium perfringen*s or *Clostridium difficile* toxins) or both may be used.

Not all patients with canine parvoviral diarrhea are severely ill, have identifiable leukopenia, have diarrhea, or have a fever. Leukopenia may persist as briefly as 24 to 36 hours and can easily be missed if a CBC is not performed during that period. Other diseases causing severe sepsis (i.e., perforating linear foreign body with peritonitis or overwhelming salmonellosis) can cause leukopenia indistinguishable from that of canine parvoviral diarrhea. Routinely used vaccination schedules do not necessarily guarantee protection against canine parvovirus. Finally, fecal shedding of viral particles may not occur for 1-3 days after signs begin and decreases rapidly with time. In-house ELISA tests for parvovirus are performed on the feces and appear to be accurate in identifying the parvoviral antigen, but testing may be negative if done too early or too late. The test result should be strongly positive within 3 days of the onset of clinical signs and remain positive for several days. A recent vaccination may result in a weakly positive fecal ELISA.

TABLE 9-4. Major Categories of Causes of Acute Diarrhea in Dogs and Cats

Intestinal Parasites
Hookworms
Roundworms
Whipworms
Coccidia
Giardia (sometimes difficult to diagnose)
Strongyloides
Tritrichomonas
Dietary Problems
Poor-quality food/food poisoning
Sudden dietary change (especially young animals)
Food intolerance/allergy
Acute Viral or Bacterial Enteritis
Parvovirus (canine and feline)
Coronavirus (canine and feline)
Clostridium perfringens
Campylobacteriosis
Salmonellosis
Escherichia coli (verotoxin-producing strains)
Intussusception
Intoxication
Garbage
Food poisoning
Heavy metal
Organophosphate
Hemorrhagic Gastroenteritis

CHRONIC DIARRHEA

Chronic diarrhea should first be defined as either small intestinal or large intestinal in origin, preferably by using the history and physical examination (Table 9-5). Occasionally, large and small intestines are concurrently involved. Patients with chronic diarrhea in which clinical disease is not severe are often treated with therapeutic trials before aggressive diagnostics are instituted. All patients should

TABLE 9-5. Differentiation of Chronic Small Intestinal from Chronic Large Intestinal Diarrhea

	SMALL INTESTINAL DIARRHEA	LARGE INTESTINAL DIARRHEA
Weight loss (most important criteria)	Expected	Uncommon except with histoplasmosis, pythiosis, or cancer
Polyphagia	Often present	Uncommon
Vomiting	May occur	Occurs in 10% to 20% of patients
Volume of feces	May be normal or larger than normal	May be normal or smaller than normal
Frequency of defecation	Normal to slightly increased	Normal to markedly increased, may have many small defecations per bowel movement
Slate-gray feces (steatorrhea)	Occasionally	No
Hematochezia	No	Sometimes present
Melena	Sometimes	No
Mucoid stools	Rare (unless ileum is diseased)	Often present
Tenesmus/dyschezia	Rarely present	Sometimes present

undergo at least three fecal examinations at 48-hour intervals. If these tests are negative, it is still acceptable to treat empirically for *Giardia* infection and whipworms before aggressive diagnostics are begun. Giardiasis may be particularly difficult to diagnose (see Fecal *Giardia* Detection) and medically manage. Adverse food reactions also cause chronic diarrhea. Dietary intolerances are a reaction to a particular substance in the diet, whereas true food allergies are immunologic reactions to specific antigens. Food reactions are common, especially in cats. Dietary food trials are indicated in suspected cases. Failing to respond to empiric therapy indicates the need for further diagnostics.

Large Intestinal Diarrhea

Once parasitism, dietary-responsive disease, and clostridial colitis are eliminated, additional simple diagnostic steps, such as rectal mucosal scrapings (not swabs) with cytologic examination (see Color Plate 3B) or fecal culture for *C. jejuni, Salmonella* spp., *Y. enterocolitica,* verotoxin-positive *E. coli*, or a combination of these might be appropriate. Persistent large intestinal disease is usually an indication for colonoscopy plus biopsy, especially if the animal has hypoalbuminemia or has lost weight. Rigid colonoscopy of the descending colon is adequate for diagnosis in most cases. Flexible endoscopy allows access to the descending, transverse, and ascending colon; ileocolic valve; cecum; and ileum. If flexible endoscopy is unavailable, abdominal ultrasonography or a barium enema may reveal lesions in areas not accessible with rigid endoscopy.

Small Intestinal Disease

Chronic and severe small intestinal diarrhea necessitates differentiation of maldigestion, protein-losing enteropathy (PLE), and malabsorptive disease without protein loss (Figure 9-3). Weight loss and diarrhea are usually present, but some patients only have weight loss.

Maldigestion

Maldigestion resulting from bile acid insufficiency as the result of biliary obstruction is rare. Intestinal lactase deficiency is uncommon, but a lactose-free diet may be tried in selected patients (especially cats). EPI is the most common cause of canine maldigestion but is rare in cats. Differentiation of EPI from malabsorptive disease is important. The diagnosis is often overlooked in afflicted dogs or may inappropriately be made in patients without the malady. Clinical trials using pancreatic enzyme preparations are commonly used to diagnose EPI. Unfortunately this method is unreliable. Powdered enzyme is often superior to tablet formulations, and some enzyme preparations are clearly superior to others. Even when appropriate enzymes are administered, some dogs with EPI also require a low-fat diet, antacid therapy (rare), or treatment for concurrent antibiotic-responsive enteropathy (ARE) (common) before the enzyme replacement therapy becomes effective. Too often, failure of the initial enzyme replacement therapy leads to unnecessary tests (i.e., exploratory laparotomy), because the correct diagnosis of EPI was incorrectly eliminated.

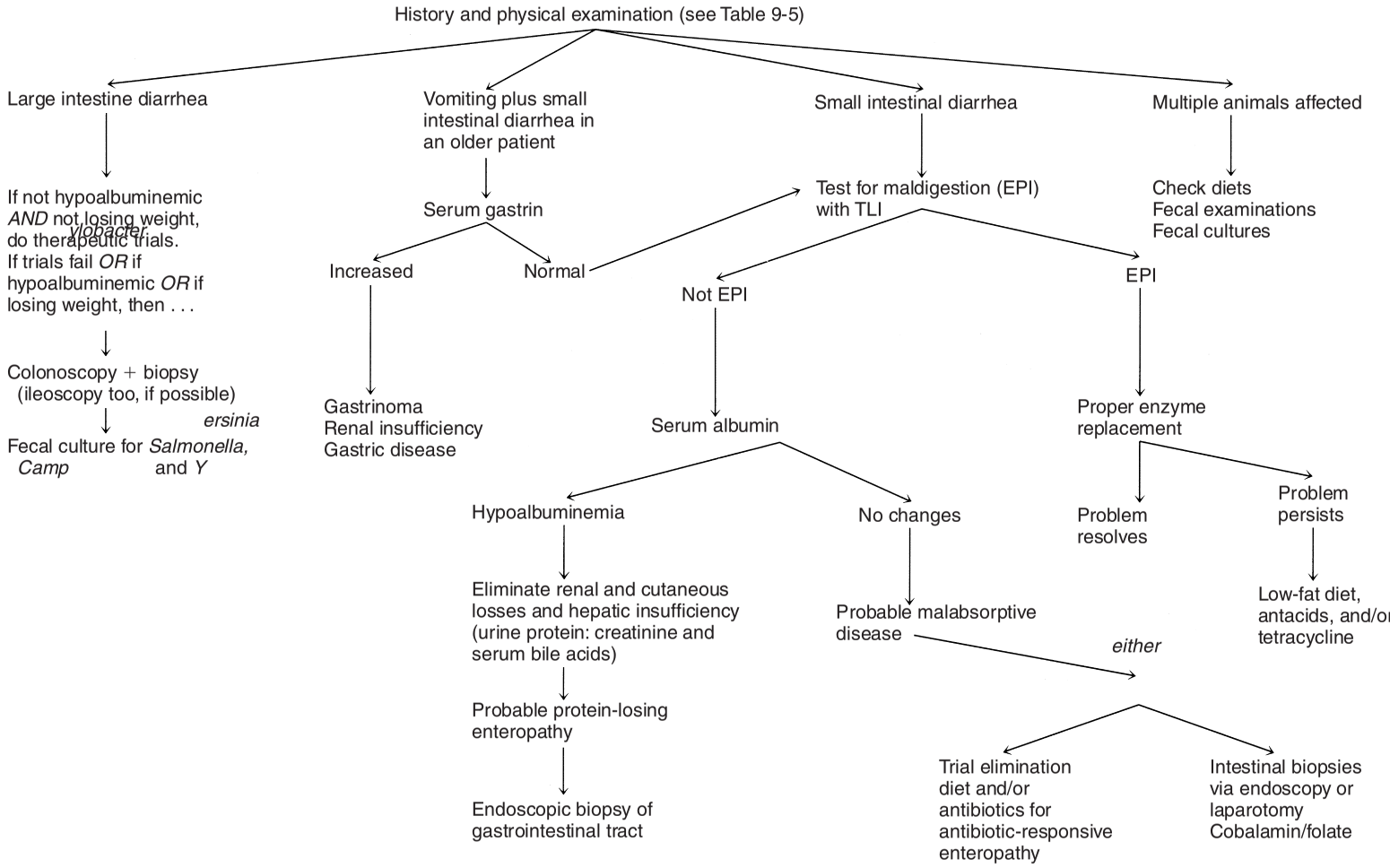

FIGURE 9-3. Diagnostic approach to chronic diarrhea in dogs and cats in which multiple fecal examination results are negative and empiric anthelmintic, antiprotozoal, and dietary therapy do not resolve the diarrhea. *EPI,* Exocrine pancreatic insufficiency; *TLI,* trypsin-like immunoreactivity.

No consistent hematologic or serum chemistry profile changes are seen, and the serum amylase and lipase values are usually normal. Undigested fats are often found in the feces; however, this is inconsistent. The fat absorption test is inexpensive but can yield false results. The TLI assay is the best test for canine EPI, and the fTLI assay is the best test for feline EPI. It is important to note that the tests are species specific. Measurement of trypsin proteolytic activity also is an accurate means of diagnosing feline EPI; however, it is more cumbersome and has limited availability.

Malabsorptive Disease Without Protein Loss

Once maldigestion has been accurately ruled out, malabsorption becomes the most likely diagnosis in diarrheic animals with weight loss. One must then decide whether to perform diagnostic therapeutic trials or diagnostic tests. A definitive diagnosis usually necessitates intestinal biopsy. Patients that are critically ill (i.e., are emaciated or have serum albumin <2.2 g/dl) usually should next undergo abdominal ultrasonography and intestinal biopsies (preferably via endoscopy). Patients that are not critically ill may be managed first using therapeutic trials. Therapeutic trials may be chosen more rationally with the aid of minimal laboratory data such as a CBC, biochemical profile, and fecal examinations. The two major therapeutic trials are (1) food trials for dietary intolerance and (2) antibiotic trials for ARE.

ARE (previously called "small intestinal bacterial overgrowth") may exist by itself or it may coexist with another GI malady. ARE may prevent therapy aimed at the underlying problem from resolving clinical signs. No consistent CBC or serum chemistry profile changes are seen in this syndrome. Fecal culture is not informative, and intestinal biopsy is seldom diagnostic. A barium contrast study may identify a segmental lesion or partial obstruction responsible for secondary ARE. Quantitated culture of duodenal or proximal jejunal fluid for aerobes and anaerobes is difficult to interpret, because clinically normal dogs may have as many or more bacteria than clinically affected dogs. Finding an increased concentration of unconjugated serum bile acids is believed to be supportive of ARE. Bacteria can deconjugate serum bile acids in the intestinal lumen, and these bile acids can be absorbed by the jejunum. However, the test is limited in its availability. Serum vitamin B_{12} and folate concentrations have been used as screening procedures for ARE once EPI has been ruled out. Some patients with ARE have normal serum vitamin B_{12} and folate concentrations, however. Response to empiric antibiotic therapy supports the diagnosis. Signs secondary to ARE usually respond to appropriate antibiotic therapy (e.g., tetracycline, tylosin, ampicillin, metronidazole) unless irreversible mucosal changes or a primary underlying intestinal disease are seen.

Dietary intolerance is relatively common, and hypoallergenic diets (e.g., fish and potato, turkey and potato, tofu and beans) are reasonable trials. At least 4 weeks (and preferably 6 to 8 weeks) should be allotted for such a dietary trial, during which time absolutely nothing else should be fed (including flavored treats or medications).

If dietary, antibiotic, and repeated anthelmintic and antiprotozoal therapies are ineffective, small intestinal biopsy is probably necessary. Laparotomy, laparoscopy, or endoscopy may be used. In most patients, the stomach, duodenum, ileum, and colon may be endoscopically sampled. Duodenal cytology is helpful in some disorders (e.g., eosinophilic enteritis, purulent enteritis, giardiasis, lymphoma). If laparotomy is performed, multiple representative full-thickness specimens (e.g., stomach, duodenum, jejunum, ileum, mesenteric lymph node) are indicated, because lesions can be sporadic. If endoscopy is performed, multiple specimens (e.g., ≥ 8) from each site are obtained. It is critical that the endoscopist be accomplished and trained in obtaining high-quality tissue samples. Many endoscopic biopsies obtain nondiagnostic samples because of the operator's lack of training in this area.

Protein-Losing Enteropathy

PLEs are often characterized by a decrease in serum concentrations of both serum albumin and globulin, which are lost through the GI tract. PLE is uncommon in cats but seen with some regularity in dogs. Dogs with inflammatory diseases causing hyperglobulinemia and some breeds (e.g., Basenji dogs) may have only hypoalbuminemia. This occurs because the serum globulin concentration is greatly increased, and even though much of this fraction is lost into the intestines, the amount remaining keeps concentrations in the normal range. If red blood cells (RBCs)

are also being lost, iron-deficiency anemia may occur (see Chapter 3).

PLE may be the result of various GI diseases (e.g., hookworms, chronic intussusception, fungal infections, ulcers and erosions), but inflammatory bowel disease, alimentary lymphosarcoma, and lymphangiectasia are the most common causes in adult dogs. Intestinal lymphangiectasia causes severe PLE in dogs (it is not reported in cats) and can produce some of the lowest serum protein levels (serum albumin < 1.0 g/dl) that occur in alimentary disease. Because of the loss of lymph into the intestines, peripheral lymphocyte counts may be decreased; hypocholesterolemia and steatorrhea are common. If hepatic insufficiency and loss from the kidneys and skin have been eliminated in a hypoalbuminemic patient, PLE becomes the major differential diagnosis by process of elimination. If PLE is suspected in a patient that has another potential explanation for its hypoalbuminemia (e.g., renal protein loss or substantive hepatic insufficiency), then detecting abnormally high concentrations of alpha-1 protease inhibitor in the feces supports a diagnosis of GI protein loss. The relatively stable alpha-1 proteinase is resistant to GI degradation and consequently can be measured in the feces. Intestinal biopsy is usually the definitive test. Full-thickness biopsy may risk dehiscence if the serum albumin level is less than 1.5 g/dl; however, serosal patch graft techniques decrease the risk of dehiscence. Gastroduodenoscopy-ileoscopy plus biopsy is safe and often (but not invariably) diagnostic. Occasionally the intestinal lesion is inaccessible via endoscopy. Although not recommended, dietary trial may be used in patients with PLE. An ultra-low–fat diet is reasonable if lymphangiectasia is suspected; however, therapeutic trials with steroids are potentially dangerous and are not recommended without a definitive diagnosis.

FECAL CHARACTER

Mucoid feces should be approached as a large intestinal or a distal small intestinal problem. In dogs and cats that have large bowel disease but no weight loss or hypoalbuminemia, multiple fecal examinations, digital rectal examination, and therapeutic trials (i.e., dietary, antibacterial or anthelmintic [or both]) are often the best initial steps. If these are unsuccessful, then colonileoscopy plus biopsy generally becomes the most useful diagnostic tool. Hematochezia should also be considered as a large bowel problem. Melena signifies swallowed blood from any source, coagulopathy, or gastric and upper intestinal bleeding. Therefore before performing an exploratory laparotomy, one should consider all the possible causes of oral bleeding (e.g., coughing up blood from the respiratory tract, posterior nasal bleeding). Ingestion of bismuth subsalicylate (Pepto-Bismol) or liver can cause feces to appear melenic. Diet and changes in intestinal bacterial flora influence fecal color but do not generally signify disease.

FECAL ENZYME-LINKED IMMUNOSORBENT ASSAY FOR PARVOVIRUS

Occasional Indications • Dogs suspected of having parvoviral enteritis (especially those not displaying classic signs); acute neutropenia of unknown cause.

Advantages • Quick, available, has good sensitivity and specificity if done at the appropriate time (e.g., approximately 1-3 days after onset of clinical signs).

Disadvantages • Dogs with parvoviral enteritis can have negative reactions, especially early in the course.

Analysis • Fresh feces, preferably taken from a dog that has begun to show signs in the last 24 to 36 hours, are used according to kit instructions (see Chapter 15). The instructions must be carefully followed or false results might be obtained.

Normal Values • Dogs should not have parvoviral antigen in feces.

Interpretation • A positive result supports canine parvoviral enteritis. Not all dogs affected with parvoviral enteritis have diarrhea and fever; some show only anorexia, vomiting, or fever. Theoretically, if coproantibody binds all of the antigen in the feces, a false-negative result may occur. If the test is performed too early in the disease, it may yield negative results. With such dogs, one should repeat the test in 36 to 48 hours. Shedding of viral particles decreases after the first week of disease, and a test performed too late in the disease might yield negative results. Modified-live vaccination results in transient fecal shedding

and can give a weak positive fecal ELISA test result (5 to 15 days after vaccination).

FECAL ANALYSIS FOR CLOSTRIDIAL TOXINS

Occasional Indications • Dogs with acute, nosocomial diarrhea or chronic large bowel diarrhea of unknown cause.

Advantages • Relatively easy to perform.

Disadvantages • Might be difficult to interpret results, especially of old fecal samples. Uncertain sensitivity and specificity for *Clostridium perfringens*—associated diarrhea.

Analysis • Fresh or frozen feces used according to the instructions on the test kit. Reversed passive latex agglutination (RPLA) and ELISA (i.e., *Clostridium perfringens* Enterotoxin Test, TechLab, Blacksburg, VA) methods are available for *Clostridium perfringens* enterotoxin. ELISA methodology is available to look for *Clostridium difficil*e toxin A (ImmunoCard Toxin A, Meridan Diagnostics, Cincinnati OH).

Interpretation • Finding *Clostridium perfringens* enterotoxin in feces plus clinical signs of clostridial diarrhea has been considered diagnostic of clostridial colitis. Results from ELISA methodology appear to correlate better with disease than do results from RPLA methodology. However, production of enterotoxin does not appear to be a consistent event (i.e., found in every bowel movement), especially in the later course of disease. In suspected cases with a negative toxin assay, it might be useful to wait and repeat the test again at the onset of recurrence of clinical signs or perform a therapeutic trial with amoxicillin or tylosin.

Fecal spore counts do not correlate well with *Clostridium perfringens* enterotoxin production or with the presence of diarrhea. Examining fecal smears (see Fecal Microscopic Cytology) to look for the presence of spores no longer seems to be an acceptable screening procedure (e.g., clinically normal dogs may have spores in their feces and be positive for enterotoxin by RPLA).

Finding evidence of *Clostridium difficile* toxin A in feces of diarrheic patients seems suggestive of a cause-and-effect relationship, but this is currently being investigated.

FECAL CULTURE

Occasional Indications • Dogs and cats with persistent diarrhea (especially large bowel) of unknown origin, suspected contagious diarrhea, or a suspected infectious cause (e.g., diarrhea with concurrent fever, leukocytosis, neutrophilic fecal cytology, bloody diarrhea). Enteric pathogens include *C. perfringens, Salmonella* spp., *C. jejuni,* verotoxin-positive *E. coli*, *Clostridium perfringens, Clostridium difficile,* and *Y. enterocolitica.*

Disadvantages • Must specify which pathogens to culture, must provide the laboratory with fresh feces or feces submitted in appropriate transport media, and requires a microbiology laboratory familiar with the specific enrichment and isolation techniques for each pathogen for which a culture is attempted. Using culture swabs is not adequate for isolation of most enteric pathogens. Finally, growing a "pathogen" does not mean that it is responsible for clinical signs.

Analysis • Fresh feces must be promptly submitted to the laboratory, and the laboratory must know the specific pathogen(s) sought. To submit old feces or feces that have not been collected or handled properly or to request a "general culture for pathogens" is generally a waste of time and money. It requires laboratories that are properly equipped to culture for enteric pathogens. Culture for *C. perfringens* and *Clostridium difficile* in particular is not usually diagnostically useful.

Interpretation • Small numbers of any of the pathogens listed earlier might be found in normal pets, although *Y. enterocolitica* is particularly uncommon in the United States. Interpretation of the fecal culture must consider the history, physical examination, laboratory data, and sometimes numbers of pathologic organisms (i.e., number of bacterial colony-forming units per gram of feces) found. With diarrhea from any cause, the GI flora may change from a predominately anaerobic to a gram-negative aerobic population.

FECAL FAT

Rare Indications • To detect malabsorption or maldigestion in animals with diarrhea or unexplained weight loss.

Advantages (Semiqualitative Analysis) • Minimal expense, availability, and reasonable accuracy as a screening test.

Disadvantages (Semiqualitative Analysis) • Occasionally misleading results.

Advantages (Quantitative Analysis) • Very sensitive.

Disadvantages (Quantitative Analysis) • Expense, difficulty in collecting and storing feces and in differentiating between the causes of steatorrhea.

Analysis • The clinician performs a semiqualitative analysis for undigested fats by mixing a drop of fresh feces with a drop of Sudan III, heating the slide to a boil, and examining the smear microscopically. The clinician performs analysis for digested fats by mixing 1 drop of fresh feces, 1 drop of 36% acetic acid, and 1 drop of Sudan III. This is put on a microscope slide, heated to boiling, and examined while still warm. In both cases, identifying orange droplets is a positive finding. It is important that the patient has been eating a moderate- to high-fat diet. Feeding low-fat diets to malabsorptive dogs may cause the test result to be negative.

Quantitative analysis is rarely indicated or performed. The technique is described in prior editions.

Normal Values • Semiqualitative: few or no undigested and digested fat globules per high-power field (hpf).

Artifacts • The semiqualitative analysis may have unexplained false-negative and false-positive reactions. Administration of barium sulfate, bismuth, psyllium fiber, mineral oil, or castor oil or feeding a low-fat diet may also confuse semiqualitative analysis.

Drug Therapy That May Alter Measurement of Fat Excretion • Decreased excretion may be caused by medium-chain triglyceride oil supplements (titrimetric analysis). Increased quantitated fat excretion may be caused by azathioprine, orally administered aminoglycosides, and cholestyramine.

Causes of Increased Fecal Fat • Finding several orange globules/hpf, if repeatable on several examinations, is principally caused by malabsorption or maldigestion. It is a reasonable screening test and helps distinguish maldigestion because of EPI (positive for undigested fats) from malabsorption (positive for digested fats). Despite occasional false-positive reactions, strongly positive results for undigested fecal fat in a dog with signs consistent with maldigestion are an indication for more specific tests (e.g., TLI). Questionable results on the semiqualitative test should always be followed by more specific tests. With Sudan staining, fecal fat may not be detectable in some dogs with EPI.

FECAL STARCH

Rare Indications • Chronic diarrhea or weight loss.

Advantages • Low cost and availability.

Disadvantages • Negative and positive results that do not correlate with malabsorption and maldigestion. This test is *not recommended*.

Analysis • Fecal smears are stained with 2% Lugol's iodine. Starch granules show up as dark blue-black granules when viewed microscopically.

Normal Values • Rare (0 to 5) granules/hpf, although this may vary with the diet.

Artifacts • Falsely increased: contamination of feces with food. Unexplained false-positive and false-negative results may also occur.

Drug Therapy That May Affect Fecal Starch • Some diets may have more fecal starch excretion than others.

Causes of Amylorrhea • EPI is most likely, but high-starch diets or conditions causing increased intestinal transit may cause amylorrhea. Amylorrhea in a patient with weight loss or diarrhea is an indication for serum TLI.

FECAL MUSCLE FIBERS

Rare Indications • Chronic, small bowel diarrhea or weight loss that is difficult to diagnose.

Advantages and Disadvantages • Same as for fecal starch. This test is *not recommended*.

Analysis • A fresh fecal smear is stained with 2% Lugol's iodine, new methylene blue (NMB), or Wright's stain.

Normal Values • Dogs, muscle fibers should not be visible; cats, assumed to be similar to dogs.

Therapy That May Alter Fecal Muscle Fiber Determination • Some diets result in more fecal muscle fibers than others. Administration of barium sulfate, mineral oil, magnesium, or bismuth may make fiber identification difficult. A meat-free diet renders this test useless.

Causes of Creatorrhea • EPI is possible, and TLI is indicated.

FECAL PROTEOLYTIC ACTIVITY

Rare Indications • To detect maldigestion in animals with chronic diarrhea or weight loss of unknown cause.

Advantages • Theoretically this test may diagnose EPI in rare patients that have EPI secondary to obstruction of the pancreatic duct or ducts.

Disadvantages • The radiograph film digestion test is useless and should never be used. The most reliable procedure for measuring fecal proteolytic activity is difficult to perform and requires special handling of the feces; it is described in prior editions.

Analysis • Described in prior editions. The fTLI test has replaced measurement of fecal proteolytic activity as the diagnostic test of choice for EPI in cats.

FECAL ALPHA-1 PROTEASE INHIBITOR ACTIVITY

Infrequent Indications • Hypoalbuminemia of uncertain cause or suspected PLE.

Advantages • Specifically indicates the GI tract as the source of protein loss. Alpha-1 protease inhibitor is a plasma protein, which, if leaked into the intestinal lumen, is resistant to GI degradation and hence can be measured in the feces. The amount of alpha-1 protease inhibitor reflects the approximate loss of plasma proteins into the GI tract.

Disadvantages • Limited availability of the test. The magnitude of alpha-1 protease inhibitor in the feces is variable and may not reflect the severity of the disease.

Analysis • Three 1 g fecal samples from three different bowel movements are submitted in tubes provided by the laboratory. It is critically important that three samples (preferably from different days or at least different bowel movements) be submitted, that the feces be collected promptly after defecation, and that the feces not be collected by digitally removing them from the rectum. Samples must be frozen while one awaits shipping and must be shipped on a cold pack. Currently the only laboratory offering this test for dogs is GI Laboratory, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843-4474.

Normal Values • 0.23 to 5.67 μg/g feces.

Causes of Abnormalities • Abnormally high values in the feces indicate loss of serum proteins into the alimentary tract and might indicate that PLE is the cause of hypoalbuminemia. Interpretation of the magnitude of the loss is as per the laboratory.

FECAL MICROSCOPIC CYTOLOGY

Frequent Indications • Large or small intestinal diarrhea.

Advantages • Availability and ease of performing the test.

Disadvantages • Variable specificity for a particular causative factor.

Analysis • Thin, air-dried, fresh fecal smears are stained with NMB or Wright's stain and examined using high-power and oil immersion. Rectal and colonic mucosal scraping obtained with a curette is also a means of examining mucosal cells.

Normal Values • A mixed population of rod and cocci bacteria, few bacterial spores or yeast, occasional epithelial cells and amorphous debris.

Artifacts • Old fecal sample (white blood cells [WBCs] do not remain identifiable in feces for long times, and the bacterial population

changes and bacterial spores may increase). Fecal debris may resemble degenerate WBCs.

Drug Therapy • Administration of barium and psyllium fiber may make interpretation difficult, and antibiotics change bacterial flora composition.

Causes of Abnormalities • Fecal WBCs (specifically neutrophils) are observed with bacterial (e.g., salmonellosis, campylobacteriosis) and inflammatory mucosal disease. Transmural colitides occasionally have increased fecal WBCs. Fecal WBCs are an indication to culture for specific bacterial pathogens or to biopsy colonic mucosa. Eosinophils may be visible with allergic or parasitic colitis. Increased numbers of yeast, fungal organisms, or a uniform population of bacteria may help identify the cause of diarrhea in a patient.

FECAL OCCULT BLOOD

Rare Indications • To detect GI bleeding that is not apparent grossly (i.e., melena, hematochezia).

Disadvantages • See Artifacts.

Analysis • Fresh feces are smeared on a test pad. The patient must have been on a meat-free diet for at least 3 days before the feces are obtained. Sensitivity varies markedly between assays.

Normal Values • See Artifacts.

Artifacts • Falsely decreased: sampling unmixed feces (blood may not be distributed homogeneously throughout the feces) and vitamin C supplementation. Falsely increased: diets containing fresh meats (i.e., hemoglobin) or fresh uncooked vegetables (i.e., peroxidases), which cause a positive reaction.

Causes of Fecal Occult Blood • Bleeding into the GI tract at any level and as the result of any cause may result in fecal occult blood. GI blood loss of volumes of 2 ml blood/30 kg body weight will give positive results.

FAT ABSORPTION TEST

Rare Indications • To detect and distinguish maldigestion from malabsorption in chronic small intestinal diarrhea or unexplained weight loss. Despite low cost and availability, this test has many false-negative and false-positive results and is *not recommended.*

Analysis • The test is described in prior editions.

BENTIROMIDE

Rare Indications • Because of the accuracy and the availability of the TLI test, the bentiromide (BT-PABA) test is rarely used and is *not recommended.*

TRYPSIN-LIKE IMMUNOREACTIVITY

Common Indications • Chronic small bowel diarrhea or weight loss.

Advantages • High sensitivity and specificity for EPI. Only need one serum sample that does not require special or cumbersome handling procedures, and most large veterinary diagnostic laboratories can perform this test for dogs.

Disadvantages • Currently the only laboratory offering the fTLI test (for cats) is the GI Laboratory, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843-4474.

Analysis • Performed on serum using ELISA. See Appendix I for availability.

Normal Values • Dogs, 5 to 35 μg/L (Figure 9-4); cats, 12 to 82 μg/L.

Danger Values • None.

Artifacts • Theoretically, EPI caused by an obstructed pancreatic duct instead of acinar cell atrophy would yield a normal or even increased serum TLI value.

Drug Therapy That May Alter TLI • Drugs causing acute pancreatitis (see Table 9-3) might increase serum TLI. Oral pancreatic enzyme supplementation does not affect serum TLI concentrations.

Causes of Decreased TLI • A serum TLI concentration less than 2.5 μg/L (dog) or

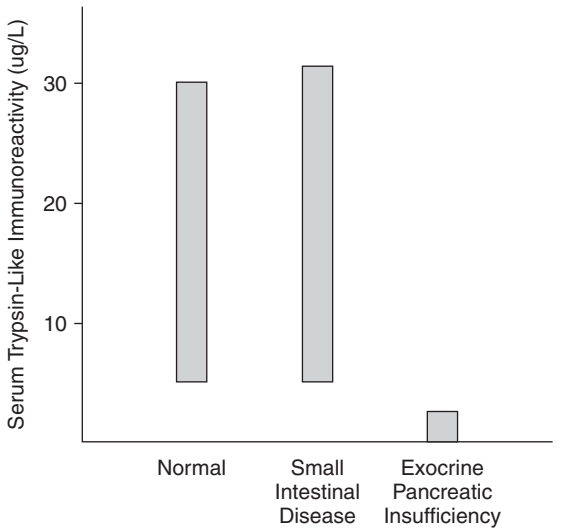

FIGURE 9-4. Typical ranges of trypsin-like immunoreactivity (TLI) values in normal dogs, dogs with small intestinal disease, and dogs with exocrine pancreatic insufficiency (EPI). (Modified from Williams DA: Sensitivity and specificity of radioimmunoassay of serum trypsin-like immunoreactivity for the diagnosis of canine exocrine pancreatic insufficiency, *J Am Vet Med Assoc* 192:195, 1988.)

8 µg/L (cat) is generally considered diagnostic for EPI, and TLI is considered to be the test of choice for EPI (see Figure 9-4). Subclinical canine EPI may be suspected by finding intermediate values (>2.5 µg/L and <5.0 µg/L). In such cases repeated testing should be performed. Some dogs will later develop EPI, whereas others will not.

Causes of Increased TLI • Values greater than 50 µg/L in dogs and greater than 100 µg/L in cats may occur with pancreatitis, renal failure, prerenal azotemia (may increase two times), and malnutrition. The fTLI test seems to be more specific for the diagnosis of pancreatitis in cats than amylase or lipase; however, the fTLI test is not clearly as sensitive or specific for feline pancreatitis as pancreatic biopsy. In dogs, TLI seems to increase early in pancreatitis but then returns to reference ranges.

ORAL GLUCOSE ABSORPTION TEST

Rare Indications • It is *not recommended* for evaluating the GI tract. See prior editions for description.

STARCH DIGESTION TEST

Rare Indications • Same as for oral glucose absorption test.

D-XYLOSE ABSORPTION TEST

Rare Indications • It is *not recommended* for evaluating the GI tract. It is described in prior editions.

SUGAR PERMEABILITY TESTING

Rare Indications • To confirm small intestinal disease that is not obviously apparent with other testing.

Advantages • This test is a sensitive means of detecting intestinal dysfunction that may not be obvious clinically. It may also detect post-treatment or post-dietary changes in intestinal function that are not obvious clinically.

Disadvantages • Currently one cannot correlate a specific disease with test results. The only laboratory currently offering this test for dogs is the GI Laboratory, College of Veterinary Medicine, Texas A&M University, College Station, TX 77843-4474.

Analysis • A solution of 2 to 5 sugars obtained from the laboratory is administered orally. Six hours later a spot urine sample is obtained and placed in a container with sodium azide to prevent bacterial degradation of the sugars. The concentration of the sugars is determined with high-pressure liquid chromatography, and the ratio of specific sugars is calculated. Results are interpreted as per the laboratory.

SERUM VITAMIN B_{12} AND SERUM FOLATE

Occasional Indications • Chronic small bowel diarrhea, unexplained weight loss, or uncertain but suspected small intestinal disease.

Advantages • Need only one serum sample.

Disadvantages • Uncertain sensitivity and specificity for small intestinal disease, ARE,

or EPI. This test should be used as an adjunct to other tests for maldigestion and malabsorption syndromes. The test is specific for cobalamin deficiency.

Analysis • Measured in serum by bioassay or immunoassay. "No boil" methods are unreliable in dogs. Serum should be transported in a covered tube.

Normal Values • Depend on the laboratory. Normal ranges vary widely between laboratories. The particular laboratory must validate the assay for dogs or cats.

Danger Values • None.

Artifacts • Falsely decreased vitamin B_{12}: degradation caused by exposure of serum to sunlight.

Drug Therapy That May Alter Serum Vitamin B_{12} Concentrations • Dietary content or vitamin supplementation of vitamin B_{12} and folate can affect serum concentrations. Drugs that affect intestinal bacterial concentrations (antibiotics or antacids) may also alter values.

Causes of Decreased Serum Vitamin B_{12} Concentrations • The major recognized reasons for decreased serum B_{12} concentrations in dogs and cats are ileal disease or resection (rare), EPI, intestinal mucosal disease, ARE, and in cats, hepatic disease. The major differentiation to be made is among EPI, mucosal disease, and ARE; therefore, decreased serum B_{12} is an indication for serum TLI. Not all dogs with EPI, mucosal disease, or ARE have decreased serum vitamin B_{12}. Cats with EPI, severe small intestinal disease (e.g., lymphoma, inflammatory bowel disease), and some hepatic diseases (e.g., idiopathic hepatic lipidosis) can have very low B_{12} concentrations. Finding a significantly decreased serum B_{12} concentration can be an indication of small intestinal disease in animals that were previously not suspected to have such disease.

Causes of Increased Serum Vitamin B_{12} Concentrations • Vitamin B_{12} supplementation.

Causes of Decreased Serum Folate • Severe mucosal disease of the proximal small intestine decreases serum folate. Not all patients with such disease have decreased folate levels.

Causes of Increased Serum Folate • ARE, EPI, and dietary supplementation are probably the major causes. Many patients with these diseases do not have increased folate levels. The combination of low vitamin B_{12} plus increased folate is an indication to treat for ARE.

HYDROGEN BREATH TEST

Rare Indications • Chronic small bowel diarrhea or unexplained weight loss. The test detects hydrogen production as a by-product of bacterial fermentation of carbohydrates. Increase in hydrogen production indicates ARE or carbohydrate malabsorption.

Advantages • Ease of the test and its lack of invasiveness.

Disadvantages • Need for special equipment, unknown sensitivity and specificity, multiple confounding factors. This is not a routine diagnostic test, because it requires special hydrogen analysis equipment.

Analysis • The concentration of hydrogen in expired air is measured after ingestion of food or a carbohydrate such as D-xylose or lactulose.

Normal Values • Dogs, varies with laboratory analysis and the carbohydrate administered.

Artifacts • Abnormal intestinal motility may delay or hasten expiration of hydrogen owing to colonic bacterial fermentation of carbohydrates.

Drug Therapy That May Alter Hydrogen Breath Test • Antibiotics and drugs that delay intestinal transit may cause decreased or delayed expiration of hydrogen.

Causes of Decreased Expired Hydrogen • Normal.

Causes of Increased Expired Hydrogen • Carbohydrate malabsorption and ARE may increase expired hydrogen. The only source of hydrogen is bacterial fermentation of carbohydrates. The sensitivity and specificity of this test for ARE in dogs are unknown.

FECAL SMEAR (WET MOUNT) FOR PARASITES

Common Indications • A screen for parasites and parasitic ova; any patient with diarrhea, melena, hematochezia, fecal mucus, weight loss, or vomiting.

Advantages • Availability, ease of performing the test, and low cost.

Disadvantages • Need for fresh feces and the frequency with which parasites and their ova or cysts are not detected.

Analysis • A thin smear is made of very fresh (< 5 minutes old) feces, usually mixed with a drop of saline solution and coverslipped to prevent dehydration. It should be examined immediately. If protozoa are visible and better cytologic detail is desired, a drop of Lugol's iodine or Dobell and O'Connor's iodine may be placed at the corner of the coverslip.

NOTE: Iodine kills protozoa, thus stopping motility.

Normal Values • Dogs and cats, no parasites or ova.

Artifacts • Cooling of the slide or dehydration inhibits the motility of some protozoa and bacteria.

Drug Therapy That May Alter Results • Orally administered compounds containing kaolin, pectin, barium sulfate, bismuth, and other intestinally active compounds (e.g., cathartics, enemas) may make it difficult to find and identify parasites, ova, and cysts.

Parasites, Bacteria, and Ova That May Be Identified • This test is most useful in identifying *Giardia* spp., *Tritrichomonas* spp., *Entamoeba histolytica, Balantidium coli, Strongyloides stercoralis*, and *Aleurostrongylus abstrusus*. Any ova may be found, but this test may be useful for detecting *Spirocerca lupi* and *Trichuris vulpis* ova. With oil immersion, small motile bacterial spirochetes in conjunction with fecal WBCs suggest *Campylobacter* spp. as a possible cause.

FECAL FLOTATION

Common Indications • As for fecal smear.

Advantages • Sensitivity, availability, and low cost.

Analysis • Feces are well mixed with either a saturated sugar solution or a zinc sulfate solution (Leib, 1999). (Zinc sulfate solution is made by mixing 331 g $ZnSO_4$ • 7 H_2O in 1 L water to attain a specific gravity of 1.18 to 1.20 [as determined with a hydrometer]. This is supposedly the best fecal flotation technique for *Giardia* spp. because it does not distort the cysts.) Ova and cysts are allowed to rise to the surface and are retrieved with a coverslip. Samples for *Giardia* detection should be examined within 15 minutes to avoid distortion and lysis of cysts. Centrifugation of the sample increases the sensitivity of the procedure. Samples that will be sent to an outside laboratory for analysis may be refrigerated (not frozen) for 1 to 2 days or preserved by mixing 1 part feces with 3 parts sodium acetate—acetic acid—formalin. This is prepared by mixing 1.5 g sodium acetate + 2 ml glacial acetic acid + 4 ml 40% formaldehyde solution + 92.5 ml water (Kirkpatrick, 1987).

Normal Values • Dogs and cats, no ova or oocysts present.

Artifacts • Falsely decreased: Diarrhea may decrease ova concentration within a sample.

Parasite Ova and Cysts That May Be Identified • *Ancylostoma* spp., *Toxocara* spp., *Toxascaris leonina*, *T. vulpis, S. lupi, Physaloptera rara* (using dichromate solution), *Capillaria aerophilia*, *Capillaria plica, Onciolo canis, Dioctophyme renale, Isospora* spp., *Giardia* spp., *Toxoplasma gondii, Cryptosporidium* spp., *Paragonimus kellicotti,* and some tapeworms.

FECAL SEDIMENTATION

Rare Indications • Same as for fecal smear and flotation, especially if flukes are being considered. If feces contain excessive fat, formalin and ethyl acetate is probably better than water sedimentation.

Disadvantages • Requires more time than direct fecal smear or fecal flotation.

Analysis • Feces are mixed with the sedimentation solution (e.g., water), usually strained once or twice to remove large debris, and

allowed to settle for 30 minutes to 2 hours. The sediment is then examined microscopically. When formalin and ethyl acetate is used, the strained feces are centrifuged, the pellet is resuspended in 9 ml of 5% formalin solution, 3 ml ethyl acetate is added, and the mixture is shaken vigorously. This is recentrifuged, the debris at the formalin and ethyl acetate interface is discarded, and the sediment is then examined (Kirkpatrick, 1987).

Normal Values • Dogs and cats, no ova.

Artifacts • Same as under Fecal Flotation.

Parasite Ova That May Be Identified • All the ova that may be found by fecal flotation, plus *Alaria canis* and *Nanophyetus salmincola*.

FECAL *GIARDIA* DETECTION

Occasional Indications • Chronic diarrhea, unexplained weight loss, intermittent bilious vomiting, or when *Giardia* is suspected clinically and multiple (i.e., at least 3) zinc sulfate flotations using centrifugation are negative. Techniques include duodenal aspiration and cytology, fecal ELISA antigen test (e.g., ProSpecT Microplate ELISA Assay for *Giardia*, Alexon, Lenexa, KS), and IFA (e.g., MeriFlour *Cryptosporidium/Giardia*, Meridian Diagnostics, Cincinnati, OH) performed on feces.

Advantages • Provides additional methods for detection of *Giardia*.

Disadvantages • Duodenal aspirates require surgery or endoscopy.

Analysis • Duodenal fluid aspirates require fresh direct wet-mount observation of motile trophozoites. Fresh samples should be used for analysis with fecal ELISA and fecal IFA.

Normal Values • No trophozoites or fecal antigen present.

FECAL *CRYPTOSPORIDIUM* DETECTION

Rare Indications • Chronic diarrhea. Cats (especially with feline immunodeficiency virus [FIV] infection) may be more likely to have cryptosporidiosis than dogs, but the prevalence of this disorder is currently unknown.

Disadvantages • Oocysts are small and may be difficult to find.

Analysis • Fresh fecal samples should be sent to a referral laboratory experienced in finding *Cryptosporidium*. Special fecal flotation techniques, direct fecal smears stained with an acid-fast stain, or ELISA methodology (e.g., ProSpecT *Cryptosporidium* Microplate Assay, Alexon, Lenexa, KS) can be used. The ELISA methodology appears to be the most sensitive.

Normal Values • Dog and cat feces should be negative for *Cryptosporidium*.

HEPATIC ABNORMALITIES

Hepatic disease may be heralded by relatively specific signs (e.g., hepatomegaly, microhepatia, icterus, ascites, hepatic encephalopathy associated with meals) or may be associated with nonspecific signs (e.g., depression, weight loss, anorexia, vomiting). The latter are common presenting complaints of many diseases, which is why serum biochemistry profiling is indicated in patients with chronic signs or evidence of systemic disease. It is important to note that no consistent signs or laboratory abnormalities are found in all patients with hepatic disease. When screening for hepatic disease, one should request at least CBC, serum ALT, SAP, gamma-glutamyl transpeptidase (GGT), total bilirubin, albumin, cholesterol, BUN, glucose, urinalysis, and abdominal imaging. Hepatic function tests (bile acids, ammonia tolerance, clotting times, and others) ultrasonographic examination, hepatic biopsy, or contrast angiography and portography is usually necessary for definitive diagnosis. Abnormalities in hepatic-specific enzymes may result from primary hepatic disease but also occur because of secondary hepatic involvement from a primary nonhepatic disease (e.g., glucocorticoid hepatopathy, inflammatory bowel disease, pancreatitis). After identifying abnormalities in ALT, aspartate transferase (AST), SAP, or GGT, one should investigate first for a primary nonhepatic disease, because nonhepatic disease is the most common cause of increased values. In such cases the liver usually has reactive but reversible degenerative changes. Laboratory tests should be used for two main purposes: (1) to identify the presence of hepatic disease and (2) to determine if a

biopsy or radiographic contrast procedure is indicated.

Microhepatia: Small Liver

A small liver suggests atrophy (due to portosystemic shunts, hepatic arteriovenous [AV] fistulas), fibrosis and cirrhosis, or diffuse massive hepatic necrosis (Figure 9-5). Radiographically, hepatic atrophy tends to be characterized by sharp borders as opposed to the rounded or blunted hepatic margins typically associated with fibrosis and cirrhosis. Some patients with primary hepatic fibrosis severe enough to cause portal hypertension also have sharp hepatic margins, however. Many patients with marked hepatic atrophy due to portosystemic shunting are relatively young (<1 to 2 years) and have had signs of hepatic disease since (or before) weaning, whereas most patients with cirrhosis are middle-aged or older and clearly have late onset of clinical signs. Hepatic AV fistula is an uncommon cause of microhepatia, but it is usually diagnosed in dogs less than 2 years of age. However, some dogs are first diagnosed as having a single congenital portosystemic shunt when they are more than 10 years old. Likewise, although acquired portosystemic shunts are classically thought of as occurring in older dogs, they can be diagnosed in dogs less than 6 months old.

Hepatic atrophy causes abnormalities in hepatic function tests (e.g., bile acids, ammonia, or ammonium chloride tolerance test) but may yield normal or abnormal ALT, SAP, BUN, and serum albumin. A single normal or abnormal hepatic function test result does not mean that other hepatic function tests will have similar results. Preprandial and postprandial serum bile acid concentrations are sensitive function tests. (NOTE: Cholestatic diseases also increase bile acids; therefore, bile acids are not a "pure" test of hepatic function.) However, if hepatic disease is strongly suspected and the serum bile acid concentrations are not as high as anticipated, one should not hesitate to perform other tests to characterize the liver. If hepatic atrophy is likely, abdominal ultrasonography, contrast portography, hepatic biopsy, or a combination of these might be considered.

Small livers with clearly rounded or blunt hepatic margins are usually cirrhotic. Significant increases in serum ALT and SAP are often present, but some dogs with marked hepatic cirrhosis have normal hepatic enzymes. Serum albumin and BUN are more variable. If cirrhosis appears likely, a biopsy is indicated. Most cirrhotic livers can be identified grossly by their nodular or "cobblestone" appearance. However, significant fibrosis can be present without major gross changes, and severe nodular hyperplasia may resemble a cirrhotic liver. Acquired multiple shunts visible at laparoscopy or laparotomy are usually due to cirrhosis but can be secondary to congenital hepatic AV fistula, venoocclusive disease, or portal vein obstruction. If the liver is not clearly cirrhotic or fibrotic, a mesenteric venoportogram may be indicated in patients with acquired shunting.

Hepatomegaly: Enlarged Liver

Focal or asymmetric hepatic enlargement generally necessitates further laboratory investigation, imaging, and possibly biopsy. Neoplasia is a prominent but not invariable cause of focal hepatomegaly. The magnitude of the enlargement is not prognostic.

Generalized hepatomegaly necessitates careful clinicopathologic evaluation. Hepatomegaly may be the result of primary or secondary hepatic disease. Diagnosis may be confirmed with a history of exposure to certain toxins (Tables 9-6 and 9-7) or diagnosis of a systemic disease (e.g., hyperadrenocorticism) known to affect the liver. *Changes in ALT, SAP, hepatic function tests, and hepatic size, although suggestive of hepatic disease, are not diagnostic of specific entities*. This is true even in breeds with specific predispositions (e.g., Doberman pinschers, Bedlington terriers). Changes in the SAP or serum ALT may also be the result of primary nonhepatic disease (e.g., hyperadrenocorticism, inflammatory bowel disease, diabetes mellitus, heart failure). A definitive diagnosis usually requires hepatic biopsy. The clinician should first seek to rule out nonhepatic causes of secondary hepatic dysfunction. Hepatic biopsy should be considered in patients with obviously significant hepatic disease, those that do not have hyperadrenocorticism, and those that have persistent (more than 1 month) changes in serum ALT or SAP consistent with chronic or progressive hepatic disease or abnormal hepatic function tests (see Figure 9-5). It is not always possible to make these distinctions accurately; therefore, whenever hepatic biopsy is performed via laparotomy or laparoscopy, the rest of the abdomen should be explored and other organs sampled if the clinician

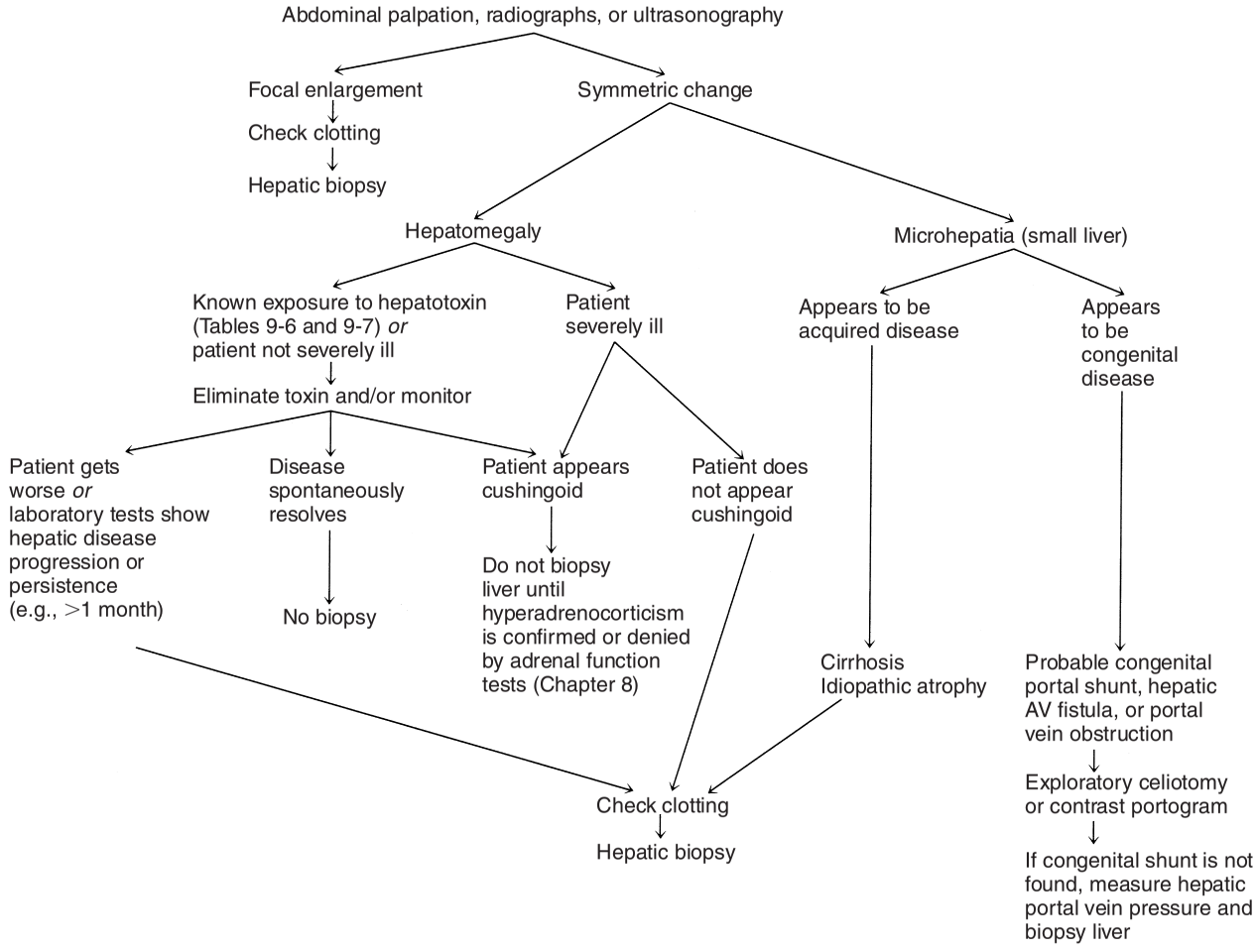

FIGURE 9-5. Diagnostic approach to altered hepatic shape or size in dogs and cats.

TABLE 9-6. Drugs That Have Been Documented or Suspected to Cause Increased Alanine Aminotransferase (ALT) Levels Due to Hepatic Disease

Acetaminophen *(important)* especially cats
Amiodarone
L-Asparaginase
Azathioprine
Barbiturates *(important)*
Carprofen
Doxycycline
Diazepam
Erythromycin estolate
Glucocorticoids *(dogs only) (important)*
Griseofulvin
Halothane
Ibuprofen
Itraconazole
Ketoconazole
Mebendazole
6-Mercaptopurine
Methimazole
Methotrexate
Methoxyflurane
Nitrofurantoin
Oxacillin
Oxibendazole
Phenobarbital *(important)*
Phenylbutazone
Phenytoin
Primidone *(important)*
Quinidine
Salicylate
Salicylazosulfapyridine
Sulfonamides
Tetracycline
Thiacetarsemide *(important)*
Trimethoprim-sulfa drug *(important)*

NOTE: These drugs do not reliably cause hepatic disease. In a patient with an increased ALT that is receiving one of these drugs, the medication probably should be stopped, if possible, and the ALT rechecked 2 to 4 weeks later. Those drugs that most reliably increase ALT are marked *(important)*. The other drugs are less consistent but may still cause severe hepatic disease. Almost any drug could cause an increased ALT in a particular patient.

TABLE 9-7. Drugs That Have Been Documented or Suspected to Cause Cholestasis or Hepatic Enzyme Induction Resulting in Increased Serum Alkaline Phosphatase (SAP) Levels

Anabolic steroids/androgens
Asparaginase
Azathioprine
Barbiturates *(important)*
Cephalosporins
Cyclophosphamide
Dapsone
Erythromycin estolate
Estrogens
Glucocorticoids *(important in dogs only)*
Gold salts
Griseofulvin
Halothane
Ibuprofen
6-Mercaptopurine
Methimazole
Methotrexate
Nitrofurantoin
Oxacillin
Oxymetholone
Phenobarbital *(important)*
Phenothiazines
Phenylbutazone
Phenytoin
Primidone *(important)*
Progesterone
Salicylates
Sulfur
Testosterone
Tetracyclines
Thiabendazole
Trimethoprim-sulfa drug
Vitamin A

NOTE: Those drugs that most reliably increase SAP are marked *(important)*. The other drugs are less consistent.

doubts their involvement. Fine-needle aspirates with cytology are sometimes useful in detecting diffuse hepatic infiltrative disease and hepatic lipidosis (see Color Plate 5E); however, fine-needle aspirates (even when guided by ultrasound) often miss infiltrative processes, and a negative cytologic finding never excludes an infiltrative disease in the liver. In general, laparoscopy allows for much superior hepatic biopsies compared with ultrasound-guided biopsies.

Hepatic Encephalopathy

Abnormal behavior, sometimes associated with eating, may be caused by hepatic encephalopathy, although hypoglycemia, primary CNS disease, and epilepsy must also be considered. Whenever possible, glucose should be measured on blood obtained during an episode. Evaluation of hepatic function is indicated in patients with behavioral changes, transient blindness, seizures, coma, or vague CNS abnormalities. Congenital (e.g., portosystemic shunt) and severe acquired hepatic disease (e.g., cirrhosis) may cause encephalopathy. Routine biochemical profiling may be suggestive, but hepatic function testing is mandatory, because these diseases may not significantly change serum ALT, SAP, albumin, BUN, glucose, or bilirubin determinations. Resting plasma ammonia concentrations are meaningful only if they are increased. A patient in an episode of hepatic encephalopathy may have increased or normal resting plasma ammonia concentrations. Ammonia tolerance testing (ATT) and pre- and postprandial serum bile acid concentrations appear to be the most sensitive

and specific tests for hepatic dysfunction that causes hepatic encephalopathy. A very rare congenital urea cycle enzyme deficiency may cause hepatic encephalopathy and hyperammonemia without affecting enzymes or bile acids. Analysis of urea cycle enzymes in biopsy samples is necessary for diagnosis.

Icterus

Icterus is detected at physical examination or when serum or plasma is inspected at the laboratory. Hyperbilirubinemia always denotes hepatobiliary or hematopoietic disease (Figure 9-6). Hepatic and hematopoietic diseases are not always associated with icterus, and disease in either system may be secondary to other disorders. The presence or absence of icterus is not diagnostic or prognostic. Sepsis, pancreatitis, and inflammatory bowel disease sometimes cause secondary hepatic dysfunction that may include icterus.

TOTAL SERUM BILIRUBIN

Occasional Indications • Icterus (on either physical examination or inspection of nonhemolyzed serum or plasma), bilirubinuria (any amount in a cat or significant amounts in a dog), or suspected hepatic disease that is not apparent on other tests. The sclera have detectable icterus when the serum bilirubin is greater than 3 to 4 mg/dl, and the plasma is icteric when the serum bilirubin is greater than 1.5 to 2 mg/dl.

> NOTE: Icterus is absent in many animals (especially dogs) with hepatic disease. Serum bilirubin is not a sensitive test for hepatic disease.

Measurement of direct (conjugated) and indirect (unconjugated) bilirubin fractions is not useful and should not be done. Hemolytic, hepatic, and biliary tract diseases have unpredictable variation in the amount of each fraction. Other tests are required to identify the cause of hyperbilirubinemia.

Analysis • Measured in serum or heparinized plasma by spectrophotometric and dry reagent methods. The latter require dilutions if the bilirubin is greater than 7.5 mg/dl. Bilirubin is stable at 4° C for 7 days if not exposed to bright light. Measurement of urine bilirubin is discussed in Chapter 7.

Normal Values • Dogs, less than 1.0 mg/dl; cats, less than 1.0 mg/dl.

Danger Values • Dogs, uncertain, but values greater than 20 mg/dl cause concern (i.e., kernicterus); cats, unknown.

Artifacts • Exposure to bright sunlight or fluorescent lighting can decrease bilirubin by 50% per hour. See Introduction to Serum Chemistries.

Drug Therapy That May Alter Serum Bilirubin • Decreased bilirubin may be caused by drugs that cause hepatic enzyme induction (e.g., phenobarbital). Increased bilirubin may be the result of drugs causing hemolytic anemia (Table 9-8) or acute hepatic necrosis (see Table 9-6).

Causes of Hypobilirubinemia • Do not exist.

Causes of Hyperbilirubinemia • Hemolytic disease and hepatobiliary disease are the two main causes (see Figure 9-6). A CBC should be determined in every icteric patient to help rule out hemolytic disease. RBC numbers must decrease rapidly and significantly to cause clinical icterus. Very regenerative anemias may suggest that icterus is due to immune-mediated hemolytic anemia (IMHA). Reticulocytosis, hemoglobinemia, hemoglobinuria, erythrocytic autoagglutination, spherocytosis, positive Coombs' test results, splenomegaly, or hepatomegaly are often present. See Chapter 3 for further discussion of IHA and other regenerative anemias (e.g., Heinz body, zinc intoxication, *Haemobartonella*). Bilirubinuria theoretically should be absent in hemolytic disease but is often present in IHA because canine kidneys conjugate bilirubin. The clinician must not be misled by increases in ALT because severe, acute hemolytic anemia may cause increased ALT (ostensibly caused by acute hepatic hypoxia).

Severe hepatic disease (especially acute necrosis) is sometimes accompanied by DIC and subsequent hemolytic anemia. These cases may be difficult to distinguish from IHA. However, anemia caused by DIC is usually not as regenerative as in IHA; in addition, the presence of RBC fragments, thrombocytopenia, increased fibrin degradation products (FDP), decreased antithrombin III, prolonged clotting time, and abnormal hepatic function

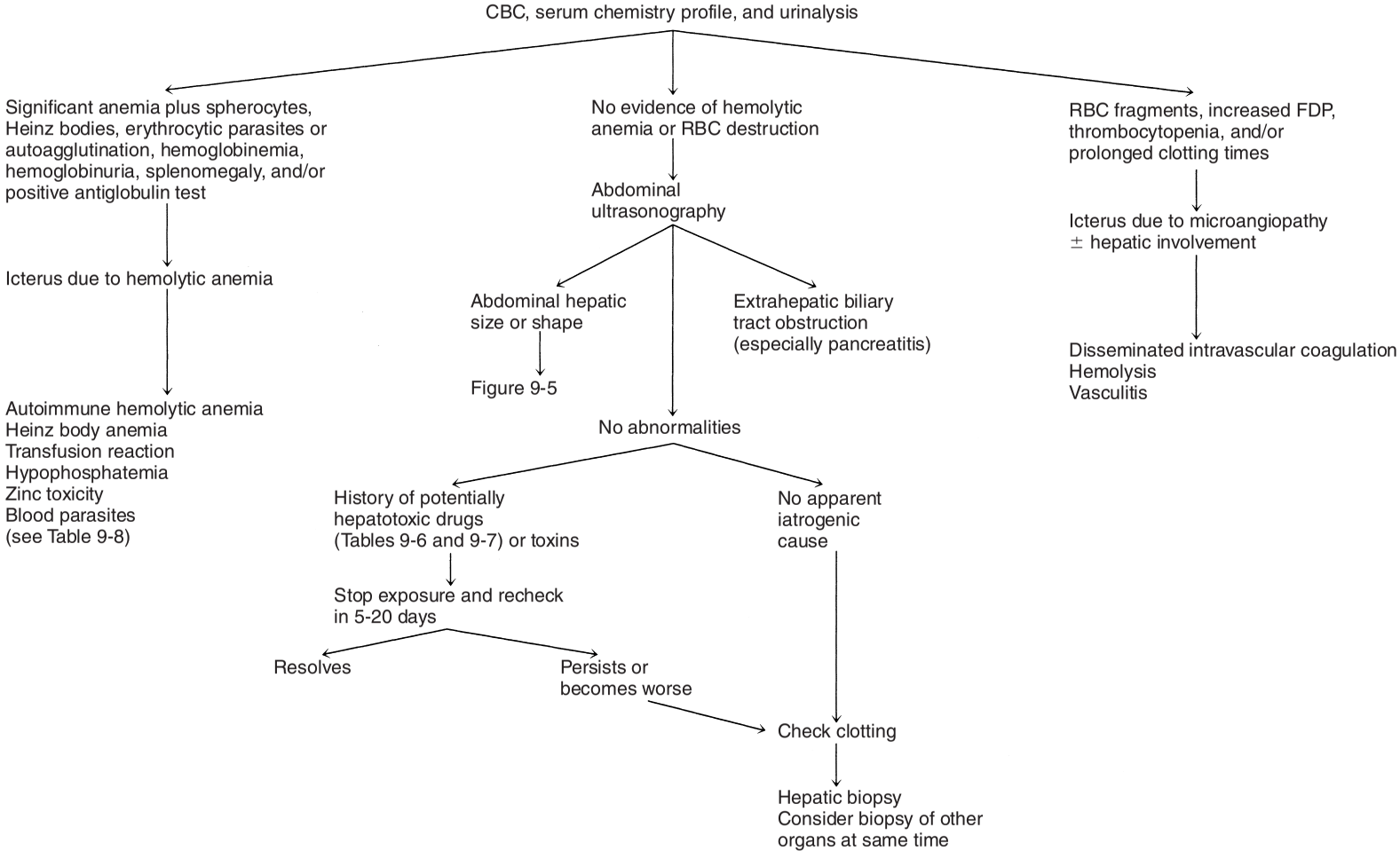

FIGURE 9-6. Diagnostic approach to hyperbilirubinemia in dogs and cats. *CBC,* Complete blood count; *RBC,* red blood cell; *FDP,* fibrin degradation products.

TABLE 9-8. Selected Substances That Have Been Documented or Suspected to Cause Hemolytic Anemia

Acetaminophen *(especially cats)*
Benzocaine *(especially cats)*
Cephalosporins
Dapsone
Methylene blue *(especially cats)*
Nitrofurantoin
Onions
Penicillins
Phenacetin *(especially cats)*
Phenazopyridine
Phenylbutazone
Sulfonamides
Vaccinations
Vitamin K_3 *(cats)*
Zinc

NOTE: These substances do not always cause anemia, but they have the potential and should be withdrawn, if possible, in patients with hemolytic anemia.

tests usually allows differentiation, as do vomiting, abdominal pain, and encephalopathy when present.

Dogs and cats often have relatively severe hepatic disease before icterus is observed; however, the magnitude of the total serum bilirubin is not prognostic or diagnostic. Secondary hepatic disease (reactive disease or so-called *bystander phenomenon* as the result of septicemia, toxemia, or inflammation) may have icterus similar to that occurring in primary hepatic disease. Certain bacterial endotoxins and acute-phase inflammatory mediators are thought to alter normal bilirubin metabolism and cause increases in total bilirubin concentrations.

Most feline hepatic diseases cause icterus; the most common conditions include hepatic lipidosis, cholangitis and cholangiohepatitis, hepatic lymphoma, and FIP. Icterus in cats is an indication for CBC and a serum biochemistry panel. Icterus in cats that is not caused by hemolysis usually indicates a hepatic biopsy, because most of these cats have primary hepatic disease. Biopsy is necessary to differentiate causes and institute specific treatment.

Common causes of nonhemolytic icterus in dogs include pancreatitis obstructing the bile duct, cholecystitis, chronic hepatitis, hepatic lymphoma, acute hepatic necrosis, hepatic cirrhosis, and intrahepatic cholestasis. Icterus in dogs is an indication for CBC and a serum biochemistry panel (to include at least ALT, SAP, BUN, cholesterol, and albumin). Imaging (radiographs, ultrasonography, or both) is indicated to help determine if primary hepatic disease or biliary tract obstruction exists. If primary hepatic disease is diagnosed, hepatic biopsy is usually indicated. If pancreatitis is present, surgery is not indicated unless a chronic bile duct obstruction necessitates bypassing the common bile duct with a cholecystoduodenostomy (rarely needed) or a pancreatic abscess is present. If coexisting extrahepatic disease is found, it should be investigated.

ALANINE TRANSFERASE

ALT was formerly known as *serum glutamic-pyruvic transaminase* (SGPT).

Common Indications • Systemic disease including weight loss, hepatomegaly, vomiting, diarrhea, icterus, ascites, depression, and anorexia; also, as a screening procedure for hepatic disease in any patient with undiagnosed illness. Most patients with known chronic hepatitis should undergo periodic ALT determinations to monitor the problem.

Advantages • Specificity for the liver.

Disadvantages • Lack of sensitivity (i.e., patients with significant hepatic disease such as cirrhosis or hepatic neoplasia may have normal ALT) and inability to distinguish among different hepatic diseases or when there is secondary nonhepatic disease involvement.

Analysis • Measured in serum (heparinized plasma in selected assays) by spectrophotometric and dry reagent methods. ALT is stable in separated serum for approximately 1 (at 22° C) to 7 (at 4° C) days.

Normal Values • Serum enzyme activity may vary markedly among laboratories, depending on the technique and the units used.

Danger Values • Despite correlation between ALT and active hepatic damage, no correlation exists between ALT and hepatic function; hence, no danger values exist.

Artifacts • See Introduction to Serum Chemistries.

Drug Therapy That May Alter Serum ALT • Any drug causing hepatocellular damage (i.e., drug-induced hepatopathy) may cause increased ALT. The list of all drugs suspected to cause increased ALT is extensive

and includes many that are safe in the majority of patients. A list of selected drugs documented to cause increased ALT in human beings, dogs, and cats is given in Table 9-6. Administration of one of these drugs does not automatically explain an increased ALT, however.

NOTE: A patient can have an idiosyncratic reaction to almost any drug, causing an increased ALT.

Causes of Decreased ALT • Not significant.

Causes of Increased ALT • Increase in ALT is principally caused by hepatocellular damage from any cause (Table 9-9). RBCs and striated muscle cells contain small amounts of ALT, and damage to these may cause relatively minor increases (i.e., less than two to three times normal) in serum ALT, as may exercise. Dogs with muscular dystrophy may have major increases in ALT, but should also have increases in AST and creatine kinase (CK) values.

Hepatocytes contain substantial amounts of ALT in the cytosol, and major increases in serum ALT (i.e., three or more times normal) indicate hepatocellular leakage of the enzyme but do not always signify primary or irreversible hepatic disease. Hepatic disease may have normal to significantly increased serum ALT activity. The magnitude of the increase in ALT does not correlate with the seriousness of the hepatic disease and is not a prognostic indicator unless a specific disease is being considered. The serum ALT half-life is approximately 1 to 2 days or less, and serum ALT is expected to decrease over 1 to 2 weeks once active hepatic damage ceases. It is thought that ALT remains elevated during hepatic regeneration.

After increased serum ALT is identified, many factors must be considered (Figure 9-7). If no other evidence of disease is found, the increased ALT indicates the need for periodic monitoring because it may be the first detectable sign of significant hepatic disease. If other abnormalities consistent with hepatic disease are found, the approach is like that in any other patient with hepatic disease. Common causes of serum ALT more than three times normal include hepatic anoxia, poor hepatic perfusion, spontaneous and surgical trauma (e.g., hit by a car, surgery), chronic hepatitis, cirrhosis, cholangitis and cholangiohepatitis, acute biliary obstruction, hepatic necrosis as the result of any cause, acute pancreatitis, hepatic neoplasia, sepsis, and certain drugs. Sepsis, especially septicemia and toxemia, may secondarily damage hepatocytes. Abdominal inflammation may do the same. The pancreas is close to the liver, and inflammation in the pancreas may cause mechanical damage to the liver. In Doberman pinschers, Bedlington terriers, Dalmatians, and West Highland white terriers, a persistently increased serum ALT suggests chronic hepatitis that may or may not be associated with increased hepatic copper concentrations.

ASPARTATE TRANSFERASE

AST was formerly known as *serum glutamic-oxaloacetic transaminase* (SGOT).

TABLE 9-9. Selected Causes of Increased Serum Alanine Aminotransferase Levels

DOGS	CATS
Hepatic Parenchymal Disease	**Hepatic Parenchymal Disease**
Cholangitis	Cholangitis
Cholangiohepatitis	Cholangiohepatitis
Cirrhosis	Feline infectious peritonitis (FIP)
Copper storage disease	Hepatic lymphoma
Hepatic malignancy	Cirrhosis
Chronic hepatitis	Hepatic toxin
Hepatic toxin	Trauma
Trauma	Pancreatitis
Pancreatitis	Hyperthyroidism
Other Disorders	**Other Disorders**
Anoxia because of anemia/shock	Anoxia because of anemia/shock
Iatrogenic (see Table 9-6)	Iatrogenic (see Table 9-6)

NOTE: Almost any disease affecting the liver can cause increased ALT levels. The disorders listed are those that may be more likely to cause a significant increase. However, any of these diseases can exist with minor or no increase in ALT values.

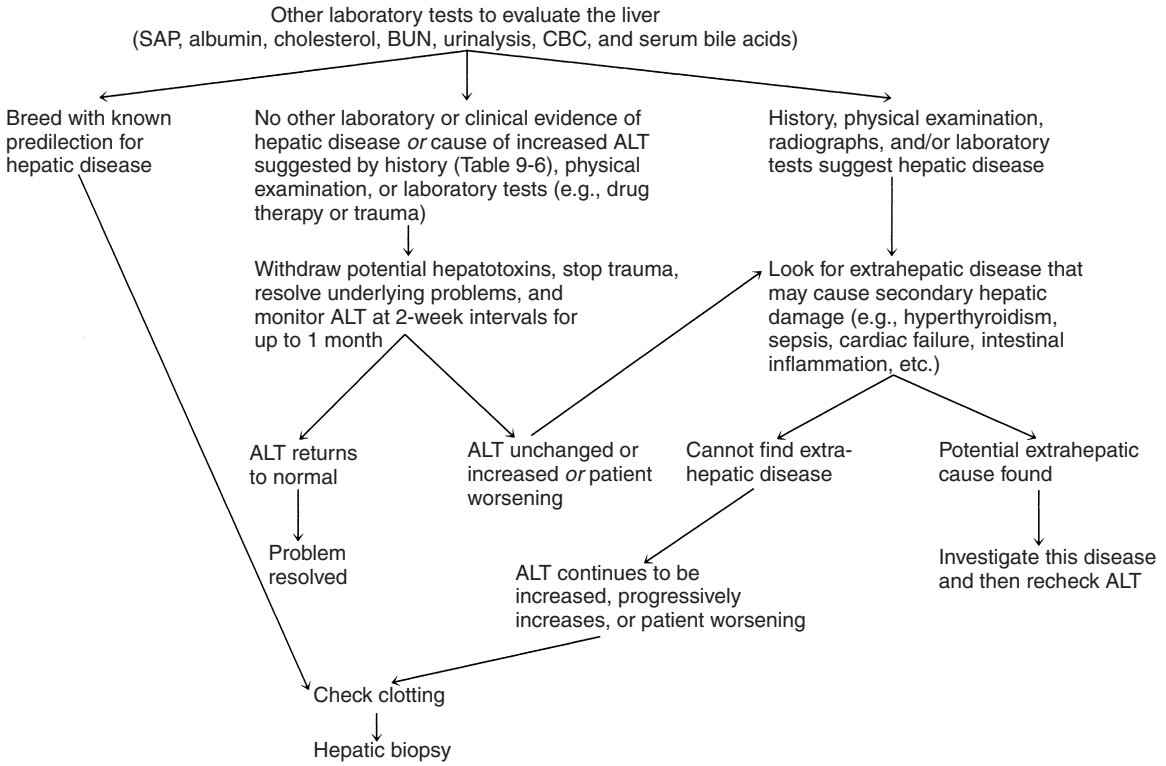

FIGURE 9-7. Diagnostic approach to increased alanine aminotransferase (ALT) in dogs and cats. *BUN,* Blood urea nitrogen; *CBC,* complete blood count; *SAP,* serum alkaline phosphatase.

Occasional Indications • Same as for ALT.

Disadvantages • Not as specific for the liver as ALT.

Analysis • Same as for ALT.

Drug Therapy That May Alter AST • Decreased AST may be caused by metronidazole therapy. Hepatotoxic drugs may cause increased AST (see Table 9-6).

Causes of Decreased AST • None.

Causes of Increased AST • Like ALT, AST is present in significant quantities in hepatocytes. Although ALT is present in the cytosol, AST is present in the mitochondria. Increased serum ALT reflects cell membrane damage and leakage; significant AST increases tend to reflect more serious hepatic damage because the mitochondria are not damaged as readily as is the cell membrane. AST is, however, present in significant quantities in many other tissues, including muscle and RBCs; therefore, increased AST is not as specific for hepatic injury as is increased ALT. Exercise and intramuscular (IM) injections may increase serum AST. The most common causes of increased AST include hepatic disease, muscle disease (inflammation or necrosis), or hemolysis (spontaneous or artifactual). Increased AST is an indication to check for ongoing hemolysis by measuring the hematocrit and observing the color of the plasma and serum on a centrifuged blood sample. If no hemolysis is found, the next step is to measure serum ALT to determine whether the increased AST is from the liver (significant increases in both ALT and AST suggest that AST increases are of hepatic origin).

SERUM ALKALINE PHOSPHATASE

Common Indications • Systemic disease, including weight loss, hepatomegaly, vomiting, diarrhea, ascites, icterus, depression, or

anorexia; also as a screen for hepatic disease and hyperadrenocorticism.

Advantages • Useful in evaluating the liver for subtle cholestatic disease.

Disadvantages • Affected by corticosteroids, bone lesions, and osteoblastic activity in young growing dogs.

Analysis • Measured in serum or heparinized plasma by spectrophotometric methods. Stability in heat (55° C) has been used to attempt to differentiate SAP of bone origin (i.e., heat sensitive) from SAP of hepatic origin (i.e., heat stable). It is difficult to obtain reproducible results with the heat-inactivation test; however, L-phenylalanine inhibits steroid-induced SAP and can be used to help determine if increased SAP is due to corticosteroids. Alternatively, cellulose acetate electrophoresis can separate the isoenzymes more definitively. The diagnostic usefulness of determining the percentage of steroid fraction is questionable, because dogs with various types of hepatic disease often have considerable steroid involvement.

Normal Values • May vary markedly from laboratory to laboratory. Immature dogs characteristically have SAP (bone origin) activities up to twice that of sexually mature dogs.

Danger Values • Because of the lack of correlation with hepatic function, no danger values exist for SAP.

Artifacts • See Introduction to Serum Chemistries.

Drug Therapy That May Increase SAP • Any drug that causes hepatic enzyme induction or cholestasis (see Table 9-7) may increase SAP. Glucocorticoids, primidone, and barbiturates typically increase SAP in dogs, but other drugs are less consistent. Although glucocorticoids can cause marked SAP increases in dogs, cats are almost never affected.

Causes of Decreased SAP • Not significant.

Causes of Increased SAP • SAP of bone origin is commonly increased (SAP less than three times normal) in dogs less than 6 to 8 months old. Bone disease (e.g., osteosarcoma, osteomyelitis) may increase SAP (usually a minor increase) and generally denotes a guarded prognosis from presumed metastatic disease in the bones.

Increased SAP is interpreted differently in dogs and cats (Table 9-10). Cats have less hepatocellular SAP, which is readily excreted by their kidneys. Therefore, any increase in feline SAP is considered significant, indicating further tests. Not all cats with hepatic disease have increased SAP. The major causes of increased SAP in cats are hepatic lipidosis, cholangitis and cholangiohepatitis, hyperthyroidism, and diabetes mellitus. SAP increases are generally more specific than GGT in cats with hepatic lipidosis (cats with lipidosis classically have very high SAP with little to no increase in GGT; however, this finding is not consistent enough to make a diagnosis). Hyperadrenocorticism (spontaneous and iatrogenic) very, very rarely increases SAP in cats. Increased SAP in a cat is an indication for serum thyroid hormone determination, urinalysis, blood glucose and serum ALT measurement, and perhaps a hepatic function test (e.g., bile acid). If hepatic disease is the apparent cause of the increased SAP, one must determine if hepatic biopsy is indicated (see the later discussion under Bile Acids).

The major causes of SAP values more than three times normal in dogs are hepatobiliary disease, hyperadrenocorticism, and therapy with glucocorticoids or anticonvulsants. Hepatic disease with increased SAP usually has a cholestatic component; however, this does not imply icterus or gross obstruction of the biliary tract. Intrahepatic cholestasis caused by diffuse or focal compression of bile canaliculi may occur in various hepatopathies, even those secondary to septicemia, toxemia, and chronic stress-induced vacuolar (i.e., hydropic change) hepatopathy. Acute hepatocellular necrosis can transiently increase SAP (usually less than five times normal). Extrahepatic biliary tract obstruction and enzyme induction caused by endogenous or exogenous glucocorticoids or drug administration may increase SAP more than 10 times normal. As with ALT, the magnitude of the increase in SAP does not correlate with the seriousness or prognosis of the disease.

In dogs it is important first to rule out young age, drug therapy, and hyperadrenocorticism to avoid performing an unnecessary hepatic biopsy (Figure 9-8). Hyperadrenocorticism can easily be confused with primary hepatic disease because it typically causes hepatomegaly, pu-pd, increased ALT, and sometimes increased serum bile acids. Unless a patient

TABLE 9-10. Causes of Increased Serum Alkaline Phosphatase Levels

DOGS	CATS
Biliary Tract Abnormalities	**Biliary Tract Abnormalities**
Pancreatitis	Same as for dogs
Bile duct neoplasia	
Cholelithiasis	
Cholecystitis	
Ruptured gallbladder	
Hepatic Parenchymal Disease	**Hepatic Parenchymal Disease**
Cholangiohepatitis	Cholangiohepatitis
Chronic hepatitis	Hepatic lipidosis
Copper storage disease	Hepatic lymphoma
Cirrhosis/fibrosis	Feline infectious peritonitis (FIP)
Hepatic neoplasia	
Lymphoma	
Hemangiosarcoma	
Hepatocellular carcinoma	
Metastatic carcinoma	
Toxic hepatitis	
Aflatoxin	
Other Disorders	**Other Disorders**
Diabetes mellitus	Diabetes mellitus
Hyperadrenocorticism	Hyperthyroidism
Chronic passive congestion because of right heart failure	
Diaphragmatic hernia	
Septicemia	
Ehrlichiosis*	
Young dog with bone growth Osteomyelitis*	
Iatrogenic (see Table 9-7)	Iatrogenic (see Table 9-7)*

NOTE: Almost any disease affecting the liver can cause increased SAP levels. The disorders listed are those that may be more likely to cause a significant increase. However, any of these can exist with minor or no increase in SAP values.
*Rarely of importance.

has signs of hepatic failure (i.e., icterus, hepatic encephalopathy, hypoglycemia, weight loss, vomiting, hypoalbuminemia, ascites, microhepatia), hyperadrenocorticism must be precluded by adrenal gland function testing. If a hepatic biopsy specimen is obtained from a patient with hyperadrenocorticism, vacuolar hepatopathy is documented.

GAMMA-GLUTAMYL TRANSPEPTIDASE

Occasional Indications • Same as for SAP. SAP appears to be more sensitive for hepatobiliary disease in dogs; however, in cats, GGT has slightly greater sensitivity and perhaps greater specificity for hepatic disease except hepatic lipidosis. Therefore, it is more frequently indicated in cats than in dogs. GGT is less influenced than SAP by secondary hepatic disease conditions or enzyme-inducing drugs. The use of SAP and GGT together has a higher predictive value of hepatic disease.

Analysis • Measured in serum, urine, and body fluids by spectrophotometric methods. GGT is stable in serum at 4° C for at least 3 days and at 20° C for up to 1 year.

Normal Values and Danger Values • Same as for SAP.

Artifacts • See Introduction to Serum Chemistries.

Drug Therapy That May Affect GGT • Same as for SAP.

Causes of Decreased GGT • Not significant.

Causes of Increased GGT • Causes are similar to increased SAP and tend to parallel the magnitude of the rise in SAP, but bone lesions are not recognized to increase GGT. It is induced by glucocorticoid therapy and certain drugs, as is SAP. In cats, GGT may increase more than SAP, except in hepatic

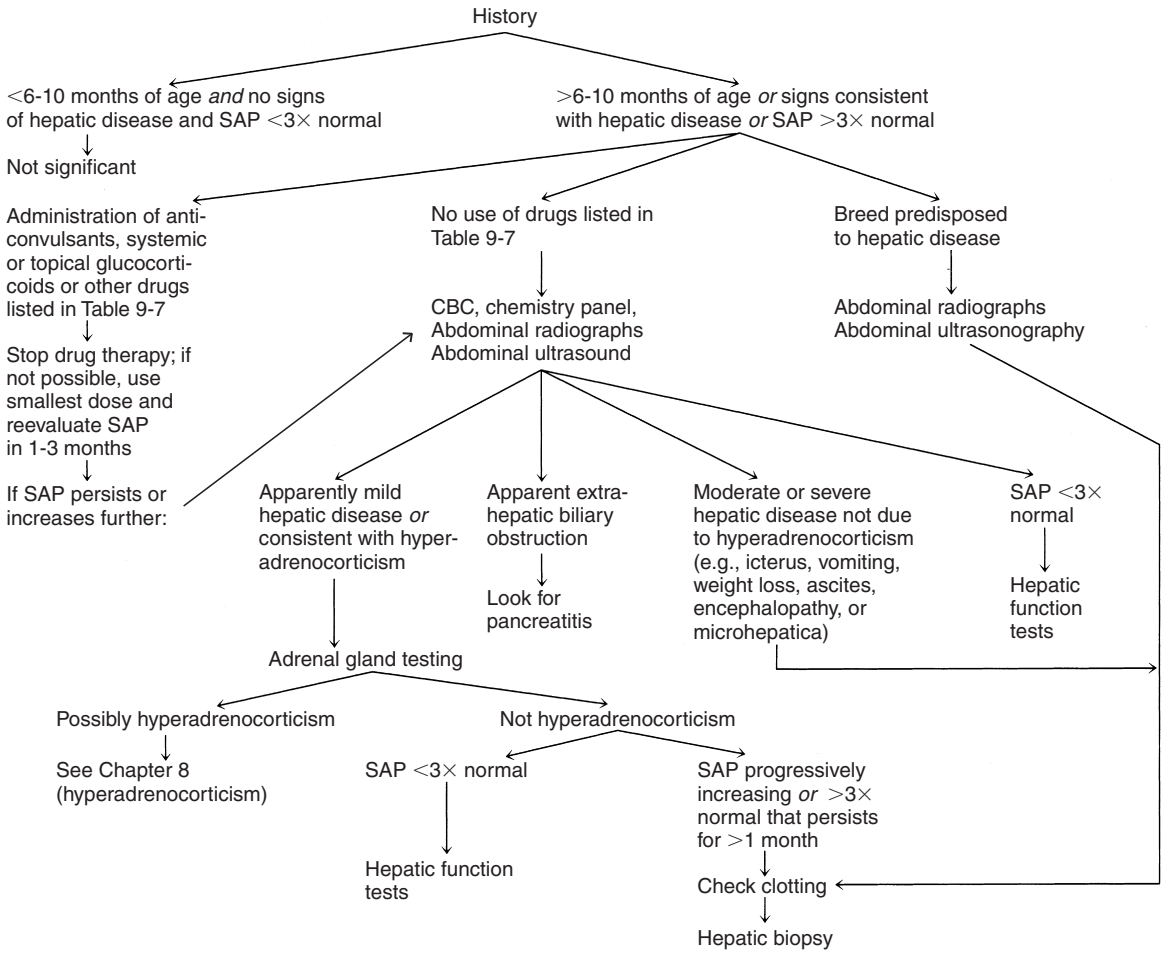

FIGURE 9-8. Diagnostic approach to increased serum alkaline phosphatase (SAP) in dogs. *CBC,* Complete blood count.

lipidosis (where classically the SAP is usually quite high, but GGT values show only a mild [or no] increase). GGT does not tend to increase after acute hepatic necrosis, as does SAP. Increased GGT should be pursued as for increased SAP (see Figure 9-8). Increased GGT may suggest pancreatitis obstructing the bile duct, as for SAP.

Causes of Increased Urine GGT • Increased 24-hour urinary excretion of GGT can be caused by various nephrotoxins (e.g., gentamicin).

LACTIC DEHYDROGENASE

Rare Indications

Disadvantages • Lack of specificity. The lactic dehydrogenase (LDH) test is *not recommended.*

Analysis • Measured in serum, heparinized plasma, or cerebrospinal fluid (CSF) by spectrophotometric methods.

Normal Values and Danger Values • Same as for ALT and SAP.

Causes of Decreased LDH • Not significant.

Causes of Increased LDH • LDH is found in so many body tissues that serum LDH is of questionable diagnostic value. Inexplicable increases of small to great magnitude are not uncommon.

SULFOBROMOPHTHALEIN RETENTION

Rare Indications • In general, sulfobromophthalein (BSP) dye retention is rarely used

anymore, except by research laboratories; it is *not recommended*.

Analysis • See prior editions.

INDOCYANINE GREEN

Rare Indications • Same as for BSP. In general, indocyanine green (ICG) is *not recommended*.

Analysis • See prior editions.

BILE ACIDS

Frequent Indications • Suspected occult hepatic disease, chronic weight loss, abnormal CNS signs, icterus, hepatomegaly, and microhepatia; also to monitor hepatic function in patients with known hepatic diseases. Because of the ease of this test compared with BSP, ICG, and ammonia, serum bile acids are used routinely as a screening test for hepatic dysfunction.

Advantages • Ease of use, few extrahepatic factors affect it.

Disadvantages • Does not reliably distinguish among different hepatobiliary diseases. Values may change enough from day to day that it can be difficult to use the serum bile acid concentrations to determine if a change in hepatic function has or is occurring.

Analysis • Measured in serum by either a direct enzymatic method that quantifies total serum 3-alpha-hydroxylated bile acids or uses an RIA procedure that measures specific bile acids. It is important that a validated assay for dogs and cats be used because some methods are not accurate. Values for enzymatic and RIA procedures cannot be compared.

Maximum information is obtained by determining a 12-hour fasting preprandial and 2-hour postprandial concentration. Dogs and cats should be fed canned food containing moderate fat content, causing the gallbladder to contract. Preprandial and postprandial concentrations together improve the sensitivity of the test, making it more sensitive than other function tests (e.g., resting serum ammonia concentrations).

Normal Values • Because of different techniques and assays (μmol/L or μg/ml), normal values must be established for each laboratory.

Danger Values • None.

Artifacts • Very increased serum dehydrogenase activities may require modification of the spectrophotometric technique. Severe lipemia (i.e., chylomicronemia) and hemolysis may falsely decrease bile acid measurements, and hypertriglyceridemia may falsely increase concentrations when spectrophotometric techniques are used, but they do not affect RIA. This test is not indicated in icteric patients.

Drug Therapy and Other Factors That May Alter Serum Bile Acid Concentration • Cholestyramine lowers serum concentrations by binding to bile acids in the intestinal lumen, preventing their reabsorption. Ursodeoxycholic acid (a synthetic bile acid) therapy may increase total serum bile acid concentrations. Resection of the ileum (the principal site of bile acid reabsorption), severe ileal disease, or cholecystectomy may also cause serum bile acids to inaccurately reflect hepatic function. Prolonged anorexia (>1 to 2 days) may cause fasting serum bile acid concentrations to be less than would be found if the patient were eating normally. Intestinal hypomotility may cause the 2-hour postprandial sample to be a less sensitive indicator of hepatic disease because of failure to deliver the bile acids to the ileum in a timely fashion. ARE may increase total serum bile acid concentrations because of bacterial deconjugation of bile acids with subsequent increased small intestinal uptake. Hepatic insufficiency does not decrease serum bile acid concentrations.

Causes of Decreased Serum Bile Acid Concentration • Delayed gastric emptying, rapid intestinal transit, malabsorption disorders, and ileal resection may cause subnormal values. With ARE, total measurable moieties may or may not decrease, but it is expected that unconjugated serum bile acid concentrations may increase.

Causes of Increased Serum Bile Acid Concentration • Serum bile acid concentrations are increased because of hepatocellular disease, cholestatic disease, or portosystemic shunting. When both fasting and 2-hour

postprandial serum bile acid levels are determined, the sensitivity of these tests becomes greater than with other hepatic function tests. Because of the ease of performing and wide availability of the test, it has replaced other clinical hepatic function tests. Serum bile acids offer no additional information in icteric patients with hepatic or extrahepatic biliary tract disease. In nonicteric patients suspected of having hepatic disease, serum bile acids are a good screening test to support further diagnostic evaluations. Not all patients with hepatic disease have increased serum bile acid concentrations, and the relative increase in bile acids is not diagnostic for the type of disease or the prognosis. Reported fasting serum bile acids that are increased greater than 20 μmol/L or postprandial values of greater than 25 μmol/L suggest significant hepatic disease or portosystemic shunting and dictate further hepatic evaluation and possibly hepatic biopsy. Generally, preprandial and postprandial bile acids are determined simultaneously; however, if only fasted values are determined and found to be normal, postprandial measurements are required. The magnitude of the rise or the percent increase from preprandial to postprandial values does not imply a specific diagnosis or prognosis. Most animals with chronic hepatitis, marked hepatic necrosis, cholestasis, and hepatic neoplasia have abnormal values. Bile acids are usually not markedly altered by secondary hepatic disease from nonhepatic disorders or with glucocorticoid or anticonvulsant therapy; however, in rare cases they may be.

Increased serum bile acids are possibly the most sensitive biochemical indicator of congenital portosystemic shunts. Almost all animals with congenital portal vascular anomalies have increased postprandial bile acids; some of the highest concentrations occur in these cases.

AMMONIA AND AMMONIA TOLERANCE TESTING (ATT)

Rare Indications • Same as for bile acids (i.e., when a sensitive function test is needed to prove hepatic disease in an animal in which easier tests do not allow diagnosis).

Advantages • Good sensitivity and specificity.

Disadvantages • Procedural requirements for submitting the samples, and the likelihood of vomiting or CNS signs with ATT.

Analysis • Measured in blood, serum, plasma (heparinized is recommended), CSF, or urine by enzymatic, selective electrode, dry reagent, and resin absorption methods. There does not appear to be any advantage of arterial over venous blood. Blood must be drawn into an ice-chilled tube, which is stoppered tightly after filling, immediately put back on ice, and promptly taken to the laboratory. A control sample should be taken at the same time using the same technique. The test must be performed within 20 minutes, or the plasma must be frozen at –20° C, which stabilizes the ammonia concentration for at least 2 days. If an ATT is to be performed, samples for ammonia determination should be taken before and 30 or 45 minutes after administration of NH_4Cl, 100 mg/kg of body weight. The NH_4Cl may be administered orally as a solution in 20 to 50 ml of water, as a 5% solution, as a dry powder in gelatin capsules, or rectally as a 5% solution. The use of orally administered gelatin capsules is the easiest and the least likely to result in expulsion (i.e., vomiting or defecation of the NH_4Cl).

Warning: Administration of NH_4Cl to patients with increased resting blood ammonia concentrations may cause encephalopathy. The clinician should not perform ATT if the patient is showing obvious encephalopathic signs. Lack of obvious encephalopathic signs does not guarantee that blood ammonia levels are normal.

Normal Values • Resting ammonia: dogs, 45 to 120 μg/dl; cats, 30 to 100 μg/dl. ATT, ammonia at 30 minutes: dogs, minimal change from normal values; cats, no change from normal values.

Danger Values • Dogs, greater than 1000 μg/dl (hepatic encephalopathy may be imminent, although poor correlation exists between clinical signs of encephalopathy and plasma ammonia concentrations); cats, unknown.

Artifacts • Falsely increased: allowing the blood to stand, strenuous exercise. See Introduction to Serum Chemistries.

Drug Therapy That May Alter Ammonia • Decreased serum ammonia may be the result of intestinal antibiotics (e.g., aminoglycosides), lactulose, *Lactobacillus acidophilus* cultures, enemas, and diphenhydramine. Increased serum ammonia may be the result of valproic acid, asparaginase, narcotics,

diuretics causing hypokalemia or alkalosis, hyperalimentation, ammonium salts, and high-protein meals (including blood from spontaneous GI bleeding).

Causes of Hypoammonemia • Not significant.

Causes of Hyperammonemia • Urea cycle disorders (extremely rare) and hepatic insufficiency (especially congenital or acquired portosystemic shunting). Resting blood ammonia concentrations are probably less sensitive than fasting serum bile acids in detecting hepatic dysfunction, whereas the ATT is possibly as sensitive as preprandial and postprandial bile acids in detecting portosystemic shunting. A significantly increased fasting blood ammonia concentration renders an ATT unnecessary. Clinical signs are not well correlated with blood ammonia concentrations. An abnormal ATT result or resting ammonia value in a patient with hepatic disease is generally an indication for hepatic biopsy or a portogram. Rarely, plasma ammonia is increased because of urinary tract obstruction, especially if complicated by infection with urease-producing bacteria. Some young dogs (notably Scottish deerhounds in Great Britain) have been found to have elevated resting blood ammonia values that spontaneously return to normal as the dog ages. Therefore, caution must be used when diagnosing congenital portosystemic shunting in at least some breeds solely by evaluating the resting serum ammonia concentration.

CHOLESTEROL

See Chapter 8.

WEIGHT LOSS OR ANOREXIA OF UNKNOWN CAUSE

Weight loss has many causes (Table 9-11). Concurrent problems with fewer potential causes (e.g., regurgitation, vomiting, diarrhea, icterus) should be considered first. If a patient had a reasonable appetite when weight loss began, major differential diagnoses are intestinal disease, maldigestion, increased use of calories (e.g., hyperthyroidism, lactation), or increased loss of calories (e.g., diabetes mellitus). If no other identifiable problems (other than weight loss or anorexia) can be pursued, a systematic search is indicated (Figure 9-9). One should first preclude as many causes as possible with the history and physical examination (i.e., lack of food, calorie-deficient food, inability to eat, regurgitation, vomiting and diarrhea). Next, extensive clinicopathologic screening is indicated. Imaging is considered an extension of the physical examination, and abdominal and thoracic radiographs are appropriate. Thoracic radiographs may be very revealing, even if a patient does not have coughing or abnormal lung sounds. Abdominal ultrasonography is particularly desirable and often more useful than radiographs if the operator is accomplished. If laboratory or radiographic abnormalities are not present or are unconvincing, one may repeat the tests at 1 to 3 week intervals, depending on the clinical condition of the patient, or immediately proceed to function tests, biopsies, or both. Certain hepatic and adrenal gland diseases may require such function tests. It is noteworthy that severe gastric or intestinal disease may cause anorexia or severe weight loss without vomiting or diarrhea.

Gastroduodenoscopy and ileoscopy plus biopsy are reasonable in patients with severe weight loss of unknown cause. Some cases with gastric neoplasia may present only for anorexia and weight loss. Clinicians without

TABLE 9-11. Major Causes of Weight Loss in Dogs and Cats

Calorie-Deficient Food or No Food
Failure or Refusal to Eat
Dysphagia
Oral lesion
Anorexia for any reason
Regurgitation
Pharyngeal or esophageal disease
Vomiting (see Table 9-2)
Maldigestion
Exocrine pancreatic insufficiency (EPI) (does not always cause diarrhea)
Intestinal Malabsorption (Does not always cause diarrhea)
Malassimilation
Hepatic failure
Cardiac failure
Diabetes mellitus
Uremia
Cancer cachexia syndrome
Hypoadrenocorticism
Excessive Use or Loss of Calories
Hyperthyroidism
Excessive demand for calories because of environment or exertion
Lactation
Muscle Wasting
Myopathy
Neuropathy

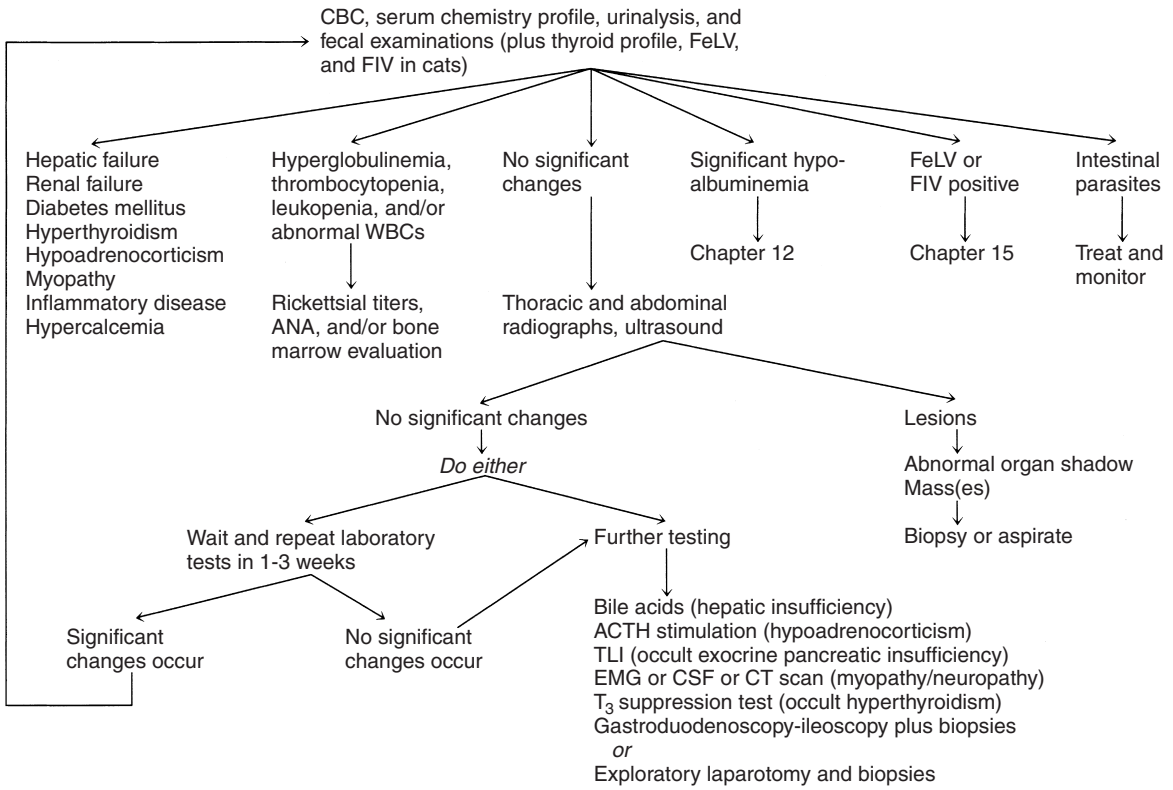

FIGURE 9-9. Diagnostic approach to chronic weight loss in dogs and cats when no other abnormalities are found on history or physical examination and the animal is not ingesting adequate calories (see Table 9-11). *ACTH,* Adrenocorticotropic hormone; *ANA,* antinuclear antibodies; *CBC,* complete blood count; *CSF,* cerebrospinal fluid; *EMG,* electromyogram; *FeLV,* feline leukemia virus; *FIV,* feline immunodeficiency virus; *TLI,* trypsin-like immunore-activity; *WBC,* white blood cell.

access to endoscopic equipment may consider exploratory laparotomy. If surgery is performed, gastric, duodenal, jejunal, ileal, mesenteric lymph node, and hepatic biopsies are usually appropriate, regardless of a normal gross appearance of the organs. In cats, the pancreas should also be biopsied.

Cancer cachexia can be particularly difficult to diagnose. It is a poorly defined, multifaceted syndrome that may involve loss of taste, malabsorption, increased metabolism with energy wasting, and other mechanisms. Almost any tumor can cause cancer cachexia, and no consistent laboratory findings exist. The causative cancer may be large or small, focal or diffuse; lymphomas and carcinomas are probably the most common causes.

Anorexia of unknown cause is similar to weight loss in being difficult to evaluate if no other identifiable abnormalities are seen. The diagnostic approach is similar to that for chronic weight loss (see Figure 9-9; Table 9-12).

TABLE 9-12. Categories of Diseases That Cause Anorexia

Psychologic (especially cats)
Inability to smell food
Dysphagia (especially when it causes pain)
Inflammation
Because of an etiologic agent
Because of immune-mediated disease
Because of neoplasia
Because of necrosis
Because of drugs
Alimentary and abdominal disease (especially that which causes nausea or abdominal pain)
Neoplasia
Because of the neoplasia itself
Because of secondary bacterial infection when the neoplasia impairs natural defense mechanisms
Toxins
Exogenous (various ones)
Endogenous (e.g., renal failure, hepatic failure)
Endocrine disease
Hypoadrenocorticism
Hyperthyroidism
Central nervous system (CNS) disease
Primary
Secondary

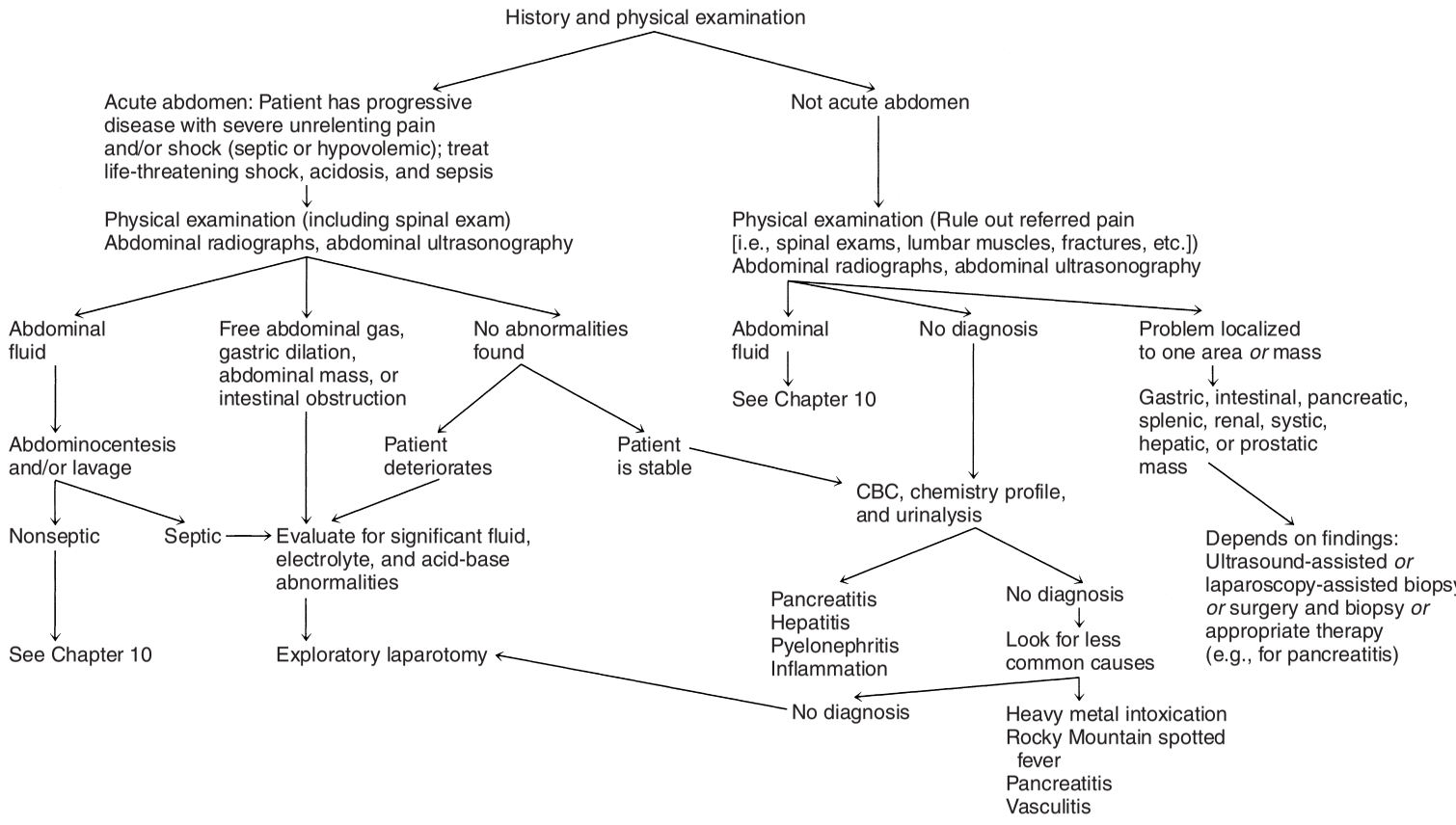

FIGURE 9-10. Diagnostic approach to abdominal pain in the dog and cat. *CBC,* Complete blood count.

Anorexia can be divided into three categories: (1) pseudoanorexia associated with inability to eat (oral, pharyngeal, or esophageal disease), (2) primary anorexia (rare) associated with a primary CNS disorder, and (3) secondary anorexia (the most common), which is the result of systemic or metabolic disease.

If necessary, one may elect a therapeutic trial to treat for a suspected problem in a patient in whom a diagnosis cannot be made. It is vital that one design such therapy so that it is safe and extremely likely to succeed if the presumptive disease is present. Then, if the trial fails, one may rule out that disease and go on to treat for something else. To do this, the clinician must be sure that the dose and duration of the treatment is sufficient.

ABDOMINAL PAIN

History, physical examination, radiographs, and ultrasonography are the initial tools in diagnosing the cause of abdominal pain (Figure 9-10). Extra-abdominal diseases such as spinal problems and patients predisposed to nonsurgical diseases (e.g., pancreatitis) must be identified early.

In patients with severe, progressive, acute abdomen (severe unrelenting pain or shock or stupor in a deteriorating patient), surgery is often indicated as soon as fluid, electrolyte, and acid-base status are acceptable for anesthesia. Imaging is desirable, but extensive laboratory testing is unlikely to identify the more common causes of acute abdomen (e.g., intestinal obstruction, gastric dilation and volvulus, peritonitis, organ ischemia, tumor, sepsis, or bleeding) and usually only delays surgical resolution of disease. Abdominal exploration offers a good chance for definitive diagnosis plus resolution of the disease process.

NOTE: These maladies do not always present as surgical emergencies.

If a patient is not in severe pain and the disease is not progressing rapidly, one must differentiate between problems that ultimately necessitate surgery and those that usually do not (e.g., pancreatitis, hepatitis, cholecystitis, upper urinary tract infection, prostatitis, pansteatitis, heavy metal intoxication, Rocky Mountain spotted fever [RMSF]). Abdominal ultrasonography is useful to examine the liver, spleen, pancreas, kidneys, and prostate, as well as to detect peritoneal fluid. If abdominal fluid is present, abdominocentesis or abdominal lavage with cytologic analysis is indicated. If these procedures are not revealing and the problem continues, exploratory surgery may be necessary. Contrast radiographs are rarely useful because thorough abdominal exploration should diagnose almost anything they reveal; finding an abnormality on radiographs simply is an indication for surgery. In rare situations the exhibited abdominal pain may be referred from other causes such as pulmonary disease or disk disease.

References

Allen L, Stobie D, Mauldin GN: Clinicopathologic features of dogs with hepatic microvascular dysplasia with and without portosystemic shunts, *J Am Vet Med Assoc* 214:218, 1999.

Cave NJ et al: Evaluation of a routine diagnostic fecal panel for dogs with diarrhea, *J Am Vet Med Assoc* 221: 52, 2002.

Center SA: Diagnostic procedures for evaluation of hepatic disease. In Guilford WG et al, editors: *Strombeck's small animal gastroenterology*, ed 3, Philadelphia, 1996, WB Saunders.

Cole TL et al: Diagnostic comparison of needle and wedge biopsy specimens of the liver in dogs and cats, *J Am Vet Med Assoc* 220:1483, 2002.

Gerhardt A et al: Comparison of the sensitivity of different diagnostic tests for pancreatitis in cats, *J Vet Int Med* 15:329, 2001.

Glick MR, Ryder KW, Glick SJ: *Interferographs: user's guide to interferences in clinical chemistry instruments*, ed 2, Indianapolis, 1991, Science Enterprises.

Guilford WG, Williams DA: Procedures for the evaluation of pancreatic and gastrointestinal diseases. In Guilford WG et al, editors: *Strombeck's small animal gastroenterology*, ed 3, Philadelphia, WB Saunders, 1996.

Hall EJ, Simpson KW: Diseases of the small intestine. In Ettinger SJ, Feldman EC, editors: *Textbook of veterinary internal medicine*, ed 5, Philadelphia, WB Saunders, 2000.

Hess PR, Bunch SE: Diagnostic approach to hepatobiliary disease. In Kirk RW, Bonagura JD, editors: *Kirk's current veterinary therapy 13*, Philadelphia, 2000, WB Saunders, 2000.

Kimmel SE, Washabau RJ, Drobatz KJ: Incidence and prognostic value of low plasma ionized calcium concentration in cats with acute pancreatitis: 46 cases, *J Am Vet Med Assoc* 219:1105, 2001.

Leib MS et al: Endoscopic aspiration of intestinal contents in dogs and cats: 394 cases, *J Vet Int Med* 13:191, 1999.

Ludlow CL, Davenport DJ: Small intestinal bacterial overgrowth. In Kirk RW, Bonagura JD, editors: *Kirk's current veterinary therapy 13*, Philadelphia, 2000, WB Saunders.

Marks SL et al: Genotypic and phenotypic characterization of *Clostridium perfringens* and *Clostridium difficile* in diarrheic and healthy dogs, *J Vet Int Med* 16:533, 2002.

Meyer DJ, Twedt DC: Effect of extrahepatic disease on the liver. In Kirk RW, Bonagura JD, editors: *Kirk's current veterinary therapy 13*, Philadelphia, 2000, WB Saunders.

Wilberg ME, Westermarck E: Subclinical exocrine pancreatic insufficiency in dogs, *J Am Vet Med Assoc* 220:1183, 2002.