CHAPTER 60

Pancreas

STRUCTURE AND FUNCTION

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Structure

Macroscopic Anatomy

The pancreas is a bilobed structure in companion animal species. The right lobe lies in the mesoduodenum in close apposition to the proximal duodenum. The right lobe extends posteriorly from the pylorus to the cecum. The left lobe lies in the greater omentum and lies in close apposition to the transverse colon caudally and the stomach cranially (Figure 60-1). The dog typically has two pancreatic ducts: a ventral or accessory pancreatic duct and a dorsal pancreatic duct. The ventral duct is the larger of the two and drains the right pancreatic lobe, while the dorsal duct drains the left lobe. These ducts usually intercommunicate within the gland. The ventral pancreatic duct is sometimes absent in the cat. In the cat, the dorsal pancreatic duct merges with the common bile duct prior to entry into the proximal duodenum.[1,2]

Microscopic Anatomy

The exocrine pancreas is a tubuloalveolar gland with a division of function between the acinar cells, which secrete the digestive enzymes, and the duct cells, which add water, bicarbonate, chloride, intrinsic factor, and antibacterial proteins. Throughout the pancreatic parenchyma are isolated clusters of cells forming the islets of Langerhans (Figure 60-2). The islets contain four major types of endocrine cells that synthesize and secrete glucagon (A cell), insulin (B cell), somatostatin and gastrin (D cell), and pancreatic polypeptide (PP cell). Although these hormones have other well-known physiologic effects, they also have important endocrine or paracrine effects on the pancreatic acini because of the islet–acinar portal venous system. Insulin appears to have long-term effects on the regulation of the biosynthesis of pancreatic digestive enzymes and short-term effects on the potentiation of pancreatic secretory response to gut hormones and neurotransmitters. Other islet hormones and peptides, including glucagon, somatostatin, and pancreatic polypeptide, probably act as inhibitory regulators of the pancreatic acini.

Blood Supply

The majority of the arterial blood supply of the right lobe of the pancreas arises from the celiac artery via the cranial and caudal pancreaticoduodenal arteries. The pancreatic branch of the splenic artery supplies the left side of the pancreas. Venous drainage of the right lobe of the pancreas is provided by the caudal pancreaticoduodenal vein, whereas the left lobe is drained by two veins that terminate in the splenic vein. Lymphatic drainage is by vessels that course into the duodenal, hepatic, splenic, and mesenteric lymph nodes.

In the dog and cat the exocrine pancreas does not have a direct arterial blood supply. Instead, an islet–acinar portal blood system exists, that is, the acini are perfused by venous blood arising from the islet vasa efferentia. Because some blood courses first to the islets, which secrete hormones into the blood, and then to the acinar cells, which secrete enzymes into the juice in response to stimulation by hormones, the pancreas has the potential to autoregulate part of its own exocrine secretion (see Figure 60-2).

Innervation

The efferent nerve supply to the pancreas is both sympathetic and parasympathetic (see Figure 60-2). Sympathetic postganglionic fibers emanate from the celiac and cranial mesenteric plexuses and accompany the arteries to the organ. Parasympathetic preganglionic fibers are distributed by branches of the vagi coursing down the antroduodenal region. Vagal fibers terminate at either acini and islets or intrinsic cholinergic nerves of the pancreas. In general, the sympathetic nerves inhibit and the parasympathetic nerves stimulate pancreatic exocrine secretion.

Function

Exocrine pancreatic secretions have four major functions: (a) initiate protein, carbohydrate, and lipid digestion through the secretion of digestive enzyme; (b) neutralize the duodenum with bicarbonate, chloride, and water; (c) facilitate cobalamin (vitamin B_{12}) absorption in the distal ileum via secretion of intrinsic factor; and, (d) regulate the small intestinal bacterial flora through secretion of antibacterial proteins.

Duct Cells

Water, anions, and cations are secreted primarily by the pancreatic duct cells. Bicarbonate is necessary to neutralize gastric acid that is emptied into the small intestine during feeding to prevent damage to the intestinal mucosa. Bicarbonate secretion also provides an increase in duodenal pH that is necessary for optimal activity of the secreted enzymes, particularly lipases. A fluid secretion isotonic to plasma and high in bicarbonate concentration is stimulated by the endocrine hormone secretin and the neurotransmitter vasoactive intestinal polypeptide from the duct cells of the exocrine pancreas.

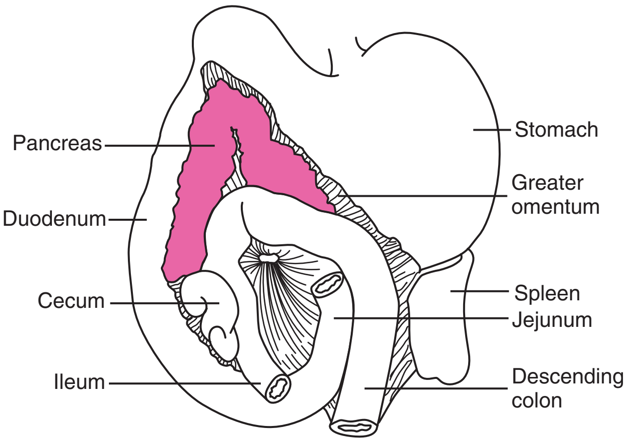

Figure 60-1 Anatomic relationship of the pancreas to other abdominal viscera. (Reprinted with permission from Johnson LR: *Gastrointestinal Physiology*, 2nd ed, Philadelphia, Elsevier, 2007.)

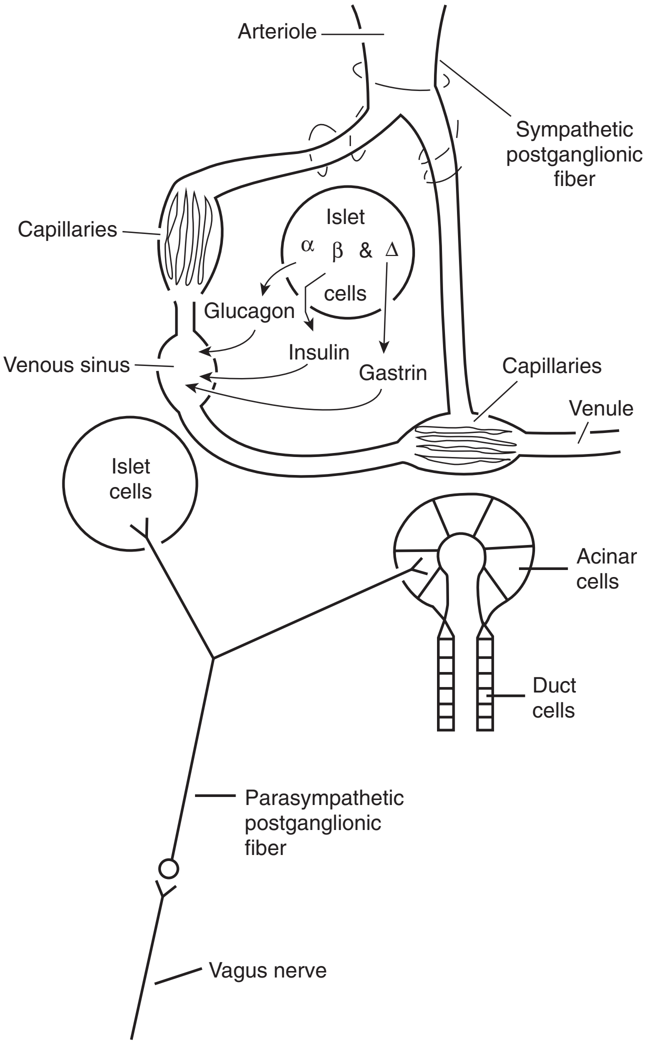

Figure 60-2 The pancreatic acinar and duct cells of the exocrine pancreatic parenchyma with their blood supply and autonomic nervous system innervation. (Reprinted with permission from Johnson LR: *Gastrointestinal Physiology*, 2nd ed, Philadelphia, Elsevier, 2007.)

Box 60-1 Enzymes Secreted from Acinar Cells in the Exocrine Pancreas

Endopeptidases: hydrolyze interior peptide bonds of polypeptides and proteins.

- Trypsin–attacks peptide bonds involving basic amino acids.
- Chymotrypsin–attacks peptide bonds involving aromatic amino acids, leucine, and glutamine.
- Elastase–attacks peptide bonds involving neutral and aliphatic amino acids.

Exopeptidases: hydrolyze external peptide bonds.

- Carboxypeptidase A–active against peptides with aromatic and aliphatic amino acids at the C-terminus.
- Carboxypeptidase B–active against peptides with basic amino acids at the C-terminus.
- Amylase–hydrolyzes dietary starch into the disaccharide maltose and α-limit dextrins.
- Lipase–hydrolyzes triglycerides into free fatty acids, 2-monoglycerides, and glycerol.
- Phospholipase–hydrolyzes phospholipids to 1-lysophospholipids and free fatty acids.
- Ribonuclease–releases pyrimidine nucleotides from polyribonucleotides.

The bicarbonate concentration increases with increasing flow rate, up to 150 mEq/L, while the chloride concentration correspondingly decreases, so that the sum of the anions remains constant. The cation concentrations are plasma-like and do not change with flow rate (Figure 60-3).

Most mammals have developed a complex process for vitamin B_{12} (cobalamin) absorption involving secretion of a gastric intrinsic factor, binding of gastric intrinsic factor to cobalamin, and subsequent attachment of this intrinsic factor–cobalamin complex to specific receptors on ileal enterocytes. The dog and cat appear to have diverged from this pattern and instead rely mostly (dog) or exclusively (cat) on pancreatic intrinsic factor synthesis and secretion. Canine and feline pancreatic duct cells secrete a pancreatic intrinsic factor that is the primary mechanism for binding and receptor-mediated endocytosis of cobalamin in the gut.[3,4]

Duct cells secrete several types of antibacterial proteins that act to regulate the endogenous microbial flora. With exocrine pancreatic insufficiency (EPI), affected animals develop predictable and severe nutrient maldigestion, acid injury to the duodenal mucosa, cobalamin and fat-soluble vitamin malabsorption, and bacterial proliferation in the gut.

Acinar Cells

The pancreatic acinar cell secretes its proteolytic enzymes in precursor form (zymogens). Other enzymes (amylase, lipase, ribonuclease) are secreted in an active form. The enzymes in pancreatic fluid have the ability to hydrolyze dietary starch (amylase), fats (lipase), proteins (trypsin, chymotrypsin, carboxypeptidase, elastase), and nucleic acids (ribonuclease, deoxyribonuclease; Box 60-1). The action of enterokinase, an enzyme secreted by the duodenal mucosa, activates trypsinogen into proteolytically active trypsin. Trypsin then acts autocatalytically to activate trypsinogen and other proteolytic zymogens (Figure 60-4).

Pancreatic acinar cells protect themselves from intraacinar activation of zymogen and acinar cell necrosis through several mechanisms: (a) potentially harmful digestive enzymes are synthesized in the form of inactive precursors or zymogens in the rough

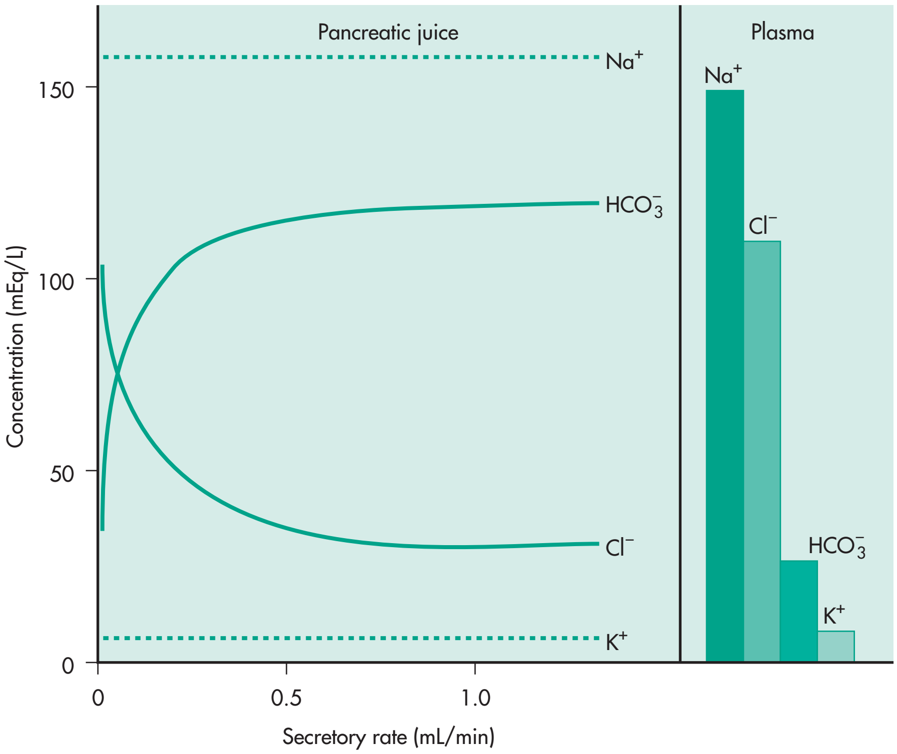

Figure 60-3 Chloride and bicarbonate secretion at low and high secretory flow rates from the canine pancreas. (Reprinted with permission from Johnson LR: *Gastrointestinal Physiology*, 2nd ed, Philadelphia, Elsevier, 2007.)

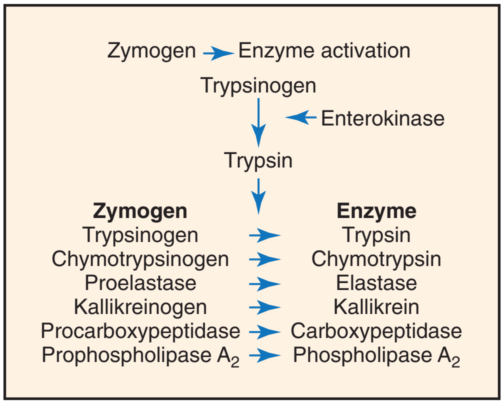

Figure 60-4 Exocrine pancreatic enzyme secretions are initiated by enterokinase activation of active trypsin from inactive trypsinogen.

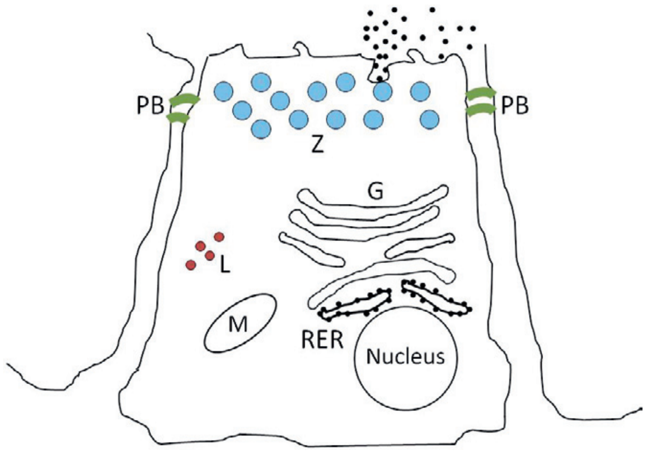

Figure 60-5 **Normal pancreatic acinar cell.** Zymogen granules are found in the apical region of the cell and their contents are excreted exclusively through the apical surface. Lysosomes are packaged and stored separately from zymogen granules and the paracellular barriers are intact. G, Golgi apparatus; L, lysosome; M, mitochondrion; PB, paracellular barrier; RER, rough endoplasmic reticulum; Z, zymogen granule. (Courtesy of Drs. Panagiotis Xenoulis and Joerg Steiner, Texas A & M University, College Station, Texas.)

endoplasmic reticulum; (b) zymogens are then transported to the Golgi complex where they undergo selective glycosylation. Lysosomal hydrolases that are eventually packaged in lysosomes are separated from zymogens bound for export as they pass through the Golgi complex. Lysosomal hydrolases are first phosphorylated at the six position of mannose residues, bound to receptors specific for 6-phosphoryl mannose, and then transported to lysosomes where the acid pH favors their dissociation from the receptors. Digestive enzymes lack the 6-phosphoryl mannose label, and are instead transported vectorially into a different secretory fraction; (c) packaging of zymogens into maturing zymogen granules sequesters them from contact with other subcellular fractions; (d) pancreatic secretory trypsin inhibitor (PSTI) is incorporated into the maturing zymogen granules. PSTI inactivates trypsin should there be any intraacinar activation of trypsinogen; (e) following stimulation (e.g., feeding and cholecystokinin secretion), mature zymogen granules and their contents are released from the cell into the ductal lumen in a process of membrane fusion and exocytosis; and (f) finally, zymogens are activated physiologically only after they enter the duodenum, where the brush-border enzyme enteropeptidase activates trypsinogen, and trypsin then activates other pancreatic zymogens (Figure 60-5).

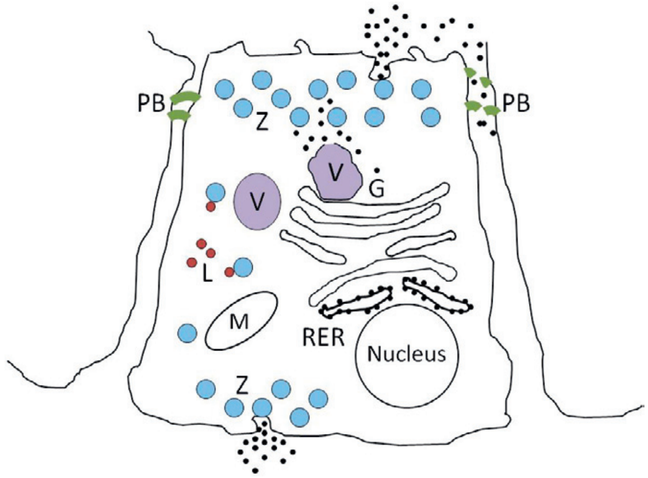

Figure 60-6 **Acute pancreatitis.** Secretion of the zymogen granules is redirected from the apical pole to the basolateral region of the acinar cell and into the interstitial space. Retention of zymogen granules is followed by co-localization with lysosomes and the formation of large vacuoles and premature intracellular activation of pancreatic enzymes. There is also disruption of the paracellular barrier in the pancreatic duct that allows its contents to leak into the paracellular space. G, Golgi apparatus; L, lysosome; M, mitochondrion; PB, paracellular barrier; RER, rough endoplasmic reticulum; V, vacuole; Z, zymogen granule. (Courtesy of Drs. Panagiotis Xenoulis and Joerg Steiner, Texas A & M University, College Station, Texas.)

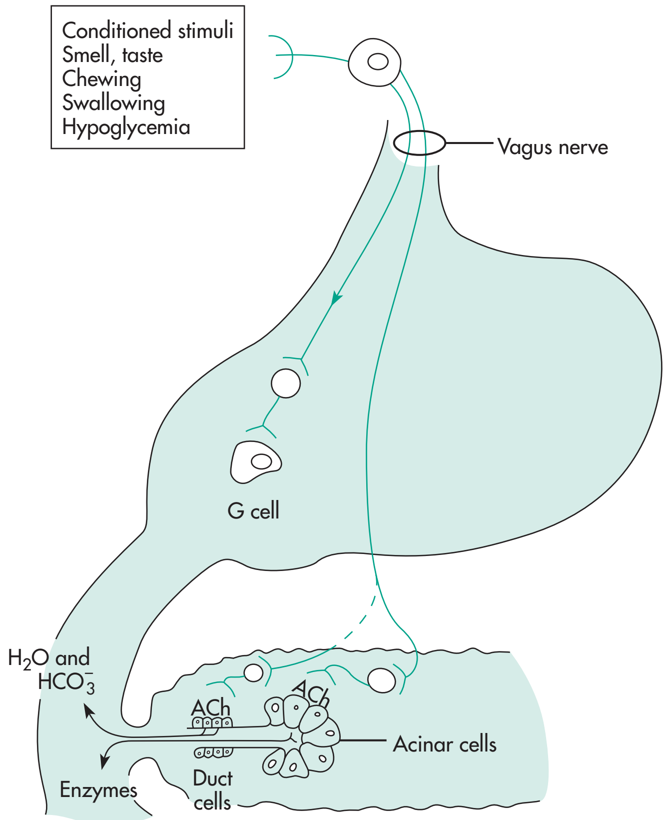

Figure 60-7 The cephalic phase of exocrine pancreatic secretion. (Reprinted with permission from Johnson LR: *Gastrointestinal Physiology,* 2nd ed, Philadelphia, Elsevier, 2007.)

A large body of experimental, and some clinical, evidence suggests that the initiating event of acute pancreatitis is the premature activation of digestive zymogens within the acinar cell.[5-8] Premature activation of digestive zymogen results in acinar cell necrosis and pancreatic autodigestion. In acute pancreatic necrosis, protein synthesis and intracellular transport to the Golgi complex appear to be normal, but digestive zymogens then become colocalized along with lysosomal hydrolases in large vacuoles. Cell biology studies reveal that lysosomal and zymogen granule fractions become colocalized through a process known as *crinophagy*, a process used by many cells to degrade accumulated secretory products when the need for secretion is no longer present. Although this process takes place in other cells without adverse consequences, it can be lethal in pancreatic acinar cells because of the peculiarity of their secretion products (digestive zymogens). Lysosomal hydrolases, such as cathepsin B and *N*-acetyl glucosaminidase, activate trypsinogen to the active trypsin form, and the enhanced fragility of these large vacuoles permits release of active enzyme into the cell cytoplasm (Figure 60-6). Trypsin acts autocatalytically to activate other trypsinogen molecules and other zymogens, each inducing a unique chemical pathology in pancreatic and extrapancreatic cells. A variety of inflammatory mediators and cytokines, interleukins, nitric oxide, and free radicals are involved in the further evolution of pancreatic acinar cell necrosis and inflammation, and often determine the outcome.[9] Thus, a bout of pancreatitis begins with an initiating event (e.g., ischemia, inflammation, or ductal obstruction) followed by acinar events (e.g., colocalization, enzyme activation, and cell injury), the outcome of which is influenced by severity determinants (e.g., inflammatory cytokines, reactive oxygen species, altered oxidation-reduction state, and apoptosis).[9] The further evolution of acute pancreatic necrosis to a systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome is determined by the balance of proinflammatory and antiinflammatory cytokines.[9]

Regulation of Secretion

Exocrine pancreatic secretions are regulated by hormonal, neural, and paracrine input during the cephalic, gastric, and intestinal phases of secretion. In the cephalic phase of exocrine pancreatic secretion, acetylcholine released by vagal postganglionic neurons stimulates H^+ ion secretion by parietal cells (Figure 60-7). Gastric acid evokes duodenal secretin release, which then stimulates pancreatic fluid and bicarbonate secretion. Vagal stimulation also releases gastrin from antral G cells. In the dog, gastrin is equipotent with cholecystokinin (CCK) in stimulating pancreatic enzyme secretion. Gastrin stimulates the parietal cells to secrete H^+.

In the gastric phase of exocrine pancreatic secretion, the same essential mechanisms are involved as those in the cephalic phase of pancreatic secretion (Figure 60-8). Protein digestion products in the stomach release gastrin, resulting in the stimulation of pancreatic enzyme secretion and gastric acid secretion. Gastric distention stimulates gastric mechanoreceptors, which in turn stimulate parietal cells through vagal reflexes. H^+ stimulates duodenal secretin release.

The intestinal phase of exocrine pancreatic secretion is the major phase of secretion (see Figure 60-8). The stimulus for the alkaline component from the duct cells is the hormone secretin. The only potent releaser of secretin is hydrogen ion. CCK is the principal humoral stimulant of enzyme secretion from the pancreatic acinar cells and is released physiologically in response to amino acids and fatty acids in the small intestine.

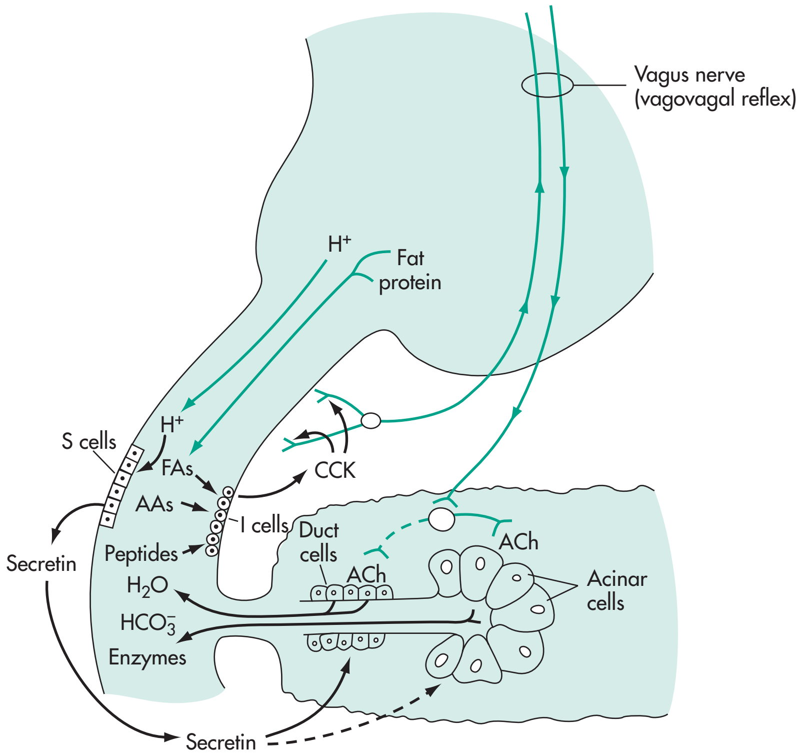

Figure 60-8 The gastric and intestinal phases of exocrine pancreatic secretion. (Reprinted with permission from Johnson LR: *Gastrointestinal Physiology*, 2nd ed, Philadelphia, Elsevier, 2007.)

DIAGNOSTIC EVALUATION OF THE PANCREAS

Panagiotis G. Xenoulis, Jörg M. Steiner

Exocrine pancreatic disorders are common in clinical practice and pancreatitis is by far the most common disorder of the exocrine pancreas in both dogs and cats. Clinical diagnosis of pancreatitis can be challenging and it has been suggested that most cases of canine and feline pancreatitis remain undiagnosed. This is supported by necropsy studies in both dogs and cats that report that histopathologic evidence of pancreatic inflammation is common in both species, even in patients that are not clinical.[1-3] Pancreatitis may be accompanied by relatively uncommon pancreatic complications such as pancreatic abscesses and pancreatic pseudocysts.

Exocrine pancreatic insufficiency (EPI) is the next most common disease of the exocrine pancreas in small animals. It is more common in dogs than in cats. It should be noted that in the past few years EPI has been diagnosed with increasing frequency in the feline population, likely as a result of increased awareness of this condition in cats and the availability of better tests for its diagnosis. In contrast to pancreatitis, the diagnosis of EPI is usually uncomplicated when appropriate tests are utilized.

Uncommon diseases of the exocrine pancreas include pancreatic neoplasia (metastatic or less commonly primary neoplasia), pancreatolithiasis, and pancreatic parasites. Nodular hyperplasia of the pancreas is a very common histopathologic finding, especially in older dogs and cats. However, its clinical relevance is unknown and it is believed that this condition is rarely if ever associated with clinical disease. However, it can potentially interfere with the diagnostic evaluation of the pancreas and display findings that are usually associated with other pancreatic diseases (e.g., pancreatitis, neoplasia).

Although the diagnostic evaluation of any patient, including those with exocrine pancreatic disease, should always take into consideration the clinical presentation and general clinicopathologic findings, this chapter mainly focuses on the diagnostic evaluation of the pancreas using diagnostic modalities that are believed to specifically assess pancreatic structure, function, and/or pathology. Table 60-1 summarizes the clinical performance of commonly used diagnostic modalities with regards to the diagnosis of pancreatitis in dogs and cats.

Pancreatitis

Signalment, History, and Risk Factors

Although dogs of any age, breed, or sex can develop pancreatitis, certain groups might be predisposed. Most dogs presented with pancreatitis are middle-aged or older (usually more than 5 years old).[4,5] Several breeds have been reported or suspected to be at increased risk (e.g., Miniature Schnauzers, Yorkshire Terriers, Cocker Spaniels, Cavalier King Charles Spaniels, Collies, and Boxers) but none of these predispositions are consistent among studies.[3-6] Also, no clear sex predisposition has been identified.

Several pathologic conditions have been identified as potential risk factors for pancreatitis in dogs and, although a cause-and-effect relationship has not been established for most of them, their presence along with compatible clinical signs may raise the concern for pancreatitis. Many dogs with pancreatitis are overweight or obese.[5] Also, endocrinopathies such as hyperadrenocorticism, hypothyroidism, and diabetes mellitus may be risk factors for pancreatitis.[5] A history of drug administration (e.g., potassium bromide, phenobarbital, azathioprine, L-asparaginase, meglumine antimonite) in

Table 60-1 Biochemical and Imaging Findings in Dogs and Cats Affected with Acute Necrotizing Pancreatitis

Pancreatic Enzymes	Sensitivity (%)	Specificity (%)	Comment
PERFORMANCE OF SELECTIVE DIAGNOSTIC TESTS FOR PANCREATITIS			
DOGS			
Serum amylase	18-69	~50	Somewhat useful for initial evaluation. Both positive and negative results require verification with more sensitive and specific tests.
Serum lipase	14-73	~50	Somewhat useful for initial evaluation. Both positive and negative results require verification with more sensitive and specific tests.
Serum TLI	36-47	Relatively high	Low sensitivity—normal concentrations do not exclude pancreatitis. Renal failure and intestinal disease might give false positive results. High concentrations in the absence of renal or intestinal disease are suggestive of pancreatitis.
Serum PLI	64-93	93	Highly sensitive and specific. Most accurate serum test for pancreatitis currently available.
Serum TAP	53	88	Not adequately evaluated. High cost. Limited availability.
Imaging Methods			
Abdominal radiography	24	Low	Not useful for the diagnosis or exclusion of pancreatitis. Useful for the evaluation of other diseases.
Abdominal ultrasonography	68	Relatively high	Useful for the diagnosis of pancreatitis. It is very operator- and equipment-dependent. Relatively high specificity if stringent criteria are applied. Negative results do not rule out pancreatitis.
Computed tomography	N/A	N/A	Not adequately evaluated. High cost.
Pancreatic Cytology	N/A	High	Minimally invasive. Highly specific, but pancreatic lesions might be missed if they are localized (low sensitivity?).
Pancreatic Histopathology	Can be high	High	The gold standard for confirmation of pancreatitis. It is invasive, it has high cost, and cannot be performed in severely compromised patients. Lesions are often highly localized so multiple biopsies must be evaluated before pancreatitis can be ruled out (potentially low sensitivity if only one biopsy is evaluated).
CATS			
Pancreatic Enzymes			
Serum amylase	Low	Low	Not useful for the diagnosis of pancreatitis.
Serum lipase	Low	Low	Not useful for the diagnosis of pancreatitis.
Serum TLI	28-64	82	Low sensitivity—normal concentrations do not exclude pancreatitis. Renal failure and intestinal disease might give false positive results. High concentrations in the absence of renal or intestinal disease are suggestive of pancreatitis.
Serum PLI	54-100	91	Highly sensitive and specific. Most accurate serum test for pancreatitis currently available.
Serum TAP	100	82	Not adequately evaluated. High cost. Limited availability.
Imaging Methods			
Abdominal radiography	Low	Low	Not useful for the diagnosis or exclusion of pancreatitis. Useful for the evaluation of other diseases.
Abdominal ultrasonography	11-67	Relatively high	Somewhat useful for the diagnosis of pancreatitis. It is very operator- and equipment-dependent. Relatively high specificity if stringent criteria are applied. Negative results do not rule out pancreatitis.
Computed tomography	Low	N/A	Low sensitivity. Not recommended.
Pancreatic Cytology	N/A	High	Minimally invasive. Highly specific, but pancreatic lesions might be missed if they are localized (low sensitivity?).
Pancreatic Histopathology	Can be high	High	The gold standard for confirmation of pancreatitis. It is invasive, it has high cost, and cannot be performed in severely compromised patients. Lesions are often highly localized so multiple biopsies must be evaluated before pancreatitis can be ruled out (potentially low sensitivity if only one biopsy is evaluated).

Table 60-1 Biochemical and Imaging Findings in Dogs and Cats Affected with Acute Necrotizing Pancreatitis–cont'd

CLINICAL PERFORMANCE OF SELECTED DIAGNOSTIC MODALITIES FOR THE DIAGNOSIS OF PANCREATITIS				
DOGS				
Pancreatic Enzymes	**Sensitivity (%)**	**Specificity (%)**	**Comment**	**Usefulness**
Serum amylase	18-69	~50	Low sensitivity and specificity. Somewhat useful for initial evaluation. Both positive and negative results require verification with more sensitive and specific tests.	Somewhat useful
Serum lipase	14-73	~50	Low sensitivity and specificity. Somewhat useful for initial evaluation. Both positive and negative results require verification with more sensitive and specific tests.	Somewhat useful
Serum TLI	36-47	Relatively high	Low sensitivity–normal concentrations do not exclude pancreatitis. Renal failure and intestinal disease might give false positive results. High concentrations in the absence of renal or intestinal disease are suggestive of pancreatitis.	Somewhat useful
Serum PLI	64-93	93	Highly sensitive and specific. Most accurate serum test for pancreatitis currently available.	Useful
Imaging Methods				
Abdominal radiography	24	Low	Not useful for the diagnosis or exclusion of pancreatitis. Useful for the evaluation of other diseases.	Not useful
Abdominal ultrasonography	68	Relatively high	Relatively high sensitivity and specificity if stringent criteria are applied. It is very operator- and equipment-dependent. Negative results do not rule out pancreatitis.	Useful
Pancreatic Cytology	N/A	N/A	Minimally invasive. Must be performed under ultrasonographic guidance. Specificity is believed to be high, but pancreatic lesions might be missed if they are localized (low sensitivity?).	Potentially useful
Pancreatic Histopathology	Can be high	High	The gold standard for confirmation of pancreatitis. It is invasive and cannot be performed in severely compromised patients. Lesions are often highly localized so multiple biopsies must be evaluated before pancreatitis can be ruled out (potentially low sensitivity if only one biopsy is evaluated).	Useful
CATS				
Pancreatic Enzymes				
Serum amylase	Low	Low	Not useful for the diagnosis of pancreatitis.	Not useful
Serum lipase	Low	Low	Not useful for the diagnosis of pancreatitis.	Not useful
Serum TLI	28-64	82	Low sensitivity–normal concentrations do not exclude pancreatitis. Renal failure and intestinal disease might give false positive results. High concentrations in the absence of renal or intestinal disease are suggestive of pancreatitis.	Somewhat useful
Serum PLI	54-100	91	Highly sensitive and specific. Most accurate serum test for pancreatitis currently available.	Useful
Imaging Methods				
Abdominal radiography	Low	Low	Not useful for the diagnosis or exclusion of pancreatitis. Useful for the evaluation of other diseases.	Not useful
Abdominal ultrasonography	11-67	Relatively high	Relatively high sensitivity and specificity if stringent criteria are applied. It is very operator- and equipment-dependent. Negative results do not rule out pancreatitis.	Useful
Pancreatic Cytology	N/A	N/A	Minimaly invasive. Must be performed under ultrasonographic guidance. Specificity is believed to be high, but pancreatic lesions might be missed if they are localized (low sensitivity?).	Potentially useful
Pancreatic Histopathology	Can be high	High	The gold standard for confirmation of pancreatitis. It is invasive, it has high cost, and cannot be performed in severely compromised patients. Lesions are often highly localized so multiple biopsies must be evaluated before pancreatitis can be ruled out (potentially low sensitivity if only one biopsy is evaluated).	Useful

conjunction with compatible findings should also raise a concern for pancreatitis.[5,7] Hypertriglyceridemia, when severe (higher than approximately 850 mg/dL), is a risk factor for pancreatitis in Miniature Schnauzers.[8] This might also be true for dogs of other breeds that exhibit severe hypertriglyceridemia, but this has not yet been proven. Dietary factors (e.g., getting into the trash, consuming table scraps, ingestion of "unusual" food) and surgery at any time prior to diagnosis of pancreatitis also have been suggested as risk factors for pancreatitis in dogs.[6]

Similarly to dogs, cats of any age, breed, or sex can develop pancreatitis. Older cats appear to be more likely to develop chronic pancreatitis.[2,9-11] Domestic shorthair and Siamese breeds are reported to be at an increased risk in some studies, but this has not been confirmed by other studies.[2,9-11]

Clinical Signs and Physical Examination Findings

Dogs with pancreatitis can present with a wide variety of clinical signs, which can range from mild partial anorexia with no apparent gastrointestinal signs to cardiovascular shock, disseminated intravascular coagulation (DIC), and death. There is no single clinical sign or combination of clinical signs that is pathognomonic for pancreatitis in dogs. Recent reports suggest that pancreatitis may be subclinical in some cases, or be associated with only mild and nonspecific clinical signs such as anorexia and weakness.[1] In more typical cases, in addition to anorexia and weakness, dogs present with vomiting, diarrhea, and/or abdominal pain.[5,12] The concurrent signs of vomiting and cranial abdominal pain is considered suggestive, but not pathognomonic, of pancreatitis in dogs. Evidence of dehydration, abdominal pain, icterus, fever or hypothermia, icterus, bleeding diathesis, or ascites may be seen on physical examination.[5] Severe systemic complications (e.g., cardiovascular shock, DIC, or multiorgan failure) might occur in patients with severe pancreatitis.[12,13] Other clinical signs may be observed as a consequence of concurrent disease (e.g., polyuria/polydipsia in animals with diabetes mellitus).[5]

The most common clinical signs in cats with pancreatitis do not specifically indicate gastrointestinal disease and include complete or partial anorexia and lethargy.[9-11,14] Vomiting, weight loss, and diarrhea are reported less commonly in the cat.[9-11,14] Abdominal pain may be evident in cats with acute pancreatitis but could be missed during routine physical examination. The most common physical examination findings are dehydration, pallor, and icterus.[9-11,14] Tachypnea and/or dyspnea, hypothermia/fever, tachycardia, signs of abdominal pain, and a palpable abdominal mass may also be noted.[9-11,14] Severe systemic complications (e.g., DIC, pulmonary thromboembolism, cardiovascular shock, and multiorgan failure) occasionally may be seen in cats with severe pancreatitis.

Routine Clinical Pathology[5,9-12,14,15]

Results of complete blood count, serum biochemistry profile, and urinalysis are nonspecific and thus not useful in the definitive diagnosis of pancreatitis in dogs and cats. However, these tests should always be performed in animals with suspected pancreatitis because they are useful for the diagnosis or exclusion of other diseases, and also give important information about the general condition of the patient.

The complete blood cell count, serum biochemistry profile, and urinalysis are often normal in mild cases. Possible hematologic findings in dogs and cats with pancreatitis include anemia or hemoconcentration, leukocytosis or leukopenia, and thrombocytopenia. Coagulopathies and DIC may be seen in more severe cases. Increases in hepatic enzyme activities and hyperbilirubinemia are common in both dogs and cats, and might erroneously direct the clinician to suspect primary liver disease. Azotemia is variably present and is most often associated with dehydration due to vomiting or diarrhea. Other possible findings include hypoalbuminemia, hypertriglyceridemia, hypercholesterolemia, and hyperglycemia. Electrolyte abnormalities are commonly present, most importantly, hypokalemia, hypochloremia, and hyponatremia. Hypocalcemia is much more commonly seen in cats than in dogs, and is one of the most clinically important electrolyte disturbances in this species. Some cats with pancreatitis have hypocobalaminemia, which likely may reflect concurrent intestinal disease.

Clinical Enzymology

Serum Pancreatic Lipase Immunoreactivity Concentration. There are multiple circulating lipases of various cellular origins (e.g., pancreatic, hepatic, and gastric) and all of them share the same function (i.e., hydrolysis of triglycerides). Therefore, in assays of lipase activity, many of the different lipases may contribute to the total serum lipase activity. More recently, it was shown that lipases of different cellular origins are encoded by different genes and consequently have differing amino acid sequences. Pancreatic lipase is expressed exclusively by pancreatic acinar cells and is structurally different from other lipases. Thus immunoassays for the specific measurement of pancreatic lipase have been developed and analytically validated for dogs and cats.[16,17] In contrast to the traditional activity assays for lipase, which indiscriminately measure the activity of lipases of any origin, these immunoassays specifically quantify lipases based on their unique structure. Consequently, they are considerably more useful for exocrine pancreatic disease than assays for serum lipase activity. During pancreatitis pancreatic lipase leaks from acinar cells and enters the circulation in larger than normal quantities and can be detected by specific immunoassays for pancreatic lipase.

The originally developed immunoassays for pancreatic lipase were in-house immunoassays that used polyclonal antibodies and had limited availability. Commercial immunoassays (e.g., Spec cPL for dogs and Spec fPL for cats) are now more routinely available.[18,19]

Canine pancreatic lipase is believed to be exclusively of pancreatic origin.[20-22] An immunolocalization study has identified the pancreatic acinar cell as the cell of origin.[20] Dogs with EPI have near total absence of serum canine pancreatic lipase immunoreactivity (cPLI) again suggesting that cPLI is likely of exocrine pancreatic origin.[21] The specificity of Spec cPL was reported to be 96.8% in another study of 31 dogs with normal pancreatic histology.[22] In a recent multicenter study, the specificity of cPLI was estimated to be at least 78% in dogs with a clinical diagnosis of pancreatitis.[23] Experimentally induced chronic renal failure and prednisone administration have not been found to have any clinically significant effect on serum cPLI concentration.[24,25]

Serum cPLI concentration is also sensitive for the diagnosis of pancreatitis in dogs.[18,23,26,27] The reported sensitivity of cPLI for the diagnosis of canine pancreatitis ranges from 64% to 93%, depending on the severity of the disease. This is considerably higher than the sensitivity reported for serum canine trypsin-like immunoreactivity (cTLI) concentration (36.4% to 46.7%), serum amylase activity (18.2% to 73.3%), and serum lipase activity (13.6% to 69%), and is similar to or higher than that of abdominal ultrasound (67% to 68%) performed by a board-certified radiologist.[5,18,23,26-28] In a recent preliminary report of a multicenter study, the sensitivity of this assay was estimated at 93%.[23] Because of its high sensitivity, normal serum cPLI concentrations make a diagnosis of clinically relevant pancreatitis very unlikely. However, it remains to be determined if, as a consequence of its high sensitivity, cPLI detects pancreatic pathology that is not clinically relevant. Based on the aforementioned studies, serum cPLI concentration is the most sensitive and specific test currently available for pancreatitis in dogs.

Recently, a point-of-care test for the estimation of pancreatic lipase in serum (SNAP cPL) was released. Studies evaluating the performance of this test are currently lacking and comparative studies (e.g., with serum Spec cPL assay) have not yet been reported. The recommended use of this new test is mainly for rapid rule-out diagnosis in dogs suspected of having pancreatitis. A positive test result should always be followed up by laboratory measurement of serum Spec cPL concentration to confirm the diagnosis and to serve as a baseline for monitoring disease progress. A negative test result makes a diagnosis of pancreatitis unlikely.

Studies in cats with both experimental and spontaneous pancreatitis have shown that serum feline pancreatic lipase immunoreactivity (fPLI) concentration is very sensitive for pancreatitis.[29-31] In one of these studies, fPLI was found to be 100% sensitive for moderate to severe spontaneous feline pancreatitis, which was superior to the sensitivities of serum feline trypsin-like immunoreactivity (fTLI) concentration (28%) or abdominal ultrasound (80%).[29] In a recent preliminary report, the sensitivity of serum fPLI concentration was reported at 78%.[31] Considering the overall sensitivities for pancreatitis reported for serum fPLI concentration (67% to 78%), fTLI (28% to 64%), and abdominal ultrasonography (11% to 67%), serum fPLI concentration currently appears to be the most sensitive test for the diagnosis of feline pancreatitis.[29,31-35] The specificity of serum fPLI concentration of 82% to 91%, has been reported to be superior to that of fTLI (82%) or abdominal ultrasound (73%).[15,29,31] Further studies are needed to confirm the reproducibility of these findings, but serum fPLI concentration currently appears to be the most useful test for the diagnosis of feline pancreatitis.

A point-of-care test for the estimation of Spec fPL (SNAP fPL) has not been released at the time of writing of this chapter, but is expected to be available in the near future.

Serum Amylase and Lipase Activities. Serum amylase and lipase activity assays have long been considered markers for pancreatitis in dogs.[36,37] Serum activities of these two enzymes increase during experimental canine pancreatitis, but studies of spontaneous canine pancreatitis have shown poor sensitivity and specificity.[18,36-41] Gastric mucosal and hepatic parenchymal amylases and lipases are routinely detected in activity assays, which has contributed to limitations in sensitivity and specificity. Moreover EPI and pancreatectomized dogs both have significant residual circulating lipase and amylase activity, indicating that tissues other than the pancreas account for a large portion of the serum activity of lipase and amylase.[21,41] Traditional catalytic assays, are not able to differentiate amylases and lipases according to their tissue of origin. This leads to a low specificity of serum amylase and lipase activities for pancreatitis in dogs.[28,36]

Many dogs that have extrapancreatic disease have increased serum lipase and/or amylase activities.[36] The main nonpancreatic conditions associated with increased serum amylase and/or lipase activities include renal, hepatic, intestinal, and neoplastic diseases, as well as corticosteroid administration (only for lipase activity). It has been suggested that only increases of amylase and lipase activities of more than three to five times the upper limit of the reference range should be considered suggestive of pancreatitis in dogs, so as to increase the specificity of these assays.[42,43] However it has been shown that even such increases can result from nonpancreatic disorders.[28,36,43,44] Therefore increased serum amylase and/or lipase activities do not confirm the presence of pancreatitis in any case and more specific tests need to be utilized.

The sensitivity of serum amylase and lipase activities for spontaneous canine pancreatitis varies but is generally low (32% to 73% for lipase activity and 41% to 69% for amylase activity) and it is even lower when a cutoff value of three or five times the upper limit of the respective reference interval is used (14% for lipase activity and 18% for amylase activity in one study that used a cutoff of three times the upper limit of the reference range).[5,18,27] Thus many dogs with pancreatitis may have normal serum activities , and therefore normal serum amylase and/or lipase activities do not rule out pancreatitis.[5,36] The low sensitivity of serum amylase and lipase activity assays is at least partially associated with the broad reference intervals for these assays, which are the result of extrapancreatic amylase and lipase activities. A new lipase assay (using the substrate 1,2-O-dilauryl-rac-glycero glutaric acid-[69-methyl resorufin]-ester (DGGR) was recently evaluated and might be more useful for the initial evaluation of dogs suspected of having pancreatitis because of its higher sensitivity (93%) compared with the traditional assays.[45] However, the specificity of this assay was very low (53%), limiting the clinical usefulness of this assay.[45]

Serum lipase activity increases and serum amylase activity decreases in experimentally induced acute pancreatitis in cats.[30,46,47] Although well-designed clinical studies are lacking, both serum lipase and amylase activities do not appear to be of any clinical value in the diagnosis of spontaneous feline pancreatitis.[10,32,48] Therefore these two tests are not recommended for the diagnosis of pancreatitis in cats.[10,48]

Trypsin-Like Immunoreactivity. Trypsin-like immunoreactivity (TLI) assays are species-specific immunoassays that measure trypsinogen and trypsin in serum. Trypsinogen is the inactive preform (or zymogen) of trypsin, a proteolytic enzyme synthesized exclusively in pancreatic acinar cells and normally secreted into the duodenum where it is activated by enterokinases. Only minimal amounts of trypsin are released into the circulation. During pancreatitis, trypsinogen and prematurely activated trypsin enter the circulation in large quantities, and can be measured with the TLI assay.

Serum cTLI concentrations increase after experimental induction of pancreatitis in dogs, but rapidly decrease to reference interval concentrations within 3 days of disease induction.[40] The sensitivity of serum cTLI for the diagnosis of spontaneous pancreatitis is low (36% to 47%), probably as a result of its short half-life.[18,27,28] In addition, although there is strong evidence that trypsinogen is exclusively of pancreatic origin,[41] it is believed that it is cleared by glomerular filtration, and serum cTLI concentration can be increased in dogs with glomerular and other renal diseases.[28,40] This clearly affects the specificity of the test and complicates the interpretation of increased cTLI concentrations in dogs with azotemia.

In cats with experimentally induced pancreatitis, fTLI concentration increases sharply after induction of pancreatitis, but returns below the cutoff value for pancreatitis within 48 hours.[30] fTLI has been evaluated for the diagnosis of spontaneous pancreatitis in cats and several cutoff values have been suggested.[33-35] When cutoff values allowing adequate specificity of the assay are used (i.e., 100 μg/L), the sensitivity of fTLI for the diagnosis of pancreatitis in cats is generally low (28% to 33%), with the highest reported sensitivity for this cutoff value being 64%.[33-35] In addition, the specificity of fTLI has been questioned, because mildly increased serum fTLI concentrations have been reported in cats with no demonstrable pancreatic disease, but other gastrointestinal disorders (e.g., inflammatory bowel disease or gastrointestinal lymphoma) and azotemia.[15,33,35]

In the face of availability of better serum markers (cPLI and fPLI), cTLI and fTLI are currently considered to be of limited usefulness for the diagnosis of canine and feline pancreatitis, respectively.

Other Diagnostic Markers. Several other diagnostic markers for pancreatitis have been developed and studied, but none can be recommended for the diagnosis of canine and feline pancreatitis in clinical practice, either because their diagnostic performance has not been sufficiently evaluated clinically, or because they have been shown to have a low sensitivity and/or specificity. In addition, the availability of most of these diagnostic tests is currently limited. Such tests include the determination of serum concentrations of phospholipase A_2, trypsin-α_1-antitrypsin complexes, and α_2-macroglobulin, plasma and urine concentrations of trypsinogen activation peptide, and lipase activity in peritoneal fluid.

Diagnostic Imaging

Abdominal Radiography. Conclusive diagnosis or exclusion of pancreatitis is not possible based on abdominal radiography alone.[5,9-11,34,43] In the majority of cases of canine and feline pancreatitis abdominal radiographs are normal or reveal nonspecific findings. Despite that, radiography remains a logical initial approach for patients suspected of having pancreatitis because it is relatively inexpensive and useful for the diagnosis and/or ruling out of other differential diagnoses.

In a group of 70 dogs with fatal acute pancreatitis the sensitivity of abdominal radiography was very low (24%).[5] Radiographic findings that have been reported for dogs with pancreatitis include an increased soft tissue opacity and decreased serosal detail in the cranial right abdomen, indicating localized peritonitis.[5] Other findings may include displacement of the stomach and/or duodenum from their normal positions and gaseous dilation of bowel loops adjacent to the pancreas.[5] Abdominal effusion or the presence of an abdominal mass might also be detected. Radiographic findings in cats with pancreatitis are similar to those in dogs.[10,11,34,49] In any case, radiography should always be followed by use of more sensitive and specific tests for the definitive diagnosis or exclusion of pancreatitis.

Abdominal Ultrasound. Abdominal ultrasound is considered the imaging method of choice for the diagnosis of pancreatitis in dogs and cats. However, the performance of ultrasonography in the diagnosis of pancreatitis is highly dependent on the experience of the ultrasonographer and the quality of the instrumentation.

Abdominal ultrasound has been reported to have a relatively high sensitivity of approximately 68% for severe acute pancreatitis in dogs,[5] although with increasing equipment quality the sensitivity might have increased since this report.[5] Abdominal ultrasound has mainly been assessed in dogs with fatal acute pancreatitis, in which lesions are usually pronounced, but its sensitivity would be expected to be lower in cases with mild or moderate pancreatitis.[5] It must be emphasized that a normal pancreas on ultrasound examination does not rule out pancreatitis in dogs.

Ultrasonographic findings in dogs with pancreatitis include hypoechoic areas within the pancreas (possibly indicating necrosis or fluid accumulation), increased echogenicity of the surrounding mesentery (because of necrosis of the peripancreatic fat), enlargement and/or irregularity of the pancreas, dilation of the pancreatic or biliary duct, and abdominal effusion (Figure 60-9).[5,50] On occasion,

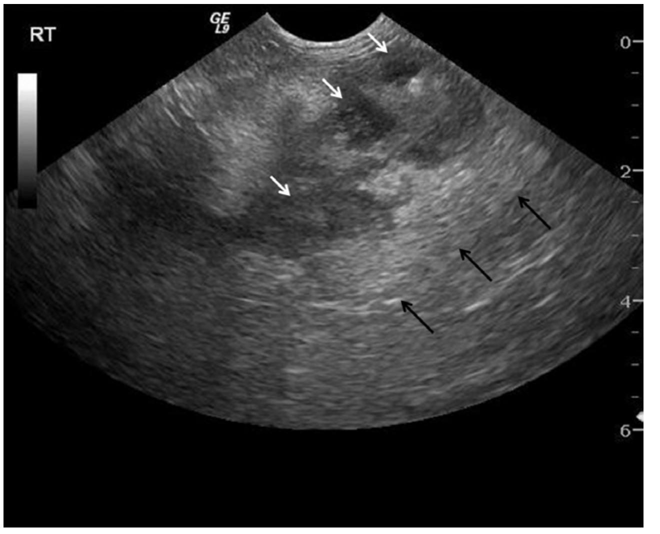

Figure 60-9 Ultrasonographic appearance of the pancreas of a dog with pancreatitis. The pancreas is enlarged and appears heterogenous, with hypoechoic areas (*white arrows*) and hyperechoic surrounding fat (*black arrows*). These findings are highly suggestive of pancreatitis. (Courtesy Dr. B. Young, Texas A&M University.)

hyperechoic areas of the pancreas can be identified, possibly indicating the presence of pancreatic fibrosis. Cavitary lesions, a thickened duodenum, and biliary obstruction might also be noted.[50] If stringent criteria are applied, the specificity of abdominal ultrasonography for canine pancreatitis is considered to be relatively high, although other diseases of the pancreas (e.g., neoplasia, hyperplastic nodules, edema caused by portal hypertension or hypoalbuminemia) may display similar ultrasonographic findings and cannot be differentiated from pancreatitis in many cases.[51,52] In a recent study where ultrasonography was performed in 26 animals (both dogs and cats) with suspected gastrointestinal disease, 6 (23.1%) of the animals had ultrasonographic evidence consistent with pancreatitis, while histopathology revealed either a normal pancreas or pancreatic hyperplasia.[53] In the same study, there was only a 22% agreement between the ultrasound report and pancreatic histopathology in dogs.[53] These data raise concerns regarding the accuracy of ultrasonography in evaluating the canine pancreas and underscore the importance of not overinterpreting ultrasonographic findings.

The reported sensitivity of abdominal ultrasonography for the diagnosis of feline pancreatitis is generally low (11% to 35%), with only one study reporting a sensitivity of 67%.[11,29,33,49] This high range of sensitivity likely reflects differences in the level of suspicion or the skills of the examiner, the equipment used, and the severity of lesions, and highlights the lack of standardized diagnostic criteria.[33,34,49] The low sensitivity of abdominal ultrasonography suggests that many cats with pancreatitis remain undiagnosed if the diagnosis is based solely on ultrasound examination.[11,33,49] The sensitivity of abdominal ultrasonography is believed to have increased since the reports mentioned previously as a result of advances in equipment and an increasing level of awareness of the importance of feline pancreatitis, although this has not yet been confirmed. Abdominal ultrasonography has been thought to be relatively specific for the diagnosis of pancreatitis is cats but, similarly to dogs, other diseases (e.g., pancreatic neoplasia, edema) may be associated with similar findings.[54] In a recent study, there was an overall agreement of only 33% between the ultrasound report and pancreatic histopathology in cats, and some cats that had ultrasonographic evidence of

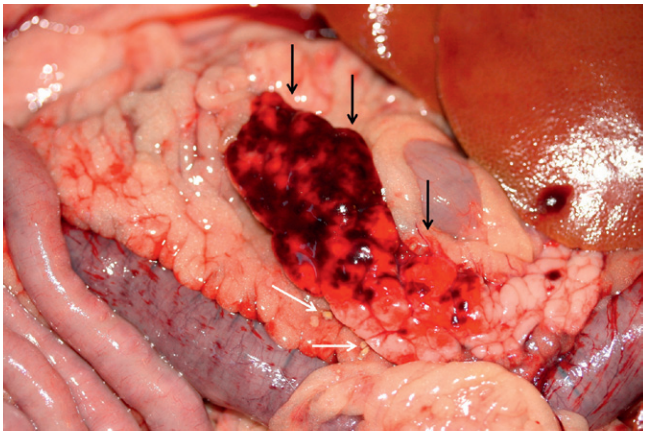

Figure 60-10 Gross Appearance of the pancreas of a dog with acute pancreatitis. The pancreas appears severely hemorrhagic, necrotic, and edematous (*black arrows*). There is also peripancreatic fat necrosis (*white arrows*). Such appearance is highly suggestive of pancreatitis. (Courtesy Dr. D. Ajithdoss, Texas A&M University.)

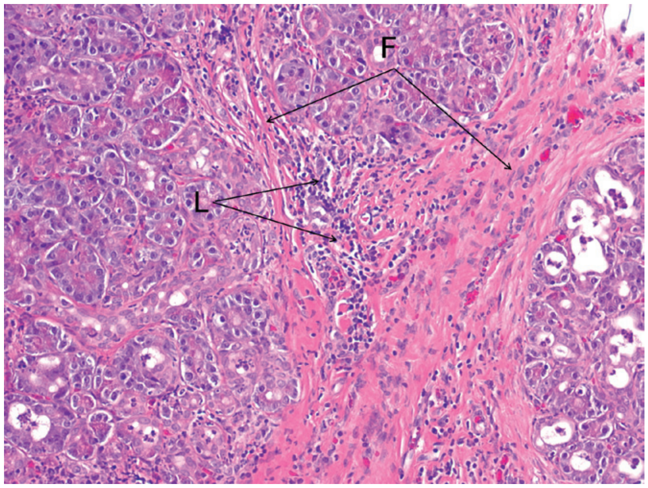

Figure 60-11 Histopathologic appearance of the pancreas of a cat with chronic pancreatitis. There is extensive fibrosis (*F*) and lymphocytic infiltration (*L*). Hematoxylin and eosin; magnification: 200×. (Courtesy Dr. B.F. Porter, Texas A&M University.)

pancreatitis had no evidence of pancreatitis on histopathology.[53] Ultrasonographic findings in cats with pancreatitis are similar to those described in dogs.[11,33,49,50,55] It has been suggested that a dilation of the pancreatic duct is suggestive of pancreatitis in cats, but studies have not confirmed this hypothesis.[56] In general, feline pancreatitis is often difficult to diagnose by abdominal ultrasound examination and it is important to note that a normal ultrasound examination does not rule out feline pancreatitis.[29,33]

Overall, abdominal ultrasonography is very useful for the diagnosis of pancreatitis in dogs and cats, especially when performed by an experienced ultrasonographer. Caution should be taken however not to overinterpret ultrasonographic findings. Abdominal ultrasonography is also helpful in detecting possible concurrent abdominal disease in dogs and cats suspected of having pancreatitis. In addition, ultrasound-guided fine-needle aspiration is a useful tool for the diagnosis of pancreatitis and some of its complications (e.g., pancreatic pseudocyst and pancreatic abscess), as well as the management of noninfectious fluid accumulations (e.g. pancreatic pseudocyst).[55]

Other Imaging Modalities. Although contrast-enhanced computed tomography is an extremely valuable tool for the evaluation of human patients with suspected pancreatitis, initial studies in dogs have not been promising.[57] Also, computed tomography performed in cats with histologically confirmed pancreatitis showed disappointing results and currently cannot be recommended.[29] Other imaging methods (e.g., endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography), have been used in healthy dogs and cats, in dogs with experimentally induced pancreatitis, and in dogs with gastrointestinal diseases, with varying results. Because of the lack of standardized criteria for the diagnosis of pancreatitis, the complexity of these modalities, their limited availability, and the cost of the equipment, they cannot currently be recommended for the diagnosis of canine or feline pancreatitis.

Pathology

Direct visualization of the pancreas is possible during exploratory laparotomy and laparoscopy. Gross pancreatic lesions suggestive of pancreatitis include peripancreatic fat necrosis, pancreatic hemorrhage and congestion, and a dull granular capsular surface (Figure 60-10).[10,18,49] However, gross pathologic lesions may not always be apparent in dogs and cats with pancreatitis.[1,10,49]

At present, a definitive diagnosis of pancreatitis can only be made by histopathologic examination of the pancreas. Histopathology is also the only way to differentiate acute and chronic pancreatitis. Histopathologic scoring systems for the evaluation of severity of pancreatitis have been proposed for both dogs and cats.[1-3,58] However, histopathologic criteria for the classification of pancreatitis have not been universally standardized in veterinary medicine and substantial confusion exists regarding both classification and terminology of canine and feline pancreatitis, underlying the need for a universally accepted multidisciplinary classification system as is available for humans. The presence of permanent histopathologic changes (such as fibrosis and acinar atrophy) is generally considered suggestive of chronic pancreatitis (Figure 60-11).[1,43] Also, the predominant inflammatory cellular infiltrate (neutrophils or lymphocytes) is often used to describe pancreatitis as suppurative or lymphocytic, and some authors consider a suppurative inflammation compatible with acute disease and lymphocytic infiltration compatible with chronic disease (Figure 60-12).[10,11] A significant degree of necrosis is usually used to characterize the pancreatitis as necrotizing. It should be noted that some animals can show histopathologic evidence of both suppurative and lymphocytic pancreatitis.

Several limitations are associated with pancreatic histopathology as a definitive diagnostic tool for pancreatitis. First, determining the clinical significance of histopathologic findings may be challenging. In a recent study, 47 (64%) of 73 dogs that presented for necropsy for various reasons had microscopic evidence pancreatitis.[1] Similarly, histopathologic lesions of pancreatitis were found in 67% of all cats examined, including 45% of healthy cats.[2] Currently, there are no standardized criteria that distinguish microscopic findings leading to clinical disease from those that do not, and it is possible that clinically insignificant pancreatic lesions could lead to a false diagnosis of pancreatitis. At the same time, exclusion of pancreatitis based on histopathology is difficult because inflammatory lesions of the pancreas are often highly localized and can easily be missed.[1,2,10,49] Therefore, multiple sections of the pancreas must be evaluated to increase the likelihood of finding microscopic lesions, although this is not always feasible in clinical practice. The absence of histopathologic findings of pancreatitis must be evaluated with caution, especially when only one section of the pancreas has been examined.[1,2]

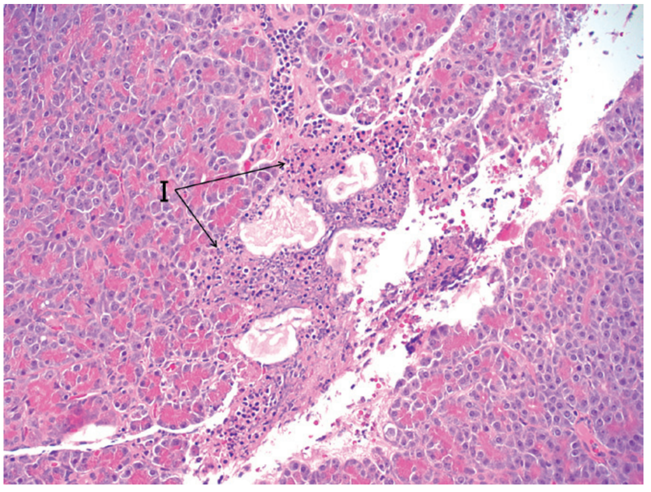

Figure 60-12 Histopathologic appearance of the pancreas of a cat with acute pancreatitis. There are areas of inflammatory infiltration (*I*) but there is no evidence of fibrosis or other permanent histopathologic changes. Hematoxylin and eosin; magnification: 200×. (Courtesy Dr. B.F. Porter, Texas A&M University.)

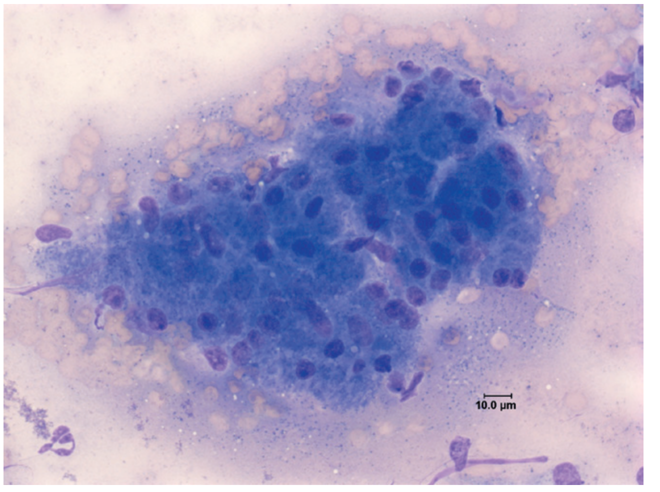

Figure 60-13 Cytologic Appearance of a fine-needle aspirate from a normal canine pancreas. Acinar cells can be seen in the form of a multicellular cluster. Diff-Quik; magnification 500×. (Courtesy Dr. P.J. Armstrong, University of Minnesota.)

Finally, although pancreatic biopsy per se is considered safe, it requires invasive procedures that are expensive and potentially detrimental in patients with pancreatitis that are hemodynamically unstable.[53]

Because concurrent inflammation of the intestines and/or liver appears to be a common problem in cats and may also occur in dogs, intestinal and hepatic biopsies should be considered in patients (especially cats) suspected of having pancreatitis that are undergoing exploratory laparotomy. Likewise, cats with inflammatory bowel disease and/or cholangitis that undergo laparotomy or laparoscopy should be considered for pancreatic biopsy.

Cytology

Fine-needle aspiration of the pancreas and cytologic examination is minimally invasive, relatively safe, and can be used for the diagnosis of pancreatitis in both dogs and cats.[59] To date no study has evaluated the sensitivity and specificity of this modality for the diagnosis of canine or feline pancreatitis, but the finding of inflammatory cells is considered specific for pancreatitis. Pancreatic acinar cells constitute the majority of the cells found in fine-needle aspiration smears from a normal pancreas (Figure 60-13).[59] In patients with acute pancreatitis the cytologic picture is mainly characterized by hypercellularity and the presence of intact and degenerated neutrophils and degenerated pancreatic acinar cells (Figure 60-14). In patients with chronic pancreatitis, small numbers of lymphocytes and neutrophils are usually present, and the specimen is often characterized by low cellularity, possibly as a result of replacement of the normal pancreatic tissue by fibrotic tissue.[59]

Fine-needle aspiration cytology should be performed either under ultrasonographic guidance or during laparotomy.[59] It should be noted that, as for histopathology, highly localized lesions might be missed. Thus negative results are not sufficient to rule out pancreatitis. Fine-needle aspiration cytology might also be useful in differentiating other conditions of the pancreas.

Assessment and Prediction of the Severity of Pancreatitis

Assessment of the severity of human acute pancreatitis is based on the application of standardized severity scores.[60] Prediction of the severity of pancreatitis constitutes a very important component of the diagnosis of pancreatitis, because it allows prediction of the likelihood of complications and morbidity, and helps determine the optimal therapeutic plan before the patient enters a critical stage. It is based on a theory that states that the severity of a pancreatitis episode is determined by events that occur within the first 24 to 48 hours of the episode.[61] These events are reflected through clinical, clinicopathologic, and imaging findings that can be used to predict the severity of the pancreatitis.[61]

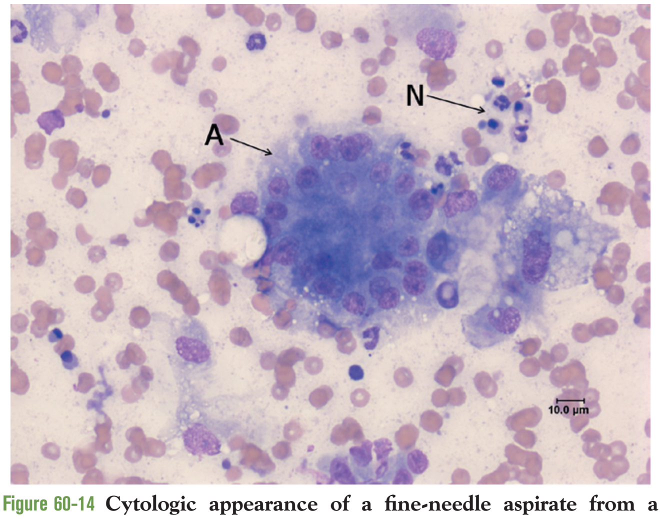

Figure 60-14 Cytologic appearance of a fine-needle aspirate from a canine pancreas with suspected pancreatitis. There is mild to moderate neutrophilic inflammation (*N*) with neutrophilic degeneration. A cluster of normal acinar cells (*A*) can also be seen. Diff-Quik; magnification 500×. (Courtesy of Dr. P.J. Armstrong, University of Minnesota.)

In veterinary medicine, no well-established and universally accepted severity scores for pancreatitis have been described. Serum PLI and TLI concentrations lack prognostic significance because they correlate poorly with histopathologic severity.[18] Currently, severity of canine and feline pancreatitis is determined based on the clinician's clinical judgment, and typically a diagnosis of severe pancreatitis is made after the animal has entered a critical stage. In general, evidence of systemic complications (e.g., oliguria, azotemia, icterus, severely increased hepatic enzyme activities, hypocalcemia, hypoglycemia, severe hyperglycemia, leukocytosis, shock, or DIC) are considered as indicators of severe disease and a poor prognosis.[62-64] However, prediction of the severity of pancreatitis has not been sufficiently studied in dogs and cats. Markers that might prove useful in predicting the severity and/or outcome of a pancreatitis episode are serum C-reactive protein concentrations, serum interleukin-6 concentrations, and plasma and urine trypsinogen activation peptide concentration as well as urine trypsinogen activation peptide-to-creatinine ratio.

Concluding Remarks

No single diagnostic modality is 100% reliable for the diagnosis of canine or feline pancreatitis. A careful evaluation of the animal's history, physical examination, and routine clinical pathology findings, as well as the use of highly specific and sensitive tests (serum cPLI and fPLI concentration, abdominal ultrasonography, cytology, and/or histopathology), are crucial for an accurate diagnosis of pancreatitis. In clinical practice, a combination of serum cPLI or fPLI concentration, abdominal ultrasound, and in some cases fine-needle aspiration of the pancreas, currently constitutes the most practical and accurate approach for the diagnosis of both canine and feline pancreatitis.

Exocrine Pancreatic Insufficiency

Clinical Features

The classical and most common presentation of dogs with EPI involves a chronic history of weight loss, a normal or increased appetite, and loose stools, which is usually characterized by passage of large volumes of semiformed feces. However, it is not uncommon for some dogs with EPI to present with a clinical picture that deviates from the classical picture. In those cases, periods of anorexia, absence of loose stools, occasionally watery diarrhea, or vomiting might be seen. Other possible clinical signs include coprophagia, borborygmus, flatulence, abdominal discomfort, and a poor hair coat. In some cases, EPI may be subclinical and those cases can only be diagnosed with appropriate laboratory testing (see "Trypsin-Like Immunoreactivity" section that follows). Cats with EPI have a similar presentation to that of dogs. In cases where chronic pancreatitis is the cause of EPI, polyuria and polydipsia may be seen as a result of concurrent diabetes mellitus.

Trypsin-Like Immunoreactivity

Serum cTLI is the test of choice for the diagnosis of EPI in dogs. This test is highly sensitive and specific for the diagnosis of EPI, and a positive test (usually defined as <2.5 μg/L) in a dog with compatible clinical signs is sufficient to make a diagnosis of EPI.[65] A cTLI result that is well within the reference range is sufficient for excluding EPI, and a normal cTLI result should direct clinicians toward the investigation of other disorders as the cause of the clinical signs observed.[65] Single cTLI results within the equivocal range (usually between 2.5 and 5.7 μg/L) in dogs with clinical signs of gastrointestinal disease need to be interpreted with caution.[66] In these patients, subsequent retesting of serum cTLI concentration shows either a normal concentration or progression to EPI.[66] Therefore, patients with cTLI results in the equivocal range should be investigated for chronic intestinal disease, while reevaluating the cTLI a few weeks later. Some dogs with no clinical signs characteristic of EPI have repeatedly subnormal (<5.7 μg/L) cTLI concentrations.[66,67] These dogs have been shown to have subclinical EPI and some are expected to develop clinical EPI in the future.[66,67] The time of progression from the subclinical to the clinical stage varies greatly and might be from a few months to years.[67] Thus these patients should be closely monitored for the development of clinical signs of EPI and cTLI testing should be repeated every 3 to 6 months.[66,67] Finally, because renal disease might increase serum cTLI concentrations and obscure a diagnosis of EPI, reevaluation of nondiagnostic serum cTLI concentrations in azotemic dogs suspected of having EPI is recommended. Similarly, concurrent inflammation might falsely increase the serum cTLI concentration.

Because EPI appears to be less common in cats than in dogs, diagnosis of this disease has been less-well investigated. Similar to dogs, the fTLI test appears to be the most reliable test for the diagnosis of EPI in cats, having a specificity of at least 85%.[68] The sensitivity of this assay for the diagnosis of feline EPI has not been evaluated to date. Although there are currently two assays that measure fTLI in serum (one radioimmunoassay that is available in the United States and one enzyme-linked immunosorbent assay that is available in Europe), the analytical validation has only been published for the radioimmunoassay, which is available through the Gastrointestinal Laboratory at Texas A&M University. Similar to dogs, it can be recommended that equivocal serum fTLI concentrations in azotemic cats suspected of having EPI be reevaluated, because renal disease might falsely increase serum fTLI concentrations. The same is true for cats with concurrently increased serum fPLI concentrations indicating residual pancreatic inflammation.

Pancreatic Fecal Elastase

An enzyme-linked immunosorbent assay for the measurement of pancreatic elastase in feces is commercially available and is marketed in Europe (Shebo Biotech, Germany) for the diagnosis of canine EPI.[69,70] A recent study reported false-positive results in 23.1% of cases[71] and its sensitivity has not been sufficiently evaluated. The fact that this test is easy and quick to perform might make it a reasonable initial approach for dogs with suspected EPI, but as a consequence of its poor positive predictive value a positive test result must be verified by measurement of serum cTLI concentration. This test might also be useful for EPI cases that are a result of pancreatic duct obstruction. However, to date such a case has only been anecdotally reported in the veterinary literature.

Other Tests

Serum amylase and lipase activities have been shown to have no value in the diagnosis of EPI in either dogs or cats.[21,41,72] Canine PLI concentrations are low or undetectable in most dogs with EPI, but some overlap between healthy dogs and dogs with EPI does exist, making this test inferior to cTLI for the diagnosis of EPI.[21] However, cPLI might be used to diagnose isolated pancreatic lipase deficiency, a rare form of EPI, where serum cTLI and other pancreatic zymogen concentrations are expected to be normal.[73] Commercial assays for the measurement of serum PLI concentration (Spec cPL and Spec fPL) are not useful for the diagnosis of EPI in dogs and cats, respectively, because they have been optimized to detect changes in the higher ranges of their respective working ranges.

Measurement of the fecal proteolytic activity has been used in the past for the diagnosis of EPI in dogs and cats, but are now only used for species for which a TLI assay is not available.[74,75] A plethora of other tests, including microscopic examination of feces and the bentiromide absorption (benzoyl-tyrosyl-paraaminobenzoic acid [BT-PABA]) test, have also been described for the diagnosis of EPI in the past. However, these tests often give false-positive and/or false-negative results and many of them are impractical, expensive, or of limited availability. Thus none of these tests are recommended for the diagnosis of canine or feline EPI.

Histopathology

Because EPI is a functional and not a histopathologic diagnosis, histopathology is not indicated for the diagnosis of EPI. Given that it has been estimated that more than 90% of the pancreatic parenchyma needs to be destroyed before clinical signs of EPI develop, it is almost impossible to accurately grossly or histopathologically determine the extent of pancreatic atrophy. The only usefulness of histopathology is limited to the determination of the underlying cause of EPI (pancreatic acinar atrophy or pancreatitis). However, in dog breeds that have been shown to be predisposed to EPI because of acinar atrophy (i.e., German Shepherds, Rough-Coated Collies, and Eurasians), histopathology is redundant.[76] Therefore histopathology should only be used in atypical cases where the cause of EPI needs to be definitively determined.

NECROSIS AND INFLAMMATION: CANINE

Panagiotis G. Xenoulis and Jörg M. Steiner

Strictly speaking, *pancreatitis* refers to inflammation (i.e., infiltration with inflammatory cells) of the exocrine pancreas. However, the term pancreatitis is commonly expanded to also include diseases of the exocrine pancreas characterized mainly by necrosis that may have a minimal inflammatory component (often referred to as acute pancreatic necrosis or necrotizing pancreatitis).[1] It is widely believed that pancreatic necrosis is associated with a severe and often fatal course of disease, whereas pancreatitis without necrosis (e.g., edematous interstitial pancreatitis) is usually mild. However, no convincing scientific evidence currently exists to support this assumption in clinical cases of canine pancreatitis.

Pancreatitis is generally divided into acute pancreatitis (which typically includes acute pancreatic necrosis) and chronic pancreatitis (characterized by the permanent histopathologic changes of fibrosis and atrophy). The term *recurrent acute pancreatitis* is sometimes used to describe recurrent episodes of pancreatitis that are not associated with permanent histopathologic changes. A plethora of other clinical (e.g., mild or severe, fatal or nonfatal) and histopathologic (e.g., edematous, interstitial, necrotizing, neutrophilic, lymphocytic) terms have been used to further classify pancreatitis in dogs. However, no universally standardized terminology and definitions exist for pancreatitis in animals, and different authors classify pancreatitis is different ways. It is not clear at this time whether the different forms of pancreatitis (e.g., acute edematous pancreatitis, acute pancreatic necrosis, chronic pancreatitis) represent different phenotypes of the same disease or distinct disease entities, whether they share the same etiologic and pathogenic mechanisms, or which factors determine the development of each form.

Prevalence

Pancreatitis in dogs is common and is associated with significant morbidity and mortality. The prevalence of pancreatitis in dogs varies widely based on the methods used to diagnose the disease. Clinically, its overall prevalence has been estimated at approximately 0.8% in dogs, although certain canine breeds seem to have a higher prevalence.[2] Histopathologic evidence of canine pancreatitis is considerably more common, even in dogs that died from unrelated causes, and has been reported to be as high as 65% when multiple sections of the pancreas are examined.[3] It remains to be determined, however, which degree and/or forms of histopathologic pancreatitis are clinically significant. The mortality for dogs with pancreatitis also varies widely; most dogs with mild pancreatitis recover within a few days and have a very good prognosis, whereas mortality rates in patients with more severe forms of acute pancreatitis have been reported to be 20% to 42%.[4-7]

Pathogenesis and Pathophysiology

Most of our understanding regarding the pathogenesis of pancreatitis is based on animal models and some clinical studies in human patients. There is mounting evidence that genetic and possibly also environmental factors may sensitize the pancreas to injury induced by one or more etiologic factors.[8,9] Regardless of the actual etiology, there appears to be a common pathogenic mechanism in most cases of acute pancreatitis. The initiating events that lead to pancreatitis take place in the acinar cell. Two early intracellular events that precede the development of acute pancreatitis are retention and intracellular activation of zymogens.[8,9] Zymogens are pancreatic enzyme precursors stored in zymogen granules that are normally secreted into the pancreatic duct through the apical membrane of the acinar cell. The factors that lead to retention of zymogen granules and premature intracellular activation of the zymogens are not fully elucidated. One of the most popular theories is the colocalization theory,[8,9] which suggests that zymogen granules accumulate in the acinar cell and colocalize with lysosomes. Lysosomal enzymes, such as cathepsin B, are thought to activate trypsinogen into trypsin, which subsequently activates other zymogens. The cytosolic concentration of free ionized calcium also plays an important role in the intracellular activation of zymogens.[10-12] In addition to decreased secretion and intracellular activation of pancreatic enzymes, there is evidence of disruption of the paracellular barrier in the pancreatic duct that allows its contents to leak into the paracellular space, and also redirection of secretion of zymogen granules from the apical pole to the basolateral region of the acinar cell and into the interstitial space (Figure 60-15).[9]

Once intracellular activation of pancreatic enzymes has taken place, autodigestion of the acinar cell follows and activated enzymes escape into the pancreatic tissue (leading to local effects) and then into the peritoneal cavity and the systemic circulation (potentially contributing to systemic effects). Local effects vary and can range from mild interstitial edema to severe acinar cell necrosis, hemorrhage, and peripancreatic fat necrosis. The extent and severity of local effects determine to a large degree the systemic response. Acinar cell injury leads to recruitment and activation of inflammatory cells (mostly neutrophils and macrophages), which release proinflammatory cytokines and other inflammatory mediators (e.g., IL-1, IL-2, IL-6, IL-18, tumor necrosis factor-α, substance P, platelet-activating factor) that play a crucial role in modulating systemic manifestations.[8,13] Such manifestations include cardiovascular shock, disseminated intravascular coagulation (DIC), SIRS, and multiple organ failure, and are seen in cases of severe acute pancreatitis.[8,13]

Etiology and Risk Factors

In contrast to human patients, in whom an etiology of pancreatitis can be identified in the majority of cases, the etiology of canine

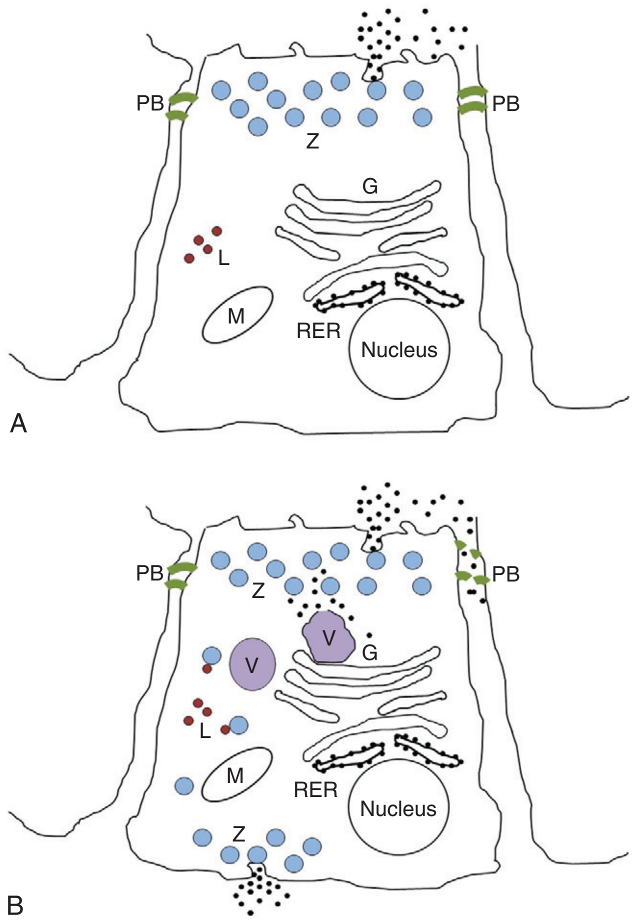

Figure 60-15 **Proposed pathogenesis of acute pancreatitis. A,** Normal acinar cell. Zymogen granules are found in the apical region of the cell and their contents are excreted exclusively through the apical surface. Lysosomes are packaged and stored separately from zymogen granules and the paracellular barriers are intact. **B,** Acute pancreatitis. Secretion of the zymogen granules is redirected from the apical pole to the basolateral region of the acinar cell and into the interstitial space. Retention of zymogen granules is followed by colocalization with lysosomes and the formation of large vacuoles (*V*) and premature intracellular activation of pancreatic enzymes. There is also disruption of the paracellular barrier in the pancreatic duct that allows its contents to leak into the paracellular space. *G*, Golgi apparatus; *L*, lysosome; *M*, mitochondrion; *PB*, paracellular barrier; *RER*, rough endoplasmic reticulum; *Z*, zymogen granule; *V*, vacuole.

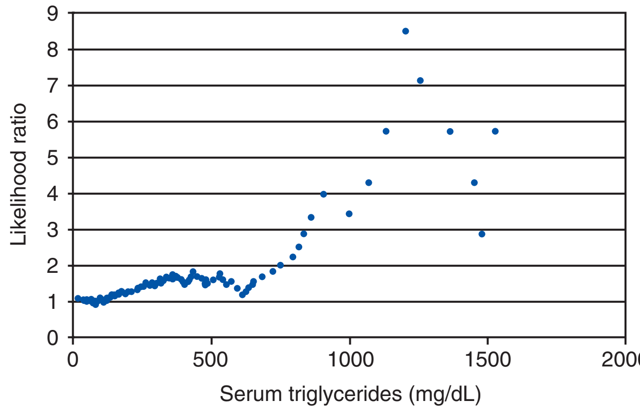

Figure 60-16 Likelihood ratios for different serum triglyceride concentrations for serum cPLI concentrations consistent with pancreatitis (≥200 μg/L; values measured with the original cPLI-ELISA). The likelihood ratio remained between 1 and 2 for serum triglyceride concentrations below approximately 800 mg/dL, and increased sharply for serum triglyceride concentrations of more than 800 mg/dL. (From Xenoulis PG, Suchodolski JS, Ruaux CG, Steiner JM: Association between serum triglyceride and canine pancreatic lipase immunoreactivity concentrations in Miniature Schnauzers. *J Am Anim Hosp Assoc* 46:229, 2010 with permission.)

pancreatitis usually remains unknown (idiopathic pancreatitis).[2,14] It is expected that recognition of new causes of canine pancreatitis will allow etiologic classification in a larger proportion of cases in the future. Several risk factors for canine pancreatitis are described, but the majority of these have been implicated by association, so few definitive causes of pancreatitis have been reported.[2] The main causes of human pancreatitis (i.e., biliary obstruction and alcoholism) do not represent common problems in small animals.[8,14] Other well-defined causes of human pancreatitis (e.g., autoimmune pancreatitis) currently have not been proven in dogs.

Hypertriglyceridemia

Hypertriglyceridemia has been suspected to be a risk factor for pancreatitis in dogs, but convincing evidence was lacking until recently.[15-17] A definitive etiologic association between hypertriglyceridemia and pancreatitis has been difficult to prove, as hypertriglyceridemia might be the result of pancreatitis rather than the cause. Two recent studies suggest that hypertriglyceridemia, which is a known risk factor for human pancreatitis, is also a risk factor for pancreatitis in Miniature Schnauzers.[18,19] Miniature Schnauzers have a high prevalence of idiopathic hypertriglyceridemia, which is often relatively severe.[20] As in humans, the severity of hypertriglyceridemia appears to be important and only Miniature Schnauzers with serum triglyceride concentrations above 862 mg/dL were found to be at increased risk for pancreatitis (Figure 60-16).[8,14,18,19] Interestingly, hypertriglyceridemia appears to be present before the development of pancreatitis and persists after the resolution of the disease, unless a low-fat diet is fed.[19] This supports the hypothesis that, at least in Miniature Schnauzers, severe hypertriglyceridemia is likely a preexisting condition and risk factor for pancreatitis, rather than an epiphenomenon. The exact role of hypertriglyceridemia in the development of pancreatitis, as well as the interaction between hypertriglyceridemia and other risk factors, remains to be determined as not all Miniature Schnauzers with severe hypertriglyceridemia develop clinical pancreatitis. It is not known whether an association between hypertriglyceridemia and pancreatitis also exists in other breeds. Further studies are also needed to determine whether secondary hypertriglyceridemia associated with diseases such as diabetes mellitus, hyperadrenocorticism, and obesity, represents a risk factor for canine pancreatitis.

Hereditary Pancreatitis

A combination of three variants in the serine protease inhibitor Kazal type 1 (*SPINK1*) gene has been identified in Miniature Schnauzers, and an association of these variants with pancreatitis is reported.[21] Mutations in the *SPINK1* gene, although different from those described in Miniature Schnauzers, have also been described and associated with pancreatitis in humans.[22] The product of the *SPINK1* gene, PSTI, is found in acinar cells and acts as one of the defense mechanisms against prematurely activated trypsin. It is possible that the mutant protein lacks this function, therefore leaving the acinar cell more susceptible to injury, although this has not been shown convincingly. The exact role of the *SPINK1* gene in the development of pancreatitis in Miniature Schnauzers remains to be determined. It is hypothesized that mutations in this gene may not actually cause pancreatitis, but they might sensitize the pancreas to injury through other factors. Genetic causes of pancreatitis have also been suspected in other breeds (e.g., Yorkshire Terriers).[16]

Breed

Several breeds are reported to be at increased risk for pancreatitis, although different studies are not always in agreement with each other. Breed predisposition most likely reflects either genetic causes of pancreatitis or a predisposition to other diseases or conditions that are risk factors for pancreatitis (e.g., hypertriglyceridemia in Miniature Schnauzers). Differences in breed predispositions probably exist in different geographical regions, as blood lines might be different, especially where a breed was introduced to a region decades ago. Miniature Schnauzers, Yorkshire Terriers, and Terriers in general are consistently shown to have a higher risk of developing pancreatitis.[4,16,17,23] Boxers, Cavalier King Charles Spaniels, Cocker Spaniels, and Collies have also been suggested to be overrepresented.[24]

Diet

The role of diet, and more specifically the fat content of the diet, in the development of canine pancreatitis remains unclear. Based on anecdotal clinical observations, high-fat foods increase the risk for pancreatitis. Older experimental studies suggested that diets with a very high fat content may induce pancreatitis and may increase the severity of experimentally induced pancreatitis in dogs.[15,25] The mechanism by which high-fat diets increase the risk for pancreatitis is not known, but it is possible that they may predispose to pancreatitis through hypertriglyceridemia. In a recent retrospective case-control study in dogs, several factors, such as access to trash, consuming table scraps, and ingestion of “unusual” food, were found to be associated with an increased risk of pancreatitis.[23] However, no specific foods were identified that were associated with an increased risk for pancreatitis.

Drugs

As in humans, drug-induced pancreatitis has been reported in the dog, but a cause-and-effect relationship has not been established for most cases.[26] Nevertheless, a history of drug administration in conjunction with compatible findings should raise a concern for drug-induced pancreatitis. Based on the remarkably large number of drugs prescribed in both human and veterinary medicine, and the fact that drug-induced pancreatitis appears to be quite rare, drugs are thought to cause pancreatitis in an idiosyncratic fashion and theoretically, any drug can potentially cause pancreatitis. However, pancreatitis in dogs seems to be more commonly associated with the use of potassium bromide, phenobarbital, L-asparaginase, azathioprine, and meglumine antimonate.[27-29]

Endocrine Disease

In one study, hyperadrenocorticism, hypothyroidism, and diabetes mellitus were reported to be more commonly present in dogs with pancreatitis than in controls.[17] In another study 29 (13%) of 221dogs with diabetes mellitus were reported to have pancreatitis.[30] However, evidence is far from convincing that these endocrine diseases represent risk factors for canine pancreatitis. It has been hypothesized that hypertriglyceridemia associated with these endocrine diseases might be a more significant risk factor for pancreatitis in this species than the conditions themselves.

Obesity

A relationship between obesity and pancreatitis has been suggested for dogs. Studies show that dogs diagnosed with pancreatitis are more frequently obese than are dogs that do not have pancreatitis.[16,17,23] However, a pathogenic link between obesity and pancreatitis has not been convincingly shown to date.

Other Factors

Age is often listed as a risk factor for pancreatitis as most dogs with pancreatitis are middle-aged or older. No clear sex predisposition has been identified. Hypotension (e.g., during anesthesia or after severe blood loss), hypercalcemia (both iatrogenic and as a result of diseases such as neoplasia and hyperparathyroidism), abdominal trauma, extensive surgical manipulation of the pancreas, certain infections (e.g., with certain *Babesia* spp.), and obstruction of the pancreatic duct (e.g., as a consequence of neoplasia) are also suspected risk factors for canine pancreatitis, but evidence is weak or lacking.[2,31] Chronic gastrointestinal (GI) disease might also be a risk factor for pancreatitis in dogs.[32] Primary or metastatic neoplasia of the pancreatic parenchyma is often associated with secondary inflammation of the exocrine pancreas. Previous surgery and epilepsy have also been reported as potential risk factors.[17,23]

Signalment

Dogs of any age, breed, or sex can develop pancreatitis. Most animals are middle-aged to old.[4,17] Miniature Schnauzers and Yorkshire Terriers appear to be at increased risk, while predisposition of other breeds is less clear.[2,16,17,23] In one study some other breeds (e.g., Boxers, Cavalier King Charles Spaniels, Cocker Spaniels, and Collies) were suggested to be predisposed, but this has not been confirmed by other studies.[24] No clear sex predisposition has been identified.

Clinical Signs and Physical Examination Findings

Dogs with pancreatitis can have subclinical disease or present with a variety of clinical signs, ranging from mild partial anorexia with no apparent GI signs to severe systemic signs with cardiovascular shock and DIC. There is no single clinical sign or combination of clinical signs that is pathognomonic for canine pancreatitis. Clinical signs of severe acute pancreatitis may include anorexia (91%), vomiting (with or without blood; 90%), weakness (79%), polyuria and polydipsia (50%), and diarrhea (with or without blood; 33%).[16] Many of the clinical signs are likely to be the result of complicating or concurrent diseases rather than pancreatitis per se (e.g., polyuria and polydipsia are more likely to be the result of concurrent diabetes mellitus). The most common physical examination findings in dogs with severe acute pancreatitis include dehydration (97%), abdominal pain (58%), fever (32%), and icterus (26%).[16] The combination of vomiting and abdominal pain, although suggestive of pancreatitis, is also seen with other diseases (e.g., GI foreign bodies, peritonitis). Other possible findings include shock, hypothermia, cardiac murmur, tachycardia, bleeding diathesis, ascites, a palpable abdominal mass, and harsh lung sounds.[16] Patients with less severe or chronic pancreatitis are typically presented with less-profound clinical signs (e.g., anorexia and depression), or might even be subclinical.

Clinical Pathology[7,16]

Results of the complete blood cell count (CBC), serum biochemistry profile, and urinalysis are nonspecific and thus of limited usefulness for the diagnosis of pancreatitis in dogs. However, these tests should always be performed in animals with suspected pancreatitis because they are useful for ruling out other differential diagnoses and provide important information about the general condition of the animal.

Often, especially in mild cases, the CBC, serum biochemistry profile, and urinalysis are normal. Possible hematologic findings in dogs with pancreatitis include anemia or hemoconcentration, leukocytosis or leukopenia, and thrombocytopenia. Evidence of coagulopathy, such as prolonged activated clotting time and prothrombin (PT) and partial thromboplastin times, are seen in some cases, and may or may not be associated with spontaneous bleeding. In other cases, there might be evidence suggestive of DIC, such as thrombocytopenia, prolongation of clotting times (activated clotting time, PT, partial thromboplastin time), and a positive D-dimer test. Different combinations of increases in liver enzyme activities and hyperbilirubinemia are common, and might erroneously direct the clinician to suspect primary liver disease. Increases in serum creatinine and blood urea nitrogen (BUN) concentrations are variably present and most often associated with dehydration as a consequence of vomiting, diarrhea, and/or decreased water intake. In severe cases, azotemia might be the result of secondary renal failure. Other possible findings include hypoalbuminemia, hypertriglyceridemia, hypercholesterolemia, and hyperglycemia or hypoglycemia. Electrolyte abnormalities are commonly present and variable, with hypokalemia, hypochloremia, and hyponatremia being the most common.

Clinical Enzymology

Serum Pancreatic Lipase Immunoreactivity

The only cell type known to synthesize pancreatic lipase is the pancreatic acinar cell. An immunoassay for the measurement of canine pancreatic lipase has been developed and analytically validated.[33] In contrast to the traditional activity assays for lipase, which indiscriminately measure the activity of lipases of any origin, this immunoassay specifically quantifies the pancreatic lipase based on its unique antigenic structure. The originally developed in-house immunoassay for canine pancreatic lipase has been replaced by a widely available commercial immunoassay (Spec cPL).[34,35]

Clinical studies suggest that serum cPLI (or Spec cPL) has a high specificity for canine pancreatitis. In one study of 31 dogs with a normal pancreas on histopathology, the specificity of Spec cPL was very high (96.8%).[36] In a recent multicenter study of dogs with clinical evidence of pancreatitis, the specificity of this assay was reported at 78%.[37] Experimentally induced chronic renal failure and prednisone administration do not significantly affect serum cPLI concentration.[38,39] The association between gastritis and serum cPLI concentration requires further evaluation as gastritis was shown to be associated with increased serum cPLI in one study.[40] However, no pancreatic biopsies were examined in that study to exclude pancreatic pathology. The specificity of cPLI also requires further investigation in dogs with various GI diseases but not pancreatitis. It also remains to be determined whether serum cPLI concentration can be increased in patients with histopathologically mild pancreatitis that might be of minor clinical importance and does not contribute to the development of clinical signs. Compared with other serum tests currently available, serum cPLI is considered to have the highest specificity for pancreatitis.[36-39,41-43] However, false-positive results cannot be excluded.

The serum cPLI concentration is also sensitive for the diagnosis of pancreatitis in dogs,[34,37,44,45] ranging from 64% to 93%, possibly depending on the severity of the disease in the patients studied. The sensitivity of serum cPLI is higher than for any other serum test currently available.[34,37,44,45] However, false-negative results are likely to occur, especially in mild cases.

Overall, serum cPLI concentration appears to be a sensitive and specific marker of canine pancreatitis, and is currently considered to be the serum test of choice for the diagnosis of pancreatitis in this species.

Based on clinical observations and the results of studies available to date,[34] serum cPLI concentrations do not appear to correlate with the severity of pancreatitis. Therefore individual measurement of cPLI concentrations cannot be used to determine the severity of pancreatitis. No studies have examined the significance of changes in serum Spec cPL concentrations over time in individual patients.

A point-of-care test for the estimation of pancreatic lipase in serum (SNAP cPL) is available. Published studies evaluating the performance of this test are currently lacking, but it is suggested that it shows the same clinical performance as the serum Spec cPL assay. The recommended use of this test is to rule out pancreatitis in dogs suspected of having the disease. Because of the high sensitivity of Spec cPL, a negative result makes a diagnosis of pancreatitis unlikely. However, false-negative results might occur in some cases. A positive test result should be followed by laboratory measurement of serum Spec cPL concentration.

Serum Amylase and Lipase Activities

Serum amylase and lipase activities have long been considered markers for canine pancreatitis, but several studies show that they have low sensitivity and specificity.[41,46] In one study, approximately 50% of dogs with increased activity of either serum amylase or lipase activity had no histopathologic evidence of pancreatitis.[41] This means that a large proportion of dogs that have diseases other than pancreatitis (e.g., certain renal, hepatic, intestinal, and neoplastic diseases) have increased serum lipase and/or amylase activities.[41] Significant increases of amylase and lipase activities can result from nonpancreatic disorders, and identification of elevated concentrations of these enzymes should always be followed up by the use of more specific and sensitive tests.[15,41,42,47] In addition, the sensitivity of serum amylase and lipase activities for spontaneous canine pancreatitis is generally low (14% to 73% for lipase and 18% to 69% for amylase).[16,34,45] Therefore pancreatitis cannot be confidently diagnosed or ruled out based on serum amylase and/or lipase activities alone.[16,41]

Serum Trypsin-like Immunoreactivity

TLI assays are species-specific immunoassays that measure trypsinogen and trypsin in serum. Trypsinogen is the inactive precursor of trypsin and is synthesized exclusively in the pancreatic acinar cells. The sensitivity of serum cTLI for the diagnosis of canine pancreatitis is low (36% to 47%), probably because of its short half-life.[34,42,45] In addition, although there is strong evidence that trypsinogen is exclusively of pancreatic origin,[48] it is believed that it is cleared by glomerular filtration in dogs, and serum cTLI concentration can be increased in dogs with renal failure.[42,43] In the face of availability of a better serum marker (cPLI), cTLI is currently considered to be of limited value for the diagnosis of canine pancreatitis. If the Spec cPL assay is not available, cTLI might be used to rule in pancreatitis if renal disease has been ruled out. However, a normal cTLI concentration cannot rule out pancreatitis.

Other Diagnostic Tests

Several other tests have been developed and evaluated for the diagnosis of canine pancreatitis. However none can be recommended for clinical use, either because their clinical value has not been determined accurately or because they have a low specificity and/or sensitivity. In addition, most of these tests have limited availability.

TAP is a small peptide that is released when trypsinogen is activated to trypsin.[42] Under physiologic conditions, trypsinogen is activated mainly in the intestinal lumen, and thus serum TAP concentrations are low or undetectable.[42] During pancreatitis, trypsinogen is prematurely activated in the pancreas and TAP is released into the circulation.[42,49] Plasma and urinary TAP concentrations have been evaluated in healthy dogs, dogs with histopathologically confirmed pancreatitis, and dogs with other systemic diseases.[42] In that study, plasma TAP concentration had good specificity (87.9%), but low sensitivity (53.3%), for the detection of pancreatitis. Urine TAP concentrations did not show any advantage over serum TAP concentrations in diagnosing pancreatitis. Both tests show increases in dogs with severe pancreatitis, but were normal or low in cases of mild pancreatitis. However, this study suggested that, as in humans, serum and urine TAP concentrations might be more useful as a prognostic indicator in dogs with pancreatitis.[42]

Measurement of lipase activity in peritoneal fluid and comparison with serum lipase activity has been evaluated as a tool for the diagnosis of acute pancreatitis in dogs.[50] However, further studies are needed before this method can be recommended for clinical use. Other tests that have been evaluated for the diagnosis of canine pancreatitis include trypsin-α_1-proteinase inhibitor complex concentrations in serum and α_2-macroglobulin concentrations in serum.[51-54]

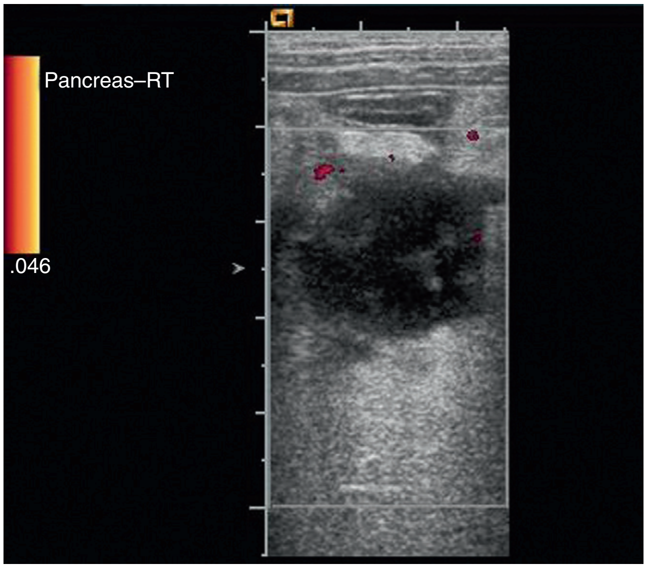

Figure 60-17 Ultrasonographic appearance of the pancreas of a dog with acute necrotizing pancreatitis. The pancreatic lobe is diffusely hypoechoic with a focal anechoic region. No blood flow is present in the necrotic portion, as shown with power Doppler interrogation. (Courtesy of Dr. B. Young, Texas A&M University, College Station, TX.)

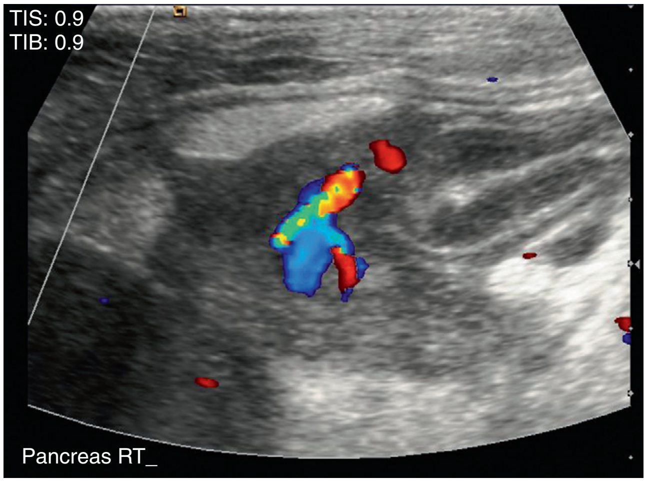

Figure 60-18 Ultrasonographic appearance of the pancreas of a dog with acute edematous pancreatitis. The affected lobe is enlarged, irregularly marginated, and hypoechoic. Note the preservation of blood flow within the pancreas on color flow Doppler interrogation. (Courtesy of Dr. B. Young, Texas A&M University, College Station, TX.)

Diagnostic Imaging

Abdominal Radiography

Conclusive diagnosis or exclusion of pancreatitis is not possible based on abdominal radiography alone.[16] In the majority of cases of pancreatitis, abdominal radiographs are normal or only show nonspecific changes.[16] Despite that, abdominal radiography remains a logical initial approach for patients suspected of having pancreatitis, because it is useful to rule out other differential diagnoses.

Possible radiographic findings in dogs with pancreatitis include increased soft-tissue opacity and decreased serosal detail in the cranial right abdomen, displacement of the stomach and/or duodenum, dilation of bowel loops adjacent to the pancreas, abdominal effusion, and the presence of a cranial abdominal mass.[16]

Abdominal Ultrasound

Abdominal ultrasound is the imaging modality of choice for the diagnosis of pancreatitis in dogs. However, abdominal ultrasonography is also associated with disadvantages, and its performance in the diagnosis of pancreatitis is highly dependent on the experience of the ultrasonographer and the quality of the equipment used. It has been reported to have a relatively high sensitivity of approximately 68% for severe acute pancreatitis in dogs.[16] In a recent study where ultrasonography was performed in 26 animals (both dogs and cats) with suspected GI disease, six (23.1%) of the animals had ultrasonographic evidence consistent with pancreatitis, while histopathology revealed either a normal pancreas or pancreatic hyperplasia.[55] In the same study, there was only a 22% agreement between the ultrasonographic and the histopathologic diagnoses.[55] Although not free of limitations, this study highlights that ultrasonographic findings in animals with suspected pancreatitis should be interpreted with caution. A normal pancreas on ultrasound examination does not rule out pancreatitis.[16,56] If stringent criteria are applied, the specificity of abdominal ultrasonography for pancreatitis is considered to be relatively high, although other diseases of the pancreas (e.g., neoplasia, hyperplastic nodules, pancreatic edema as a consequence of portal hypertension or hypoalbuminemia) may display similar ultrasonographic findings and sometimes cannot be differentiated from pancreatitis.[57,58]

The most important ultrasonographic findings suggestive of pancreatitis in dogs include hypoechoic areas within the pancreas, increased echogenicity of the surrounding mesentery (because of necrosis of the peripancreatic fat), and enlargement and/or irregularity of the pancreas.[16,56,59] Differentiation between necrotizing and edematous pancreatitis might be possible based on ultrasonographic examination (Figures 60-17 and 60-18), although this has not been confirmed in clinical studies. On occasion, hyperechoic areas of the pancreas possibly indicating the presence of pancreatic fibrosis may be present. Less-specific findings may include a dilation of the pancreatic or biliary duct and abdominal effusion. Abdominal ultrasonography is also very useful for the diagnosis of local complications of pancreatitis such as pancreatic abscesses, pancreatic pseudocysts, and biliary obstruction.[59] In addition, ultrasound-guided fine-needle aspiration is a useful tool for the management of noninfectious fluid accumulations of the pancreas (e.g., pancreatic pseudocyst) and for obtaining pancreatic specimens for cytologic evaluation.[60]

Other Imaging Modalities

Several other imaging modalities are routinely used to diagnose or evaluate pancreatitis in human patients. Contrast-enhanced CT is a valuable tool for the evaluation of people with suspected pancreatitis and might also prove to be useful in dogs, but it has not yet been evaluated in an adequate number of canine cases.[61] Other imaging modalities (e.g., endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography) have been studied in healthy dogs and in dogs with GI diseases with varying results.[62,63] However, because of the lack of standardized criteria for the diagnosis of pancreatitis, the complexity of these modalities, their limited availability, and the cost of the equipment, they cannot be currently recommended for the diagnosis of canine pancreatitis.

Pathology

Certain macroscopic lesions identified during surgery, laparoscopy, or necropsy are highly suggestive of pancreatitis and are preferred sites for biopsy collection.[34] Lesions suggestive of pancreatitis may include peripancreatic fat necrosis, pancreatic hemorrhage and congestion, and a dull granular capsular surface (Figure 60-19).[34] However, gross lesions may not always be apparent and in some cases they might be difficult to differentiate from nodular hyperplasia.[3]

A definitive diagnosis of pancreatitis can only be made by histopathologic examination of the pancreas and this is also the only way to differentiate acute and chronic pancreatitis, and in some cases, pancreatitis from pancreatic neoplasia. The presence of permanent histopathologic changes (e.g., fibrosis and acinar atrophy) is considered suggestive of chronic pancreatitis.[3,15] Acute pancreatitis is characterized by absence of permanent histopathologic changes.

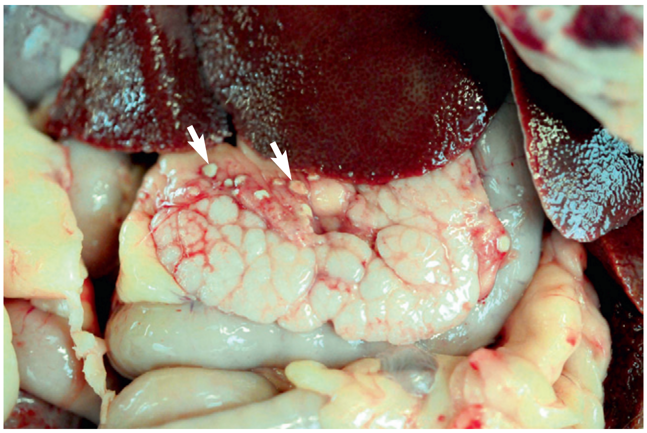

Figure 60-19 Gross appearance of the pancreas of a dog with acute pancreatitis. The pancreas appears edematous and hemorrhagic. Several areas of pancreatic fat necrosis can be seen (*arrows*). Such appearance is highly suggestive of acute pancreatitis. (Courtesy of Dr. John Edwards, Texas A&M University, College Station, TX.)

The predominant inflammatory infiltrate (i.e., neutrophils or lymphocytes) is often used to describe pancreatitis as suppurative or lymphocytic, respectively, and a significant degree of necrosis is usually used to characterize the pancreatitis as necrotizing.

Several limitations are associated with pancreatic histopathology as a definitive diagnostic tool for pancreatitis. First, determining the clinical significance of histopathologic findings may be challenging. At the same time, exclusion of pancreatitis based on histopathology is difficult because inflammatory lesions of the pancreas are often highly localized and can easily be missed.[3] Therefore, multiple sections of the pancreas must be evaluated in order to increase the likelihood of finding microscopic lesions, although this is not always feasible in clinical cases.[3] Finally, although pancreatic biopsy per se is considered safe, it requires invasive procedures that are expensive and potentially detrimental in patients that are hemodynamically unstable.[55]

Cytology

Fine-needle aspiration of the pancreas with cytologic examination was recently introduced as a diagnostic tool for pancreatitis in small animals. It should be performed either under ultrasound guidance or during laparotomy.[64] To date, no studies have evaluated the sensitivity and specificity of this modality for the diagnosis of canine pancreatitis, but the finding of acinar and inflammatory cells in the aspirate is considered specific for pancreatitis. Pancreatic acinar cells constitute the majority of the cells found in fine-needle aspirations from a normal pancreas.[64] In patients with acute pancreatitis there is hypercellularity with intact and degenerate neutrophils and degenerate pancreatic acinar cells. As for histopathology, highly localized lesions might be missed so negative results do not rule out pancreatitis. Cytology might also be useful in differentiating other conditions of the pancreas (e.g., neoplasia) from pancreatitis.

Concluding Remarks on the Diagnosis of Pancreatitis

There is currently no test that is 100% sensitive and specific for the diagnosis of pancreatitis, so false-positive and false-negative results can occur with all tests. The use of careful assessment of the clinical history, physical examination findings, results of routine clinical pathology, diagnostic imaging studies, measurement of cPLI concentration, and when appropriate cytologic and/or histopathologic findings is crucial for a correct diagnosis or exclusion of pancreatitis.

Treatment

Treatment of the Cause

The etiology of pancreatitis remains unknown in the majority of cases, and therefore, treatment of pancreatitis remains almost exclusively supportive. Future recognition of specific causes of canine pancreatitis may lead to the development of more specific treatments for different forms of pancreatitis that are now classified as idiopathic. Until then, the presence of possible risk or etiologic factors should always be investigated. If any of these factors are present, they should be managed where possible. Thus, dogs with pancreatitis should be investigated for the presence of hypertriglyceridemia, hypercalcemia, endocrine diseases, obesity, certain toxicities (e.g., zinc), certain infectious diseases, and inflammatory diseases of the intestine and liver. Important information from the history of the animal include drugs administered (especially potassium bromide, phenobarbital, and azathioprine), diet offered (especially high-fat diets), and recent surgery or trauma.

Nutrition

Nutritional approaches in people and animals with acute pancreatitis usually include one of the following: (a) enteral nutrition, (b) parenteral nutrition (total or partial), and (c) no nutritional support.[65] In the past, the main concept of nutritional approach during acute pancreatitis was to "rest the pancreas" as it was believed that feeding induced the stimulation of exocrine pancreatic secretion, which might lead to exacerbation of pancreatitis.[15,66] This was based on physiologic observations in normal people and experimental animals, which showed that CCK release during feeding led to stimulation of the exocrine pancreas.[67] Therefore, the standard approach to patients with acute pancreatitis included complete avoidance of any form of enteral nutrition, which was achieved either by providing no supplementary nutrition or by parenteral nutrition.[66] However, subsequent studies showed a decreased exocrine pancreatic secretion in response to CCK in experimentally induced pancreatitis.[67] It is now recognized that both parenteral and enteral routes of alimentation are superior to providing no nutritional support, and thus providing early and adequate nutritional support has become a priority in the treatment of human patients with acute pancreatitis.[66] In addition, several human studies show that enteral nutrition is superior to parenteral nutrition, and enteral nutrition is now the preferred method of alimentation for patients with acute pancreatitis.[65,66] Regarding the location of food delivery through enteral feeding, jejunal feeding is considered by many to be the method of choice, but studies in humans show that nasojejunal feeding offers no advantages compared with nasogastric feeding.[66,67] Thus, gastric delivery of nutrients is preferred in many cases as it is much simpler than jejunal feeding and is well tolerated by most patients.

Unfortunately, studies in dogs with pancreatitis are limited. Information from clinical experience and preliminary studies suggest that enteral nutrition is generally well tolerated and improves, or at least, does not worsen the course of pancreatitis.[68,69] Using this information and applying the knowledge based on studies in experimental animals and humans to dogs, the following recommendations can be made: (a) dogs with pancreatitis should not be kept without enteral nutritional support for more than 24 hours (including times of anorexia before presentation); (b) dogs with acute pancreatitis that are not vomiting should generally be fed by mouth. If they are anorectic, a feeding tube should be used (esophagostomy, nasoesophageal, gastrostomy, nasogastric, or jejunostomy tube) until the animal is eating again. Esophagostomy and nasoesophageal or nasogastric tubes are usually preferred because their placement is less invasive and is associated with few complications[70]; and (c) if the animal is vomiting, antiemetics should be used to control vomiting and enteral nutrition should be given as soon as possible. Jejunostomy tubes should be considered in animals with refractory vomiting or animals that undergo exploratory or therapeutic laparotomy. Their use is relatively safe with severe complications (e.g., breakdown of the surgical site) being reported in 0% to 6% of dogs.[70,71] Endoscopic techniques for percutaneous gastrojejunostomy tube placement might prove helpful in the future.[72]

A diet of choice has not been determined in people or dogs with pancreatitis, but a balanced extra-low-fat diet is currently our preferred choice for dogs. Administration of parenteral nutrition has been reported in dogs, but we rarely recommended its use (unless enteral nutrition is contraindicated in a patient), mainly because of data from human studies (see earlier discussion), its unproven efficacy in dogs with pancreatitis, and the potential for serious complications.[73-75]

Fluid Therapy

Dogs with pancreatitis are often presented with variable degrees of dehydration because of decreased water intake, vomiting, diarrhea, and/or third space losses. In these cases, dehydration results most commonly from isotonic fluid loss. The degree of dehydration can be estimated by evaluating physical parameters (e.g., dryness of mucous membranes, reduced skin turgor), or by detailed serial monitoring of body weight.[76,77] Dehydration might also be evident in clinicopathologic testing (e.g., hemoconcentration, increased total protein concentration, high urine specific gravity, prerenal azotemia, and others).[76,77] Replacement isotonic fluid solutions (e.g., lactated Ringer solution, 0.9% NaCl) are the treatment of choice for dehydrated dogs with pancreatitis. Mild dehydration (approximately 5%) may be treated by subcutaneous fluid administration. If the animal is not vomiting, oral rehydration therapy may also be used. Moderate and severe dehydration (>6%) should be treated with intravenous fluid administration. Severely dehydrated animals might be in shock, in which case they require aggressive intravenous fluid therapy (see following discussion).[76]

In dogs with severe acute pancreatitis, rapid and excessive fluid loss as a consequence of vomiting, diarrhea, and/or third space accumulation of fluid, might lead to hypovolemia and compromised perfusion of organs and tissues. Tissue hypoperfusion and especially diminished pancreatic microcirculation is believed to contribute to the development of major local and systemic complications.[78] Hypovolemic patients may or may not be dehydrated, depending mostly on the volume and rapidity of fluid loss.[76] Severe hypovolemia leading to hypovolemic shock is a life-threatening condition and must always be treated as an emergency. In addition to the volume deficit, some animals have a reduced red blood cell volume as a result of GI blood loss, which further decreases tissue perfusion. Clinical findings indicating hypovolemia include hypotension, reduced peripheral pulses, tachycardia, cold extremities, prolonged capillary refill time, and pale mucous membranes.[76,77]

In human patients, aggressive fluid resuscitation using crystalloid solutions is recommended in most cases, while colloids are used only in specific cases (e.g., where there is hypoalbuminemia).[78] Although studies are lacking in dogs, aggressive intravenous fluid therapy (fluid resuscitation) should be initiated as soon as possible when there is hypovolemic shock, before initiating the rehydration phase (if the animal is also dehydrated).[76] Current recommendations for initial fluid therapy of hypovolemic shock include rapid intravenous administration of one or more small boluses (10 to 20 mL/kg in <5 minutes) or a single bolus (90 mL/kg in 15 to 20 minutes) of an isotonic crystalloid solution and close monitoring of physical parameters for evidence of improvement (e.g., slower heart rate, improved pulse quality and capillary refill time).[77,79] Care should be taken not to cause fluid overload in these patients. Based on the response to initial treatment and the severity of hypovolemia, crystalloid fluids can then be administered at rates of 20 to 90 mL/kg/h. Colloids (e.g., dextran 70, hydroxyethyl starch) may also be added to the isotonic crystalloid solutions for more effective volume expansion of the intravascular space, especially when severe hypoalbuminemia (<1.5 g/dL) is present.[76,77,79] Studies of experimental acute pancreatitis in dogs suggest that hypertonic saline-dextran solutions may be more efficacious than crystalloid solutions in restoring tissue perfusion.[80] However, studies of dogs with spontaneous pancreatitis are lacking and current recommendations in humans favor crystalloid use in most cases.[78]

Plasma and Blood Transfusion

The use of fresh-frozen plasma (10 to 15 mg/kg once a day) is recommended by some authors for dogs with severe pancreatitis because it contains several beneficial components, such as proteinase inhibitors (e.g., α_1-proteinase inhibitor, α_2-macroglobulin), albumin, as well as coagulation and anticoagulation factors.[15,81] Proteinase inhibitors may protect from development or worsening of pancreatitis, and depletion of proteinase inhibitors has been reported in dogs with both experimental and spontaneous pancreatitis.[15,54,82] However, in one study, α_2-macroglobulin concentrations did not correlate with severity of pancreatitis in dogs.[54] Studies in humans show no benefit of plasma administration in the clinical outcome of patients with acute pancreatitis, despite the increase in plasma concentrations of proteinase inhibitors.[83] Therefore fresh-frozen plasma is generally only recommended for the treatment of people with pancreatitis when they have coagulopathies. In addition, in a recent retrospective study, dogs with pancreatitis that received fresh-frozen plasma had a worse outcome than dogs that did not receive fresh-frozen plasma.[7] In that study, there was no significant difference in the severity of pancreatitis before treatment, although treatments were not controlled in the two groups and group allocation was not randomized.[7] Thus, the actual value of plasma administration is highly questionable in dogs with pancreatitis. It is possible that, as in humans, its usefulness is limited to cases where coagulopathies are present.[81] Well designed prospective and randomized studies are needed to critically evaluate the usefulness of plasma administration in dogs with pancreatitis. Fresh whole blood (20 to 25 mL/kg once a day) might be used if fresh-frozen plasma is not available or if there is severe blood loss.

Therapy for Electrolyte and Acid–Base Abnormalities

Electrolyte abnormalities are common in dogs with acute pancreatitis. Various combinations and degrees of hypokalemia, hyponatremia, and hypochloremia can be present as a result of diarrhea, vomiting, fluid therapy, and/or anorexia.[16] Hyperkalemia, hypernatremia, and hypocalcemia or hypercalcemia are reported less frequently.[16] Unfortunately, the nature of electrolyte abnormalities in dogs with pancreatitis cannot be accurately predicted and serum potassium, sodium, chloride, and ionized calcium concentrations should always be measured and corrected in these patients. The variability of electrolyte abnormalities in animals with pancreatitis is further complicated by the presence of concurrent diseases such as diabetes mellitus. Hypokalemia may or may not be associated with clinical signs such as muscular weakness and cardiac arrhythmia. Its correction should be achieved by addition of potassium chloride to intravenous fluids, and it should be administered at a rate of 0.15 to 0.5 mEq/kg/h, depending on the severity of depletion and ongoing losses. Hyponatremia is usually asymptomatic and is usually corrected by administration of crystalloid solutions (lactated Ringer solution or 0.9% saline). Although not as common as in cats, hypocalcemia can also be seen in dogs with pancreatitis, but clinical signs attributable to hypocalcemia are rarely noted.[16,84] The value of supplementing calcium has not been evaluated in dogs. Most hypocalcemic patients with pancreatitis have no clinical signs of hypocalcemia, and thus can be treated with 10% calcium gluconate at a dose of 5 to 10 mg/kg/h of elemental calcium given in the crystalloid infusion.

Acid–base disturbances are also common in dogs with pancreatitis and may occur as a result of vomiting, diarrhea, and/or hypoperfusion. The nature of acid–base disorders in dogs with pancreatitis cannot be accurately predicted and blood gas analysis is recommended. Patients with vomiting of gastric fluid typically develop metabolic alkalosis because of loss of chloride and H^+, while patients with diarrhea are more likely to develop metabolic acidosis as a result of loss of HCO_3^-. In patients with both vomiting and diarrhea, or with vomiting that also includes duodenal content, the acid–base status is more difficult to predict. Mild acid–base disorders are corrected through fluid therapy. Treatment of more severe forms of acid–base disorders depends on the specific type of the disorder.

Analgesic Therapy

Pain is believed to accompany virtually all cases of pancreatitis in dogs, even when pain is not clinically obvious.[85] Pain induces several physiologic changes, including decreased appetite, decreased GI tone, decreased regional blood flow to several abdominal organs (including the pancreas), and tachycardia, and it may produce a catabolic state.[86,87] Therefore, analgesic therapy is extremely important and should be used in all dogs with pancreatitis.

Pain in dogs with pancreatitis can range from mild to severe. Opioid administration is mandatory in the management of pain in acute pancreatitis. The intravenous route is usually preferred because it provides fast results. For mild to moderate pain, administration of buprenorphine (0.005 to 0.015 mg/kg, IV, IM, or SC, q6-12h) is usually sufficient. In dogs with severe pain, administration of morphine (0.5 to 1.0 mg/kg, slowly IV or IM q2h; constant-rate infusion [CRI], 0.05 to 0.2 mg/kg/h), hydromorphone (0.1 to 0.2 mg/kg, slowly IV or IM q2h; CRI, 0.0125 to 0.05 mg/kg/h), methadone (0.1 to 0.5 mg/kg IV, IM, or SQ q2-6h), or fentanyl (0.005 to 0.01 mg/kg IV, IM, or SQ q2h; CRI, 0.002 to 0.006 mg/kg/h) is very effective, especially when used as a CRI. Multimodal pain management might be indicated in some cases with severe pain, because it may be more effective and associated with fewer side effects because of lower dosages of the drugs administered. Combinations commonly used in dogs include morphine (0.1 mg/kg/h), lidocaine (2.5 mg/kg/h), and ketamine (0.6 mg/kg/h). Fentanyl patches (patch size is based on patient size, every 3 to 4 days) are safe and practical, but they should be used only after analgesia has been achieved by use of injectable opioids, as it takes longer for transdermal application to achieve analgesia. Analgesic therapy in outpatients can be achieved with fentanyl patches, buprenorphine, or tramadol (4 mg/kg PO q12h).

Antiemetic Therapy

Antiemetic therapy should be initiated in all dogs with pancreatitis that are vomiting or appear nauseated. Maropitant is a neurokinin-1 (NK-1) receptor antagonist, which acts through inhibition of substance P.[88] Although not specifically tested for pancreatitis, several studies have demonstrated the effectiveness of this drug in both preventing and treating vomiting of different etiologies in dogs.[89,90] Maropitant has been shown to be effective in controlling both peripherally and centrally mediated emesis, because NK-1 receptors are located both centrally (emetic center, chemoreceptor trigger zone) and peripherally (mainly vagal nerve terminals).[89,90] Based on recent unpublished data, maropitant may also have analgesic effects, that may be primary or secondary (Dr. D. Twedt, Colorado State University, Fort Collins, CO, personal communication). For the treatment of acute vomiting, the injectable solution is administered at a dose of 1 mg/kg SC q24h for up to 5 consecutive days. If therapy is needed for longer periods, a 48- to 72-hour washout period is recommended.[88] Maropitant is generally well tolerated in dogs.

5-HT_3 antagonists such as dolasetron (0.6 mg/kg IV, SC, or PO q12h) and ondansetron (0.1 to 0.2 mg/kg, slowly IV, q6-12h) can also be used and seem to be effective in many cases. 5-HT_3 antagonists can be used in combination with maropitant in refractory cases of vomiting, although the safety of this combination is only anecdotal. Dopaminergic antagonists (e.g., metoclopramide 0.2 to 0.5 mg/kg IV, IM, SQ, or PO q6-8h) are considered to be less effective and might negatively affect the course of pancreatitis because dopamine protects against experimentally induced acute pancreatitis in experimental animals.[91,92] CRIs of metoclopramide (0.3 mg/kg/h IV) seem to be more effective than single doses. Finally, α_2-adrenergic antagonists such as chlorpromazine should be avoided because of their potentially serious side effects (mainly hypotension).

Antibiotic Therapy

Prophylactic use of antibiotics is controversial in human patients with pancreatitis. Prophylactic antibiotics have been recommended in people with pancreatic necrosis.[8] The goal of antibiotic prophylaxis in human patients with necrotizing pancreatitis is to prevent bacterial translocation from the intestinal lumen, prevent or decrease pancreatic colonization, and reduce mortality.[93,94] Meta-analysis studies have often arrived at conflicting results.[8,78,93,94] Because multicenter, double-blinded, placebo-controlled, and meta-analysis studies have failed to show a clear advantage of prophylactic antibiotic use in people with severe necrotizing pancreatitis, most authors do not recommend antibiotic prophylaxis in human pancreatitis.[8,78]

Studies on prophylactic antibiotic use in dogs with spontaneous pancreatitis are lacking. Because infectious complications occur much less frequently in dogs compared with people and given that prophylactic antibiotic use is not clearly efficacious in human patients, prophylactic use of antibiotics is believed to be of no benefit in dogs with pancreatitis. In addition, side effects such as anorexia and vomiting might be associated with some antibiotics, while others might be implicated in the initiation of pancreatitis. The use of antibiotics is recommended in cases where infectious complications are identified (e.g., aspiration pneumonia, infected pancreatic necrosis) or are suspected. Antibiotic selection should be based on culture and sensitivity but cefotaxime, ciprofloxacin, metronidazole, clindamycin, and chloramphenicol achieve therapeutic levels in the pancreas in experimental pancreatitis.[95,96]

Surgery

Surgery for Pancreatitis

Surgical management of canine pancreatitis without pancreatic complications is rarely recommended. Some clinicians recommend peritoneal lavage to treat dogs with severe pancreatitis as it was suggested to remove harmful substances, such as trypsin and inflammatory cytokines, from the peritoneal cavity.[97] However, recent well-designed and metaanalysis studies in humans show that use of peritoneal lavage is not associated with any significant improvement in morbidity or mortality.[97]

In an older study of experimental canine pancreatitis, there was a significant improvement in survival with the use of peritoneal dialysis.[98] However, experimental models for pancreatitis do not represent an ideal model of spontaneous pancreatitis, and no studies have evaluated the usefulness of peritoneal lavage in naturally occurring pancreatitis in dogs. Given that peritoneal lavage is invasive, expensive, often associated with severe complications (e.g., peritonitis, anesthesia of compromised patients), and of unproven value, it is generally not recommended for the management of acute pancreatitis in dogs.

Surgery for Pancreatic Complications of Pancreatitis

Several pancreatic complications of pancreatitis have been reported in dogs, and surgical intervention is used in some cases to treat them. Because these complications of pancreatitis have been reported infrequently in the veterinary literature, evidence-based information regarding the treatment of choice is lacking. In addition, the terminology and definition of pancreatic complications of pancreatitis used in dogs has been adapted from the human literature and does not accurately illustrate these complications in dogs. The human classification of pancreatic complications of pancreatitis is currently being updated[99] and will most likely be adapted for dogs as well. In this chapter, and in order to avoid confusion, the terminology used in the previously published reports in dogs is used.

A *pancreatic abscess*[100-105] is the most commonly reported complication of pancreatitis in dogs, and has been described in association with both acute and chronic pancreatitis. Pancreatic abscesses are believed to occur infrequently, with a reported prevalence of 1.4% to 6.5%. In contrast to people, pancreatic abscesses are usually sterile in dogs, with only up to 22% of the reported cases yielding bacterial growth, although many of these dogs had received antibiotics prior to admission. Surgical intervention is almost always recommended when a pancreatic abscess is identified, and several surgical techniques have been described. Mortality in dogs with pancreatic abscesses ranges from 50% to 86%, making the presence of a pancreatic abscess a poor prognostic indicator.

Pancreatic pseudocysts[105-108] are reported as a complication of pancreatitis (both acute and chronic), but appear to be uncommon. Their pathogenesis is unknown and they are usually sterile. Ultrasound-guided fine-needle aspiration of the cystic fluid may be used for the management of small pseudocysts. In other cases, however, clinical signs persist or worsen despite treatment and enlargement of the pseudocyst may occur over time. In these cases surgical intervention is usually recommended, although surgical techniques are poorly described. Internal drainage appears to be the treatment of choice in humans.

Necrotic masses,[101,105] usually arising from necrotizing pancreatitis, have been reported in a small number of dogs. These dogs were treated surgically (debridement and drainage) but died or were euthanized soon after surgery.

Extrahepatic biliary tract obstruction[109] has also been reported as a result of pancreatitis in dogs, and surgery is usually required in cases of complete obstruction of the bile duct or in cases where the obstruction does not subside within 2 to 3 weeks.

Other Treatments

A plethora of other therapeutic agents (e.g., dopamine, H_1- and H_2-histamine receptor antagonists, somatostatin, anticholinergics, protease inhibitors, antioxidants, platelet-activating factor inhibitors, IL-10, selenium, probiotics) have been recommended by some authors in both veterinary and human medicine. Some of these therapeutic agents have shown potential benefit in feline models of experimental pancreatitis (e.g., dopamine, H_1- and H_2-histamine receptor antagonists)[110,111] or in clinical trials in people (e.g., the protease inhibitor gabexate mesylate),[112] and may prove to be beneficial for clinical use in the future. For the majority of the therapeutic agents mentioned previously, however, either appropriate clinical trials are lacking or have shown no benefit in the treatment of acute pancreatitis in humans.[112] There is currently no convincing evidence that any of these agents is beneficial for the treatment of spontaneous pancreatitis in dogs.

There are anecdotal reports that some dogs with chronic pancreatitis respond to corticosteroid (e.g., prednisone) or other immunosuppressive therapy. It is likely that, as in humans, some cases of canine chronic pancreatitis might have an autoimmune component and these cases might benefit from corticosteroid administration. The safety and effectiveness of corticosteroids or other immunosuppressive agents in dogs with pancreatitis has not been evaluated, and therefore, these agents should be used with caution and only when all other treatments have failed.

Prognosis

The prognosis for dogs with pancreatitis depends on the severity of the disease. Mild cases usually have a good prognosis, and if recurrent episodes of pancreatitis do not occur, these animals live for long periods of time. In contrast, the prognosis for dogs with severe pancreatitis is usually guarded. The mortality associated with severe acute pancreatitis is high and the existence of pancreatic complications (e.g., pancreatic abscess) or concurrent diseases (e.g., diabetes mellitus) further contributes to a poorer outcome. It is unknown if dogs that have a single episode of pancreatitis are at risk for developing chronic or recurrent acute pancreatitis. The prognosis for dogs with chronic or recurrent acute pancreatitis is difficult to predict, and it depends on the severity of each acute exacerbation of the disease. Unfortunately, no accurate method has been reported to date for the prediction of the outcome of dogs with spontaneous pancreatitis, and the prognosis should be evaluated on an individual basis.

NECROSIS AND INFLAMMATION: FELINE

Robert J. Washabau

Several pathologies involving the feline exocrine pancreas have been identified (Figure 60-20).[1-12] Pathologic classification systems have been used to delineate these disorders,[13,14] although it should be emphasized that significant overlap exists between several disease categories particularly with regard to acute and chronic forms of pancreatitis.[8,10]

- ANP: This lesion is characterized by pancreatic acinar cell and peripancreatic fat necrosis (>50% of the pathology), with varying amounts of inflammation, hemorrhage, mineralization, and fibrosis. Inflammation may be present, but necrosis is the predominant feature. Reports of this condition were uncommon prior to the early 1990s, probably related to difficulties in diagnosis as well as lower incidence of disease. ANP is now a well-recognized gastrointestinal disorder of significant morbidity and mortality in the domestic cat.[1-10]
- Acute suppurative pancreatitis: Acute suppurative pancreatitis differs from ANP in that neutrophilic inflammation accounts for >50% of the pancreatic pathology. Necrosis may be present, but neutrophilic inflammation is the predominant feature. Acute suppurative pancreatitis is less common than ANP, appears to affect younger animals, and may have a differing pathogenesis.[2,5,6,10]
- Chronic nonsuppurative pancreatitis: This lesion is characterized by lymphocytic inflammation, fibrosis, and acinar atrophy. Necrosis and suppuration may be present in small amounts, but lymphocyte infiltration is the predominant feature. Antemortem differentiation of chronic nonsuppurative pancreatitis and ANP cannot be made on the basis of clinical, clinicopathologic, or imaging findings[10]; histopathology remains the only dependable method of differentiating these two disorders.[10] Chronic nonsuppurative pancreatitis and ANP may vary in their pathogeneses or they may represent a continuum of disease from necrosis to inflammation and fibrosis.[1,10]
- Pancreatic nodular hyperplasia: Nodules of pancreatic acinar or duct tissue are distributed throughout the pancreatic parenchyma. Fibrosis, inflammation, necrosis, and hemorrhage are not features of this condition. The clinical significance of this lesion is unknown. Pancreatic nodular hyperplasia is often detected at the time of routine abdominal ultrasonography or as an incidental finding at necropsy. Its importance resides in the need to differentiate its ultrasonographic characteristics from those of ANP.
- Pancreatic neoplasia: Neoplastic disorders of the pancreas may be primary (e.g., adenoma, adenocarcinoma) or secondary, and they are classified as benign or malignant. Pancreatic adenocarcinoma is the most common malignancy of the feline exocrine pancreas and is of ductal (primarily) or acinar origin. Neoplastic infiltration may be accompanied by necrosis, inflammation, fibrosis, hemorrhage, or mineralization in some instances.
- Pancreatic pseudocyst: Pancreatic pseudocyst is a common complication of pancreatitis in humans, and a not-so-common complication in cats and dogs.[15] Pancreatic pseudocyst is a nonepithelial lined cavitary structure containing fluid, pancreatic cells, and/or enzyme. It is observed at the time of ultrasound, CT scan, surgery, or necropsy. Its importance resides in the need to differentiate its ultrasonographic characteristics from those of pancreatic abscessation.
- Pancreatic abscess: Pancreatic abscess is a circumscribed collection of purulent material involving the right or left lobe of the pancreas. Like pseudocyst, pancreatic abscessation appears to be a complication of pancreatitis in humans and dogs.[16] The incidence and significance of this lesion in the cat are unknown. Medical and surgical therapies have been used to manage pancreatic abscesses in the dog.
- Pancreatic atrophy: Atrophy may result from degeneration, involution, necrosis, or apoptosis of the exocrine portion of the gland. Most feline cases are believed to represent the end stage of chronic pancreatitis. The endocrine portion of the gland may or may not be involved in the same process. EPI is the clinical syndrome that results from 95% or greater loss of exocrine pancreatic function. Affected animals develop a classic maldigestion syndrome characterized by weight loss, steatorrhea, and diarrhea.[11,17]

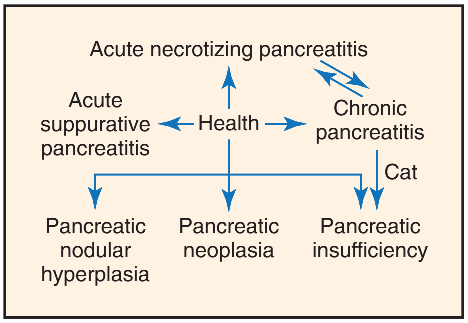

Figure 60-20 Pathogenesis of feline exocrine pancreatic disease.

Etiology

The etiologies of ANP are probably not yet completely recognized. Biliary tract disease, GI tract disease, ischemia, pancreatic ductal obstruction, infection, trauma, organophosphate poisoning, and lipodystrophy all have known associations with the development of ANP in the cat. Hypercalcemia, idiosyncratic drug reactions, and

Box 60-2 Etiologies of Feline Acute Necrotizing Pancreatitis

Known Associations
Biliary tract disease
Ischemia
Infection
Organophosphates
Gastrointestinal disease
Ductal obstruction
Trauma
Lipodystrophy

Suggested Associations
Hypercalcemia
Nutrition
Drug reactions

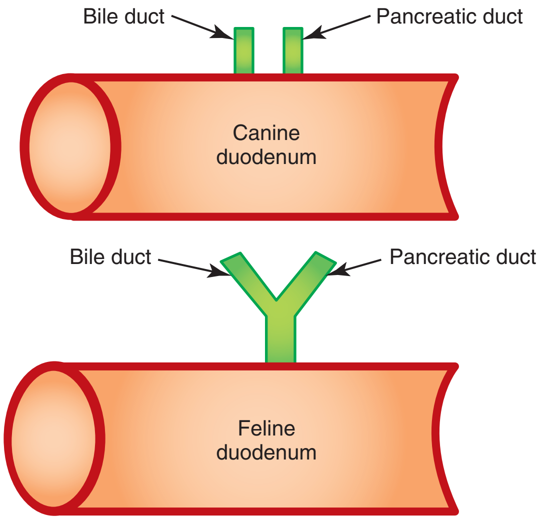

Figure 60-21 **Differences in pancreaticobiliary anatomy between cats and dogs.** Pancreatic and bile ducts have separate channels of entry in the canine small intestine, whereas these ducts merge prior to their entry in the feline small intestine.

nutritional causes are suggested but poorly documented causes of the disease (Box 60-2).

Concurrent Biliary Tract Disease

Concurrent biliary tract pathology has a known association with ANP in the cat. Cholangitis is the most important type of biliary tract disease for which an association has been made,[18] but other forms of biliary tract pathology (e.g., stricture, neoplasia, and calculus) have known associations.[2,9] Epidemiologic studies[18] show that cats affected with suppurative cholangitis have significantly increased risk for pancreatitis. The pathogenesis underlying this association is not entirely clear but relates partly to the anatomic and functional relationship between the major pancreatic duct and common bile duct in this species.[19,20] Unlike the dog, the feline pancreaticobiliary sphincter is a common physiologic and anatomic channel at the duodenal papilla (Figure 60-21). Mechanical or functional obstruction to this common duct readily permits bile reflux into the pancreatic ductal system.[21-23] Bile salt perfusion (e.g., 1 to 15 mM sodium cholate or glycodeoxycholate) of the major pancreatic duct induces changes in the permeability of the pancreatic duct,[21,22] and sustained elevations in ductal pressure (>40 cm H_2O) and bacterial infection induce pancreatic acinar necrosis.[1,22] Ductal pressures are readily increased by biliary infection, and ductal compression is a predictable consequence of sustained ductal hypertension and pancreatic interstitial edema.[22,23]

Concurrent Gastrointestinal Tract Disease

Like concurrent biliary tract disease, inflammatory bowel disease (IBD) is an important risk factor for the development of ANP in the cat.[18,24] Several factors appear to contribute to this association: (a) High incidence of IBD—IBD is a common disorder in the domestic cat.[24-26] In some veterinary hospitals and specialty referral centers, IBD is the most common GI disorder in cats. (b) Clinical symptomatology of IBD—Vomiting is the most important clinical sign in cats affected with IBD.[24-26] Chronic vomiting raises intraduodenal pressure and increases the likelihood of pancreaticobiliary reflux. (c) Pancreaticobiliary anatomy—The pancreaticobiliary sphincter is a common physiologic and anatomic channel at the duodenal papilla,[19,20] thus reflux of duodenal contents would perfuse pancreatic and biliary ductal systems. (d) Intestinal microflora—Compared with dogs, cats have a much higher concentration of aerobic, anaerobic, and total (10^9 vs. 10^4 organisms/mL) bacteria in the proximal small intestine.[27,28] Bacteria readily proliferate in the feline small intestine because of differences in GI motility and immunology.[29,30] If chronic vomiting with IBD permits pancreaticobiliary reflux, a duodenal fluid containing a mixed population of bacteria, bile salts, and activated pancreatic enzyme would perfuse the pancreatic and biliary ductal systems.[31]

Ischemia

Ischemia (e.g., hypotension, cardiac disease) is a cause or consequence of obstructive pancreatitis in the cat. Inflammation and edema reduce the elasticity and distensibility of the pancreas during secretory stimulation. Sustained inflammation increases pancreatic interstitial and ductal pressure which serves to further reduce pancreatic blood flow, organ pH, and tissue viability.[32-34] Acidic metabolites accumulate within the pancreas because of impaired blood flow.[34-36] Ductal decompression has been shown to restore pancreatic blood flow, tissue pH, and acinar cell function.[35,36]

Pancreatic Ductal Obstruction

Obstruction of the pancreatic duct (e.g., neoplasia, pancreatic flukes, calculi, and duodenal foreign bodies) is associated with the development of ANP in some cases.[9,37] Pancreatic ductal obstruction has marked effects on pancreatic acinar cell function. During ductal obstruction, ductal pressure exceeds exocytosis pressure and causes pancreatic lysosomal hydrolases to colocalize with digestive enzyme zymogens within the acinar cell.[38] Colocalization is the underlying pathogenesis for digestive enzyme activation within the acinar cell because lysosomal enzymes (e.g., cathepsin B) readily activate trypsin.[38]

Infection

Infectious agents (*Toxoplasma gondii*, feline herpesvirus 1, feline infectious peritonitis) have been implicated in the pathogenesis of feline ANP[39-41] although none have been reported as important causes of ANP in any of the recent clinical case series.[1-10,12] The pancreas is readily colonized by *T. gondii* organisms during the acute phase of infection.[39] In one survey of *T. gondii*-infected cats, organisms were found in 84% of the cases, although organ pathology was more severe in other organ systems.[39] *Feline herpesvirus 1* and feline infectious peritonitis viruses have been implicated as causative agents in several case reports,[40] and feline parvoviral infection is associated with viral inclusion bodies and pancreatic acinar cell necrosis in young kittens.[41] Pancreatic (*Eurytrema procyonis*) and liver fluke (*Amphimerus pseudofelineus*, *Opisthorchis felineus*) infections are known causes of feline ANP in the southeastern United States and Caribbean Basin.[37,42] Recent reports of virulent caliciviral infections have been reported in multiple cat households or research facilities. Affected cats manifest high fever, anorexia, labored respirations, oral ulceration, facial and limb edema, icterus, and severe pancreatitis.[43-45] Caliciviral infection has not been reported in any of the recent clinical case series of feline ANP,[1-10,12] but some cases of active infection could have been overlooked. The importance of calicivirus infection in the pathogenesis of feline acute pancreatic necrosis remains to be determined.

Trauma

Automobile and fall ("high-rise syndrome") injuries are associated with the development of ANP in a small number of cases.[46,47] These tend to be isolated cases that do not show up as important causes in clinical case surveys.

Organophosphate Poisoning

Organophosphate poisoning is a known cause of ANP in humans and dogs,[48] and several cases have been reported in the cat.[2] In one survey, several cats developed ANP following treatment for ectoparasites, and two cats developed ANP following treatment with fenthion.[2] Diminishing organophosphate usage will probably lead to a reduced incidence of this lesion.

Lipodystrophy

Lipodystrophy has been cited as an occasional cause of ANP in the cat,[49] but it has not been reported in any of the large clinical case series.

Hypercalcemia

ANP develops in association with the hypercalcemia of primary hyperparathyroidism and humoral hypercalcemia of malignancy in humans, and a weak association with hypercalcemia has been reported in dogs.[15] Moderate hypercalcemia was found as a preexisting laboratory finding in 10% of the cases of fatal canine acute pancreatitis.[15] Acute experimental hypercalcemia does indeed cause acute pancreatic necrosis and pancreatitis in cats,[50,51] but it is probably not very clinically relevant. Acute hypercalcemia is an uncommon clinical finding in feline practice. Chronic hypercalcemia, a more clinically relevant condition, is not associated with changes in pancreatic morphology or function.[52]

Idiosyncratic Drug Reactions

Therapy with azathioprine, L-asparaginase, potassium bromide, and trimethoprim-sulfa drugs are associated with the development of ANP in the dog.[15,53] Similar associations have not been made in the cat. Glucocorticoid administration has been suggested as a cause of acute pancreatitis in the dog, but a firm association has not been confirmed in either species. Indeed, antiinflammatory doses of glucocorticoids appear to be beneficial in the management of experimental canine acute pancreatic necrosis.[54]

Nutrition

High-fat feedings[55] and obesity[53] are associated with the development of pancreatitis in the dog, but similar associations have not been made in the cat. Most recent surveys associate underweight body condition with the development of feline ANP.[2,6,8,10]

Pathogenesis

The acinar and ductal cells of the exocrine pancreas are interspersed between the islet cells of the endocrine pancreas. Like the endocrine pancreas, the exocrine pancreas is a secretory organ with several physiologic functions. Exocrine pancreatic fluid contains digestive zymogens that initiate protein, carbohydrate, and lipid digestion; bicarbonate and water that serve to neutralize the duodenum; intrinsic factor that facilitates cobalamin (vitamin B_{12}) absorption in the distal ileum; and antibacterial proteins that regulate the small intestinal bacterial flora. Digestive zymogens and antibacterial proteins are secreted primarily by acinar cells, while bicarbonate, water, and intrinsic factor are secreted primarily by ductal cells. The two most common disorders of the exocrine pancreas, acute pancreatic necrosis and EPI, are readily understood on the basis of these physiologic functions. With acute pancreatic necrosis, premature activation of digestive zymogen within pancreatic acinar cells leads to acinar cell necrosis (trypsin, chymotrypsin, carboxypeptidase), hemorrhage (elastase digestion of blood vessel elastin fibers), and fat necrosis and saponification (lipase digestion of pancreatic, peripancreatic, and mesenteric fat). With EPI, affected animals develop severe nutrient maldigestion, acid injury to the duodenal mucosa, cobalamin and fat-soluble vitamin malabsorption, and bacterial proliferation in the gut (summarized in reference 56).

Pancreatic acinar cells protect themselves from intraacinar activation of zymogen and acinar cell necrosis through several mechanisms: (a) Potentially harmful digestive enzymes are synthesized in the form of inactive precursors or zymogens in the rough endoplasmic reticulum. (b) Zymogens are then transported to the Golgi complex where they undergo selective glycosylations. Lysosomal hydrolases that are eventually packaged in lysosomes are separated from zymogens bound for export as they pass through the Golgi complex. Lysosomal hydrolases are first phosphorylated at the six position of mannose residues, bound to receptors specific for 6-phosphoryl mannose, and then transported to lysosomes where the acid pH favors their dissociation from the receptors. Digestive enzymes lack the 6-phosphoryl mannose label, and are instead transported vectorially into a different secretory fraction. (c) Packaging of zymogens into maturing zymogen granules sequesters them from contact with other subcellular fractions. (d) PSTI is incorporated into the maturing zymogen granules. PSTI inactivates trypsin should there be any intraacinar activation of trypsinogen. (e) Following stimulation (e.g., feeding and cholecystokinin secretion), mature zymogen granules and their contents are released from the cell into the ductal lumen in a process of membrane fusion and exocytosis. (f) Finally, zymogens are activated physiologically only after they enter the duodenum, where the brush-border enzyme enteropeptidase activates trypsinogen, and trypsin then activates other pancreatic zymogen (Figure 60-22).[56]

A large body of experimental, and some clinical, evidence suggests that the initiating event of acute pancreatitis is the premature activation of digestive zymogens within the acinar cell.[38,57-60] Premature activation of digestive zymogen results in acinar cell necrosis and pancreatic autodigestion. In acute pancreatic necrosis, protein synthesis and intracellular transport to the Golgi complex appear to be normal, but digestive zymogens then become colocalized along with lysosomal hydrolases in large vacuoles. Cell biology studies reveal that lysosomal and zymogen granule fractions become colocalized through a process known as *crinophagy*, a process used by

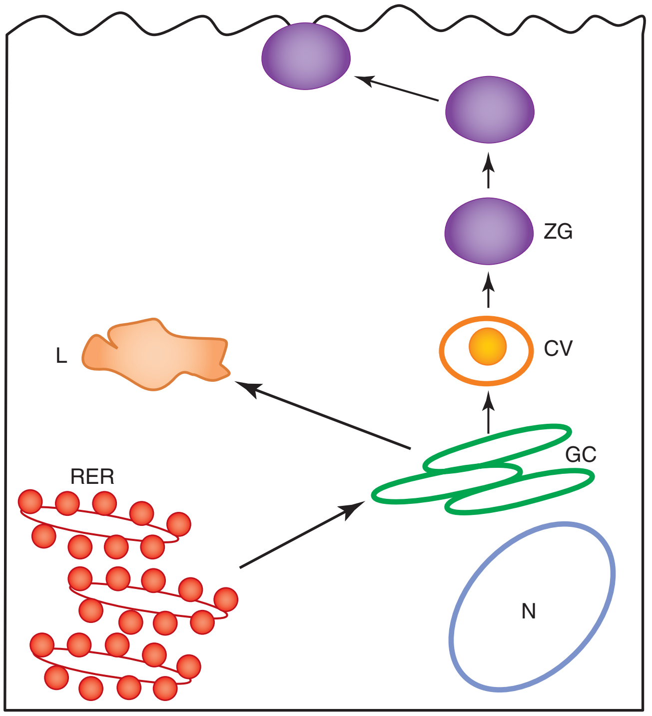

Figure 60-22 Intracellular trafficking of zymogens and lysosomal hydrolases in pancreatic acinar cells. Digestive zymogens and lysosomal hydrolases are synthesized on the rough endoplasmic reticulum (*RER*) and transported to the Golgi complex (*GC*) where they undergo selective glycosylation. Lysosomal hydrolases are phosphorylated at 6-mannose residues and transported to lysosomes (*L*) via receptors specific for 6-phosphoryl mannose. Digestive enzymes lack the 6-phosphoryl mannose label and are instead transported vectorially into condensing vacuoles (*CV*). Condensing vacuoles mature into zymogen granules (*ZG*) whose contents are released into the pancreatic ductal system following feeding. Trypsinogen is converted to active trypsin by intestinal enterokinase, and inactive zymogens are converted to active enzymes by tryptic hydrolysis. *N*, nucleus. (Modified from Steer ML: The early intra-acinar cell events which occur during acute pancreatitis. *Pancreas* 17:31, 1998.)

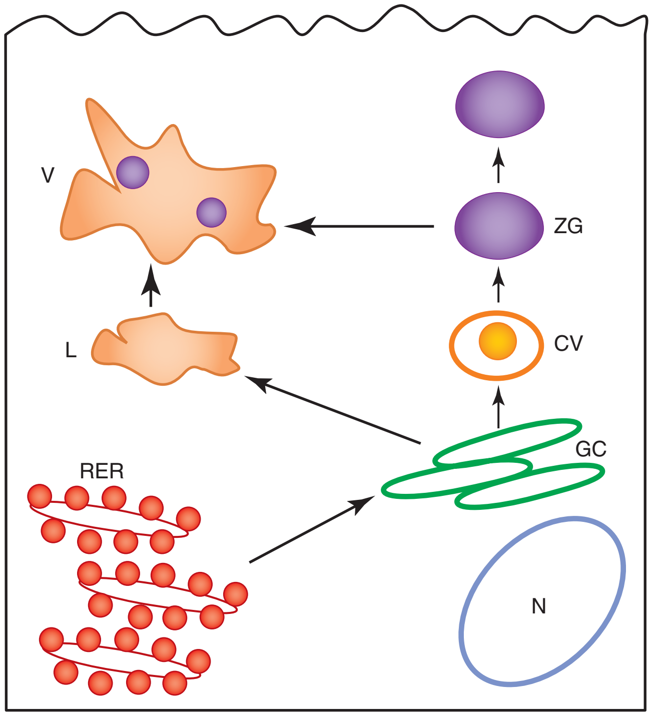

Figure 60-23 Cell biology of pancreatic acinar cell necrosis. Pancreatic enzyme secretion is inhibited and pancreatic zymogens become colocalized with lysosomal hydrolases within large vacuoles (*V*). Lysosomal hydrolases prematurely activate digestive zymogens within pancreatic acinar cells. (Modified from Steer ML: The early intra-acinar cell events which occur during acute pancreatitis. *Pancreas* 17:31, 1998.)

many cells to degrade accumulated secretory products when the need for secretion is no longer present. Although this process takes place in other cells without adverse consequences, it can be lethal in pancreatic acinar cells because of the peculiarity of their secretion products (digestive zymogens). Lysosomal hydrolases, such as cathepsin B and *N*-acetyl glucosaminidase, activate trypsinogen to the active trypsin form, and the enhanced fragility of these large vacuoles permits release of active enzyme into the cell cytoplasm (Figure 60-23). Trypsin acts autocatalytically to activate other trypsinogen molecules and other zymogens, each inducing a unique chemical pathology in pancreatic and extrapancreatic cells. A variety of inflammatory mediators and cytokines, interleukins, nitric oxide, and free radicals are involved in the further evolution of pancreatic acinar cell necrosis and inflammation and often determine the outcome.[56,61-64] Thus, a bout of pancreatitis begins with an *initiating event*, for example, ischemia, inflammation, or ductal obstruction, followed by *acinar events*, that is, colocalization, enzyme activation, and cell injury, the outcome of which is influenced by *severity determinants*, for example, inflammatory cytokines, reactive oxygen species, altered oxidation-reduction state, and apoptosis (Figure 60-24).[63] The further evolution of acute pancreatic necrosis to a SIRS and multiple organ dysfunction syndrome is determined by the balance of proinflammatory and antiinflammatory cytokines (Figure 60-25).[64]

Clinical Signs

History

Siamese cats were initially reported to be at increased risk for the disease in one of the first retrospective studies of feline pancreatitis.[2] Clinical case surveys of the past 10 years suggest that most cases of feline pancreatitis are seen in the Domestic Shorthair breed.[1-10,12] Anorexia (87%) and lethargy (81%) are the most frequently reported clinical signs in cats with acute pancreatitis, but these clinical signs are not pathognomonic for pancreatitis (Table 60-2). Anorexia and lethargy are the most important clinical signs in many feline diseases. Gastroenterologic signs are sporadic and less frequently reported in the cat. Vomiting and diarrhea are reported in only 46% and 12% of cases, respectively.[2-7,9,10,12] In dogs, vomiting (90%) and diarrhea (33%) appear to be more important clinical signs.[15,31,53]

Physical Examination Findings

Physical examination findings in cats with ANP (Table 60-3) include dehydration (54%), hypothermia (46%), icterus (37%), fever (25%), abdominal pain (19%), and abdominal mass (11%).[2-7,9,10,12] These findings suggest that a "classic textbook" description of acute pancreatitis (e.g., vomiting, diarrhea, abdominal pain, and fever) is not consistently seen in the domestic cat. Many of these physical examination findings are more commonly reported in canine acute pancreatitis. Abdominal pain (58% in dogs; 19% in cats) and fever (32% in dogs; 25% in cats), for example, are more commonly reported in dogs with acute pancreatitis.[15,31,53]

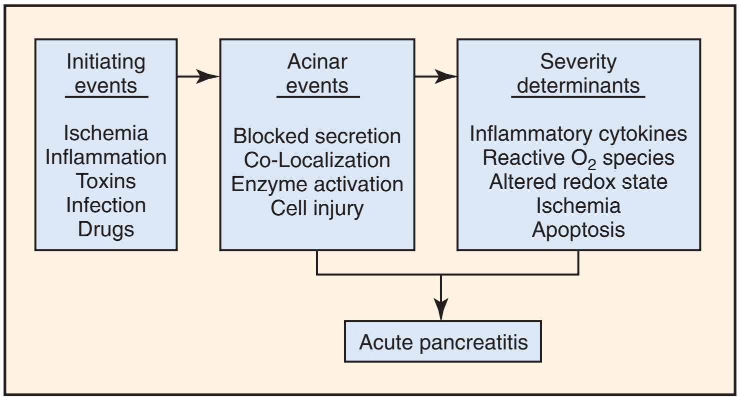

Figure 60-24 **The three phases of acute pancreatitis.** Pancreatic necrosis begins with an initiating event (e.g., ischemia, inflammation, or ductal obstruction), followed by acinar events (e.g., colocalization, enzyme activation, and cell injury), the outcome of which is influenced by severity determinants (e.g., inflammatory cytokines, oxygen free radicals, ischemia, and apoptosis). (Modified from Steer ML: The early intra-acinar cell events which occur during acute pancreatitis. *Pancreas* 17:31, 1998.)

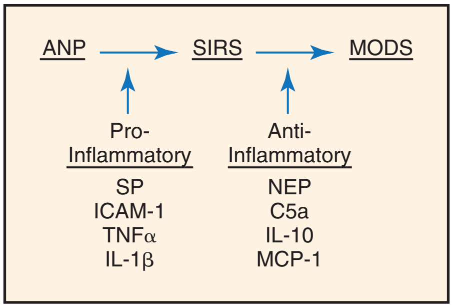

Figure 60-25 **Final evolution of acute necrotizing pancreatitis.** Severe cases of ANP may progress to a SIRS and multiple organ dysfunction syndrome. The balance between proinflammatory and antiinflammatory molecules determines the outcome. *C5a*, complement factor 5a; *ICAM-1*, intercellular adhesion molecule-1; *IL-1β*, interleukin-1β; *IL-10*, interleukin-10; *MCP-1*, monocytic chemotactic factor-1; *NEP*, neutral endopeptidase; *SP*, substance P; *TNFα*, tumor necrosis factor α. (Modified from Bhatia M, Brady M, Shokuhi S, et al: Inflammatory mediators in acute pancreatitis. *J Pathol* 190:117, 2000 with permission.)

Table 60-2 Historical Findings in Cats Affected with Acute Necrotizing Pancreatitis

Finding	Number of Cases	Incidence
Anorexia	131/150	87%
Lethargy	129/150	81%
Weight loss	75/159	47%
Vomiting	73/159	46%
Diarrhea	19/159	12%

Data from Hill R, van Winkle T: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat. *J Vet Intern Med* 7:25, 1993; Akol K, Washabau RJ, Saunders HM, Hendrick MJ: Acute pancreatitis in cats with hepatic lipidosis. *J Vet Intern Med* 7:205, 1993; Simpson KW, Shiroma JT, Biller DS, et al: Ante-mortem diagnosis of pancreatitis in four cats. J Small Anim Pract 35:93, 1994; Swift NC, Marks SL, MacLachlan NJ, Norris CR: Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *J Am Vet Assoc* 217:37, 2000; Kimmel SE, Washabau RJ, Drobatz KJ: Incidence and prognostic significance of ionized hypocalcemia in feline acute pancreatitis. *J Am Vet Assoc* 219:1105, 2001; Gerhardt A, Steiner JM, Williams DA, et al: Comparison of the sensitivity of different diagnostic tests pancreatitis in cats. *J Vet Intern Med* 15:329, 2001; Mayhew P, Holt D, McLear R, Washabau RJ: Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *J Small Anim Pract* 43:247, 2002; Ferreri J, Hardam E, Van Winkle TJ, et al: Clinical differentiation of acute and chronic feline pancreatitis. *J Am Vet Assoc* 223:469, 2003; and Forman MA, Marks SL, De Cock HE, et al: Evaluation of feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med* 18:807, 2004.

Differential Diagnosis

The major differential diagnoses for feline ANP include GI foreign body, IBD, alimentary lymphoma, infectious gastroenteritis, GI intussusception and neoplasia, cholangitis, biliary tract neoplasia, and various forms of liver and biliary tract pathology.

Diagnosis

As with the same condition in the dog, diagnosis of ANP requires the careful integration of historical, physical examination, clinicopathologic, and imaging findings. Where appropriate, additional diagnostic support may be obtained at the time of laparoscopy or exploratory laparotomy. Diagnosis should not be made on the basis of a single laboratory or imaging finding.

Laboratory Findings

In cats affected with ANP, laboratory abnormalities (Tables 60-4 and 60-5) have included normocytic, normochromic, regenerative or nonregenerative anemia (38%), leukocytosis (46%), leukopenia (15%), hyperbilirubinemia (58%), hypercholesterolemia (72%), hyperglycemia (45%), hypocalcemia (65%), hypoalbuminemia (36%), and elevations in serum alanine aminotransferase (57%) and alkaline phosphatase (49%) activities.[2-7,9,10,12] Changes in red blood cell counts, serum activities of liver enzymes, and serum concentrations of bilirubin, glucose, and cholesterol are fairly consistent findings in feline ANP, just as they are in dogs.[15,31,53] Important differences between cats and dogs appear to be reflected in white blood cell counts and serum calcium concentrations. Leukocytosis is a more important clinical finding in the dog (62% in dogs; 46% in cats).[15,31,53] Leukopenia is sometimes seen instead of leukocytosis in cats, and a worse prognosis has been attributed to leukopenia in the cat.[2,5,7,10,12] Hypocalcemia also appears to be a more frequent finding in cats (3% to 5% in dogs[15,53]; 45% to 65% in cats[2,5,6,10,12]). Hypocalcemia (total and serum ionized) may result from several mechanisms, including

Table 60-3 Physical Examination Findings in Cats Affected with Acute Necrotizing Pancreatitis

Finding	Number of Cases	Incidence
Dehydration	50/92	54%
Hypothermia	23/54	46%
Icterus	51/138	37%
Fever	15/62	25%
Abdominal pain	30/159	19%
Abdominal mass	12/159	11%

Data from Hill R, van Winkle T: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat. *J Vet Intern Med* 7:25, 1993; Akol K, Washabau RJ, Saunders HM, Hendrick MJ: Acute pancreatitis in cats with hepatic lipidosis. *J Vet Intern Med* 7:205, 1993; Simpson KW, Shiroma JT, Biller DS, et al: Ante-mortem diagnosis of pancreatitis in four cats. *J Small Anim Pract* 35:93, 1994; Swift NC, Marks SL, MacLachlan NJ, Norris CR: Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *J Am Vet Assoc* 217:37, 2000; Kimmel SE, Washabau RJ, Drobatz KJ: Incidence and prognostic significance of ionized hypocalcemia in feline acute pancreatitis. *J Am Vet Assoc* 219:1105, 2001; Gerhardt A, Steiner JM, Williams DA, et al: Comparison of the sensitivity of different diagnostic tests pancreatitis in cats. *J Vet Intern Med* 15:329, 2001; Mayhew P, Holt D, McLear R, Washabau RJ: Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *J Small Anim Pract* 43:247, 2002; Ferreri J, Hardam E, Van Winkle TJ, et al: Clinical differentiation of acute and chronic feline pancreatitis. *J Am Vet Assoc* 223:469, 2003; and Forman MA, Marks SL, De Cock HE, et al: Evaluation of feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med* 18:807, 2004.

Table 60-4 Hematologic Findings in Cats Affected with Acute Necrotizing Pancreatitis

Finding	Number of Cases	Incidence
Anemia	39/103	38%
Hemoconcentration	14/82	17%
Leukocytosis	46/99	46%
Leukopenia	14/94	15%

Data from Hill R, van Winkle T: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat. *J Vet Intern Med* 7:25, 1993; Akol K, Washabau RJ, Saunders HM, Hendrick MJ: Acute pancreatitis in cats with hepatic lipidosis. *J Vet Intern Med* 7:205, 1993; Simpson KW, Shiroma JT, Biller DS, et al: Ante-mortem diagnosis of pancreatitis in four cats. *J Small Anim Pract* 35:93, 1994; Swift NC, Marks SL, MacLachlan NJ, Norris CR: Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *J Am Vet Assoc* 217:37, 2000; Kimmel SE, Washabau RJ, Drobatz KJ: Incidence and prognostic significance of ionized hypocalcemia in feline acute pancreatitis. *J Am Vet Assoc* 219:1105, 2001; Gerhardt A, Steiner JM, Williams DA, et al: Comparison of the sensitivity of different diagnostic tests pancreatitis in cats. *J Vet Intern Med* 15:329, 2001; Mayhew P, Holt D, McLear R, Washabau RJ: Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *J Small Anim Pract* 43:247, 2002; Ferreri J, Hardam E, Van Winkle TJ, et al: Clinical differentiation of acute and chronic feline pancreatitis. *J Am Vet Assoc* 223:469, 2003; and Forman MA, Marks SL, De Cock HE, et al: Evaluation of feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med* 18:807, 2004.

acid–base disturbances, peripancreatic fat saponification, and parathormone resistance.[65] Regardless of the mechanism, hypocalcemia appears to confer a worse clinical prognosis in cats.[6,10] This finding suggests that cats should be monitored fairly closely for the development of hypocalcemia and treatment should be initiated, accordingly.

Table 60-5 Serum Biochemical Findings in Cats Affected with Acute Necrotizing Pancreatitis

Finding	Number of Cases	Incidence
↑↑ ALT, AST	37/65	57%
↑↑ ALP	32/65	49%
↑↑ Bilirubin	38/65	58%
↑↑ Glucose	32/71	45%
↑↑ Cholesterol	28/39	72%
↓↓ Calcium	55/85	65%
↓↓ Albumin	14/39	36%

Data from Hill R, van Winkle T: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat. *J Vet Intern Med* 7:25, 1993; Akol K, Washabau RJ, Saunders HM, Hendrick MJ: Acute pancreatitis in cats with hepatic lipidosis. *J Vet Intern Med* 7:205, 1993; Simpson KW, Shiroma JT, Biller DS, et al: Ante-mortem diagnosis of pancreatitis in four cats. *J Small Anim Pract* 35:93, 1994; Swift NC, Marks SL, MacLachlan NJ, Norris CR: Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *J Am Vet Assoc* 217:37, 2000; Kimmel SE, Washabau RJ, Drobatz KJ: Incidence and prognostic significance of ionized hypocalcemia in feline acute pancreatitis. *J Am Vet Assoc* 219:1105, 2001; Gerhardt A, Steiner JM, Williams DA, et al: Comparison of the sensitivity of different diagnostic tests pancreatitis in cats. *J Vet Intern Med* 15:329, 2001; Mayhew P, Holt D, McLear R, Washabau RJ: Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *J Small Anim Pract* 43:247, 2002; Ferreri J, Hardam E, Van Winkle TJ, et al: Clinical differentiation of acute and chronic feline pancreatitis. *J Am Vet Assoc* 223:469, 2003; and Forman MA, Marks SL, De Cock HE, et al: Evaluation of feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med* 18:807, 2004.

Special Tests of Pancreatic Function

Lipase and Amylase Activity Assays

Serum lipase activities are elevated in experimental feline pancreatitis,[66,67] but serum lipase and amylase activities do not appear to be elevated or of clinical value in the diagnosis of clinical pancreatitis.[68] Serum lipase activity may still have some clinical utility in the diagnosis of ANP in the dog.[15,69] Assays of serum lipase activity are complicated by the fact that there may be as many as five different isoenzymes circulating in the blood[70]; consequently general serum lipase activity assays have been superseded by the development of pancreatic lipase immunoreactivity assays (e.g., cPLI, fPLI).[70,71]

Trypsin-like Immunoreactivity

Serum TLI mainly measures trypsinogen but also detects trypsin and some trypsin molecules bound to proteinase inhibitors.[70] TLI assays are species-specific, and different assays for feline (fTLI) and canine (cTLI) have been developed and validated.[72] Serum TLI concentration is the diagnostic test of choice for feline EPI because it is highly sensitive and specific for this disease in the cat.[11] The use of this test in the diagnosis of feline ANP is less clear. Serum TLI concentrations are transiently elevated in experimental feline acute pancreatitis,[73] but elevations in clinical cases are less consistently seen.[5,7,68] The poor sensitivity (i.e., 33%) of this test precludes its use as a definitive assay for feline ANP.

Trypsinogen Activation Peptide

When trypsinogen is activated to trypsin, a small peptide, TAP, is split from the trypsinogen molecule. Under normal conditions, activation of trypsinogen takes place only in the small intestine and

TAP is undetectable in the blood. During pancreatitis, trypsinogen is activated prematurely in pancreatic acinar cells and TAP is released into the vascular space.[71] Urine TAP assays have shown some promise in experimental models of feline pancreatitis,[74] but serum and urine TAP assays are less promising in clinical studies.[75] Evidence-based data is needed to determine the true specificity and sensitivity of this assay.

Pancreatic Lipase Immunoreactivity

ELISA and radioimmunoassays for the measurement of PLI have been developed and validated in the cat.[76] fPLI elevations have been cited in preliminary reports of experimental[73] and clinical[12] feline ANP, but the true sensitivity and specificity of fPLI in the diagnosis of feline ANP have not yet been reported. As with fTLI assays, there are false positives and false negatives with fPLI in the diagnosis of feline ANP.

Imaging Findings

Radiography

The radiographic findings of feline ANP have not been very well characterized. The radiographic hallmarks of canine acute pancreatitis (e.g., increased density in the right cranial abdominal quadrant, left gastric displacement, right duodenal displacement, and gas-filled duodenum/colon)[15,77] have not been substantiated in the cat. Indeed, in several recent reports, many of these radiographic findings were not reported in cats with documented acute pancreatic necrosis.[1-10,12] In spontaneous clinical cases, hepatomegaly and abdominal effusion may be the only radiographic findings in some cases of feline ANP.[1-10,12]

Ultrasonography

Enlarged, irregular, and/or hypoechoic pancreas; hyperechogenicity of the peripancreatic mesentery; and peritoneal effusion have been observed with abdominal ultrasonography in many cats with spontaneous acute pancreatitis (Figure 60-26).[8,10,12,78] The specificity of this imaging modality appears to be high (>85%), but the sensitivity has been reported as low as 35% in some studies.[5,7,8,78] The low sensitivity suggests that imaging the pancreas in cats with pancreatitis is technically more difficult than imaging the pancreas in dogs or that the ultrasonographic appearance of pancreatitis in cats differs from that reported for dogs. Other potential ultrasonographic findings include corrugation of the duodenum, fluid/gas distended, hypomotile intestines (indicative of paralytic ileus), and ultrasonographic signs of extrahepatic biliary obstruction.[8,79-81]

Endosonography

Endosonography has been used to confirm the diagnosis of feline ANP in a small series of patients, but it appears to confer no additional advantage over routine transabdominal ultrasonography.[82]

Computed Tomography

CT scanning appears to be useful in identifying the normal structures of the healthy feline pancreas,[83] but preliminary clinical reports are somewhat disappointing.[7,12] The sensitivity of CT scanning in detecting lesions consistent with feline ANP may be as low as 20%.[7,12] Additional study is needed to determine the specificity and sensitivity of this imaging modality in the diagnosis of feline ANP.

Biopsy

If clinically indicated, pancreatic biopsy may be obtained by laparoscopy[84] or exploratory laparotomy. Clinicians should always bear in mind that many pancreatitis patients are poor anesthesia risks.

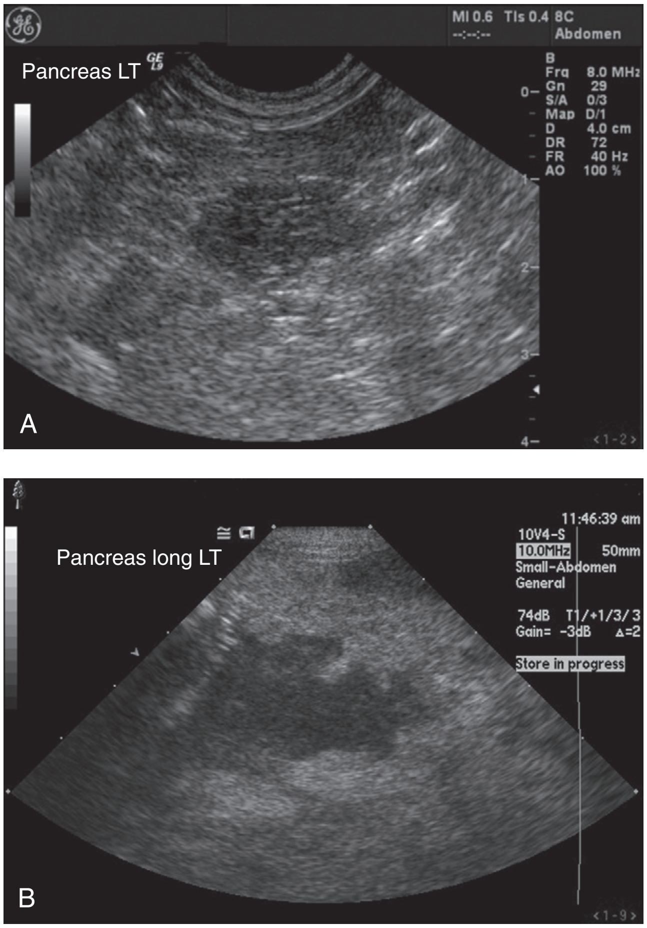

Figure 60-26 Ultrasonographic findings of feline acute necrotizing pancreatitis. A, The pancreas is severely enlarged and hypoechoic, with surrounding hyperechoic mesentery. **B,** Ultrasonographic findings of feline chronic necrotizing pancreatitis. The left lobe of the pancreas is irregularly thickened and hypoechoic.

Gross observation at the time of laparoscopy or exploratory laparotomy may confirm the diagnosis of ANP. In equivocal cases, biopsy may be safely performed as long as blood flow is preserved at the site of the biopsy. Single biopsy may be insufficient to exclude subclinical pancreatitis as inflammation of the canine pancreas occurs in discrete areas within the pancreas rather than diffusely throughout the whole organ.[85] Similar findings are reported in feline ANP.[2] Inspection of other viscera (e.g., intestine, biliary tract, liver) at the time of laparoscopy or exploratory laparotomy is of paramount importance in the cat because of the high rate of disease concurrence in this species.[2,3,9,10,18,24,25,84]

Species Differences

There are many important species differences between dogs and cats with regard to the clinical course and pathophysiology of acute pancreatic necrosis (summarized in Table 60-6 and reference 31). Fever, leukocytosis, vomiting, and abdominal pain are important physical examination findings in dogs with ANP, but these are relatively infrequent findings in cats with ANP. Cats more often have hypothermic reactions, and they may not necessarily manifest the classic gastroenterologic signs (e.g., vomiting, diarrhea, abdominal pain) reported in dogs. The imaging findings in cats are also less

Table 60-6 Clinical Difference between Feline and Canine Acute Necrotizing Pancreatitis

	Feline	Canine
Vomiting	46%	90%
Diarrhea	12%	33%
Fever	25%	32%
Abdominal pain	19%	58%
↑ White blood cell counts	46%	62%
↓ Calcium	65%	5%
Radiography	Not useful	Somewhat useful
Inflammatory bowel disease	Strong association	Weak association

Data from Hill R, van Winkle T: Acute necrotizing pancreatitis and acute suppurative pancreatitis in the cat. *J Vet Intern Med* 7:25, 1993; Akol K, Washabau RJ, Saunders HM, Hendrick MJ: Acute pancreatitis in cats with hepatic lipidosis. *J Vet Intern Med* 7:205, 1993; Simpson KW, Shiroma JT, Biller DS, et al: Ante-mortem diagnosis of pancreatitis in four cats. *J Small Anim Pract* 35:93, 1994; Swift NC, Marks SL, MacLachlan NJ, Norris CR: Evaluation of serum feline trypsin-like immunoreactivity for the diagnosis of pancreatitis in cats. *J Am Vet Assoc* 217:37, 2000; Kimmel SE, Washabau RJ, Drobatz KJ: Incidence and prognostic significance of ionized hypocalcemia in feline acute pancreatitis. *J Am Vet Assoc* 219:1105, 2001; Gerhardt A, Steiner JM, Williams DA, et al: Comparison of the sensitivity of different diagnostic tests pancreatitis in cats. *J Vet Intern Med* 15:329, 2001; Mayhew P, Holt D, McLear R, Washabau RJ: Pathogenesis and outcome of extrahepatic biliary obstruction in cats. *J Small Anim Pract* 43:247, 2002; Ferreri J, Hardam E, Van Winkle TJ, et al: Clinical differentiation of acute and chronic feline pancreatitis. *J Am Vet Assoc* 223:469, 2003; Forman MA, Marks SL, De Cock HE, et al: Evaluation of feline pancreatic lipase immunoreactivity and helical computed tomography versus conventional testing for the diagnosis of feline pancreatitis. *J Vet Intern Med* 18:807, 2004; and Hess RS, Saunders HM, Van Winkle TJ, et al: Clinical, clinicopathologic, radiographic, and ultrasonographic abnormalities in dogs with fatal acute pancreatitis. *J Am Vet Assoc* 213:665, 1998.

subtle than what has been reported in dogs; the classic radiographic hallmarks of canine ANP have not reported in the cat. Cats have a greater incidence and severity of hypocalcemia following bouts of acute pancreatic necrosis. Serum total and/or ionized hypocalcemia is significantly reduced in 45% to 65% of affected cats, whereas hypocalcemia is reported in only 5% of affected dogs. The pathogenesis of hypocalcemia in cats with ANP is incompletely understood, but it does carry a significantly worse prognosis for recovery.[6] Prior GI tract disease confers slight increased risk for the development of acute pancreatic necrosis in the dog[15,53]; this is especially true of the cat.[2,10,18,24,25]

Therapy

Supportive care continues to be the mainstay of therapy for feline acute pancreatitis (Box 60-3). Efforts should be made to identify and eliminate any inciting agents; sustain blood and plasma volume; correct acid–base, electrolyte, and fluid deficits; and treat any complications that might develop. Important life-threatening complications of acute pancreatitis in cats include hypocalcemia, DIC, thromboembolism, cardiac arrhythmia, sepsis, acute tubular necrosis, pulmonary edema, and pleural effusion.

Historically, a short period of food and water fasting has been recommended for cats with ANP. This recommendation should be applied only in those instances in which there is severe vomiting and risk for aspiration pneumonia. As obligate carnivores, cats develop fat mobilization and hepatic lipidosis during prolonged

Box 60-3 General Principles in the Treatment of Feline Acute Necrotizing Pancreatitis

1. Eliminate the inciting agent
2. NPO *only* if severe nausea and vomiting
3. Intravenous fluids
4. Supportive therapy–plasma 10 mL/kg
5. Relieve pain–meperidine, butorphanol
6. Antiemetics–α_2-adrenergic antagonists, 5-HT$_3$ serotonergic antagonists, NK$_1$ neurokinin antagonists
7. Calcium gluconate supplementation
8. H$_1$- and H$_2$-histaminergic receptor antagonists
9. Low-dose dopamine infusion–5 µg/kg/min
10. Broad-spectrum antibiotics
11. Ductal decompression

starvation. Moreover, recent studies suggest that it may be appropriate and necessary to stimulate pancreatic secretion (via feeding) in affected animals.[57-60] Esophagostomy, gastrostomy, and enterostomy tubes may be placed to facilitate nutrition in anorectic animals.

Other therapies that may be of some benefit in the treatment of this disorder include:

- Relief of pain: Analgesic agents should be used when abdominal pain is suspected. Most cats do not manifest clinical signs of abdominal pain, but clinicians inspect for it. Meperidine at a dose of 1 to 2 mg/kg administered intramuscularly or subcutaneously every 2 to 4 hours or butorphanol at a dose of 0.2 to 0.4 mg/kg administered subcutaneously every 6 hours has been recommended.[86]
- Antiemetic agents: Nausea and vomiting may be severe in affected animals. The α_2-adrenergic antagonists and 5-HT$_3$ antagonists are somewhat effective antiemetic agents in the cat.[87] Cats may be treated with chlorpromazine (α_2-adrenergic antagonist) at a dose of 0.2 to 0.4 mg/kg administered subcutaneously or intramuscularly every 8 hours, or with any of the 5-HT$_3$ antagonists (ondansetron 0.1 to 1.0 mg/kg, granisetron 0.1 to 0.5 mg/kg, or dolasetron 0.5 to 1.0 mg/kg, orally or intravenously every 12 to 24 hours). Dopaminergic antagonists, for example, metoclopramide, are less-effective antiemetic agents in the cat.[87] NK$_1$ receptor antagonists (e.g., maropitant) have been used in the cat (see Chapters 23 and 35), but their comparative efficacy is still unknown.[88]
- Calcium gluconate supplementation: Hypocalcemia is a frequent complication of feline ANP and is associated with a worse prognosis.[6] Calcium gluconate should be given at doses of 50 to 150 mg/kg intravenously over 12 to 24 hours and serum total or ionized calcium concentrations should be monitored during therapy.
- H$_1$- and H$_2$-histamine antagonists: Histamine and bradykinin-induced increases in microvascular permeability are associated with the development of hemorrhagic necrosis in experimental feline pancreatitis.[89] Treatment with H$_1$ (mepyramine, 10 mg/kg) and H$_2$ (cimetidine, 5 mg/kg; ranitidine, 1 to 2 mg/kg; famotidine, 0.5 to 1.0 mg/kg) histamine-receptor antagonists protects against the development of hemorrhagic pancreatitis in these models.[89] Efficacy has not been established in clinical pancreatitis, but the use of these drugs in suspected or proven clinical cases would appear to have some rationale as they are associated with few side effects. Diphenhydramine (2 to 4 mg/kg) or

dimenhydrinate (4 to 8 mg/kg) are examples of clinically used H_1-histamine receptor antagonists. Cimetidine (5 mg/kg), ranitidine (1 to 2 mg/kg), famotidine (0.5 to 1.0 mg/kg), and nizatidine (2.5 to 5.0 mg/kg) are examples of clinically used H_2-histamine receptor antagonists.

- Low-dose dopamine infusion: Low-dose dopamine infusion (5 μg/kg/min) improves pancreatic blood flow and reduces microvascular permeability in feline experimental pancreatitis.[67] Low-dose dopamine infusion is effective treatment in experimental pancreatitis even when it is given up to 12 hours after induction of the disease.[67] Part of the appeal of dopamine as a potential treatment for feline pancreatitis lies in the diversity of its actions. Dopamine's effect on the kidney in promoting renal blood flow and urinary output, and its cardiac inotropic effect make it a useful agent, although it has not yet been studied in controlled clinical trials.
- Broad-spectrum antibiotics: ANP may begin as a sterile process, but necrosis and inflammation predispose to colonic bacterial translocation and colonization of the pancreas.[90,91] *Escherichia coli* and other coliforms are the principal pathogens.[90,91] High colonization rates suggest that bacteria may spread to the inflamed pancreas more frequently than is currently thought, and that broad-spectrum antibiotics may be appropriate in suspected cases of feline acute pancreatitis. Cefotaxime at a dose of 50 mg/kg administered intramuscularly every 8 hours prevents bacterial colonization of the pancreas.[92]
- Ductal decompression: Surgical decompression of the pancreaticobiliary duct should be considered in cases of acute ductal obstruction, for example, calculus, neoplasia, and fluke infection. Ductal decompression may also be useful in acute cases that have progressed to the more chronic form of the disease. Ductal decompression restores pancreatic blood flow, tissue pH, and acinar cell function.[35,36]

Prevention

In cases in which IBD is the underlying pathogenesis of ANP, therapy should be directed toward regulation of the IBD. The five components of feline IBD therapy are dietary modification, antibiotics, probiotics, antidiarrheal agents, and immunosuppressive therapy.[93]

Complications of Acute Necrotizing Pancreatitis

Chronic Nonsuppurative Pancreatitis

Recurring bouts of ANP may progress to a chronic nonsuppurative form of the disease. This chronic form of pancreatitis has generally been held to be of lesser clinical severity, lower mortality, and better long-term prognosis.[1] More recent reports suggest, however, that chronic pancreatitis cannot be differentiated from acute pancreatitis by clinical, clinicopathologic, or imaging findings.[10] The clinical signs, laboratory data, and imaging findings are indistinguishable between the two groups. Histopathology remains the only dependable method of differentiating acute and chronic pancreatitis. Not surprisingly, cats with chronic pancreatitis more frequently have concurrent systemic disease (e.g., cholangitis, IBD) compared with cats with acute pancreatitis.[10]

Exocrine Pancreatic Insufficiency

EPI is an uncommon cause of chronic diarrhea in cats. Insufficiency results from failure of synthesis and secretion of pancreatic digestive enzymes. The natural history of feline EPI is poorly understood, but most cases are believed to result from chronic pancreatitis, fibrosis, and acinar atrophy. As with dogs, clinical signs reported in cats with EPI include weight loss, soft voluminous feces, and ravenous appetite. Affected cats may have an antecedent history of recurring bouts of acute pancreatitis (e.g., anorexia, lethargy, vomiting) culminating in chronic pancreatitis and EPI.

The diagnosis of EPI in cats has been technically difficult. Clinical signs in affected cats are not pathognomonic for EPI, clinicopathologic data are fairly nonspecific, imaging findings are inconsistent, and the severity of pancreatic histologic changes are not always directly related to the severity of clinical signs. Serum TLI is believed to be diagnostic of the disease.[11,17] In that study, TLI concentrations less than 8 μg/L (reference range: 17 to 49 μg/L) were reported in 27 of 30 cats with clinical signs compatible with EPI (e.g., weight loss, loose voluminous feces, greasy soiling of the hair coat) and at least one other finding, for example, decreased fecal proteolytic activity, exploratory laparotomy or necropsy findings compatible with EPI, or favorable response to pancreatic enzyme replacement therapy.[11,17] Cats affected with EPI have predictable serum cobalamin deficiency because of pancreatic intrinsic factor deficiency and cobalamin malabsorption.[94] Therapy should include subcutaneous vitamin B_{12} injections (100 μg subcutaneously every 3 to 4 weeks) in addition to pancreatic replacement enzymes.

Hepatic Lipidosis

ANP is but one of many examples in which anorexia or starvation predisposes an obligate carnivore to the syndrome of fat mobilization and hepatic lipidosis.[1,3,95] The concurrence of these two syndromes is a particularly poor prognostic sign in that affected cats have high morbidity and mortality rates. This emphasizes the importance of early interventions in the treatment of pancreatitis before the development of the metabolic syndrome of hepatic lipidosis.

Diabetes Mellitus

Several studies have related severe chronic pancreatitis to the development of diabetes mellitus.[1,4,10,11] ANP per se may not necessarily be a risk factor for the development of diabetes mellitus, but disease progression to the chronic nonsuppurative form may increase that risk.

ABSCESS, NECROSIS, PSEUDOCYST, PHLEGMON, AND INFECTION

Michael Schaer

Pancreatic Abscess and Necrosis

Definition

Abscess and necrosis are discussed together in this section because abscess formation is always preceded by necrosis, although necrosis is not always followed by abscess formation. In 1992 the International Symposium on Acute Pancreatitis defined pancreatic necrosis as the presence of one or more diffuse or focal areas of nonviable pancreatic parenchyma.[1] Pancreatic glandular necrosis is usually associated with necrosis of peripancreatic fat. By definition, pancreatic necrosis represents a severe form of acute pancreatitis (Figures 60-27 and 60-28).[2] Pancreatic abscess is a collection of purulent and necrotic pancreatic tissue (Figure 60-29). Abscessation forms if an episode of pancreatitis is severe enough to cause parenchymal

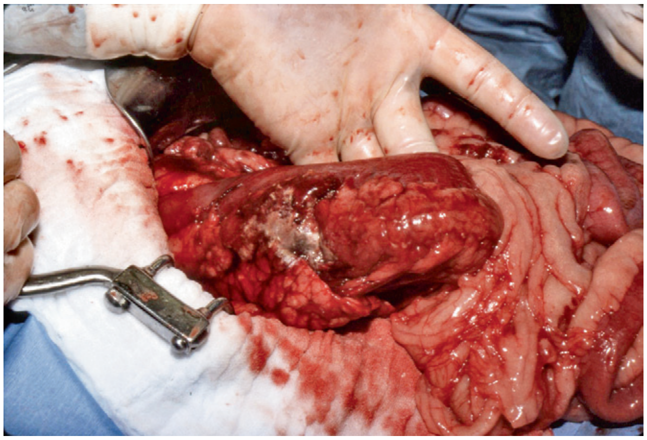

Figure 60-27 Surgical view of focal pancreatic necrosis in a dog.

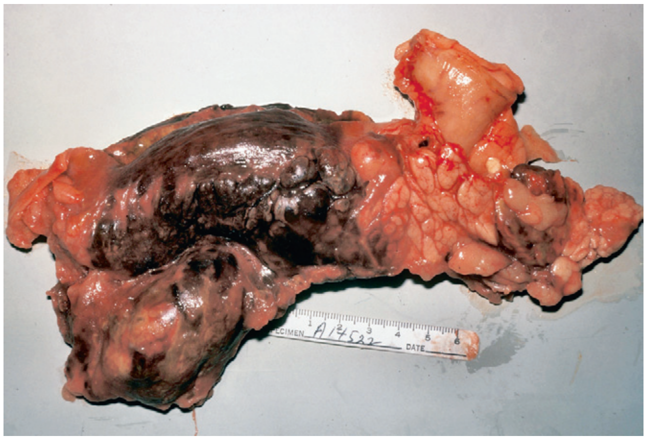

Figure 60-28 A postmortem depiction of severe ischemic necrosis of the pancreas and parapancreatic lymph node.

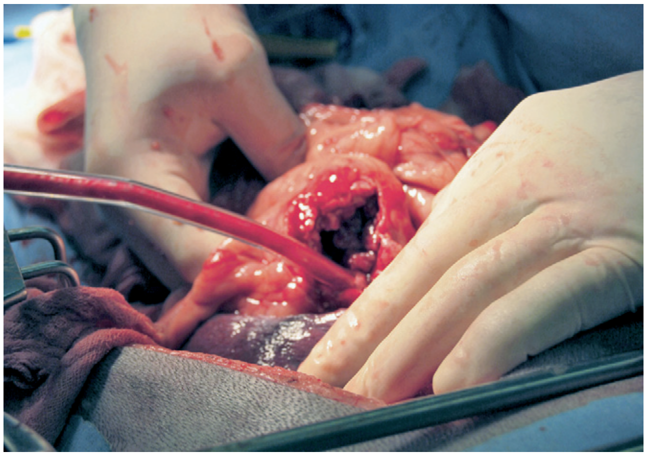

Figure 60-29 Pancreatic abscess at surgery.

necrosis.[3] In some cases, necrotic tissue is secondarily infected by bacteria. There can be multiple foci of necrotic debris rather than a recognizable discrete abscess cavity. In humans, a pancreatic abscess can also be caused by secondary infection of a pseudocyst, but the latter pathogenesis is apparently rare in dogs and cats.

Incidence

Pancreatic abscess is infrequently reported in the veterinary literature,[4] with only 73 total case reports in five separate references , most of which were reported in dogs.[5-9] The largest report of pancreatic abscess described clinical findings in 36 dogs.[9] Mortality numbers were high and ranged from 50% to 86%, but this parallels the high mortality that occurs in all cases of severe necrotic pancreatitis with and without secondary infection. Although viewed as a sequel to acute pancreatitis in some cases, abscess can be a continuation of a single severe inflammatory process with accompanying necrosis that becomes more clinically apparent in the dog 1 to 2 weeks after disease onset.

History and Physical Examination Findings

There is nothing particularly pathognomonic for pancreatic abscess in the dog. The history will always show a sudden onset of mental depression, anorexia, vomiting, and lethargy. Certain “triggers” of acute pancreatitis might be present, such as the ingestion of a fatty meal or other potential causes such as hyperlipidemia, hypercalcemia, or the ingestion of certain drugs such as potassium bromide.[10] Animals with hemorrhagic and necrotic acute pancreatitis are usually critically ill, and may have a spectrum of clinical signs including vomiting, abdominal pain, lethargy, diarrhea, and hypovolemia. Abdominal pain is often reflective of peritonitis that is associated with pancreatitis, but this sign might not be present in a recumbent patient in the advanced stages of acute necrotic pancreatitis. Icterus is seldom present acutely but may evolve with progressive cholestasis. Body temperature ranges from high fever to hypothermic reactions with hypothermia commonly reflecting an advanced decompensated stage of the systemic inflammatory response. Abdominal distention is usually caused by inflammatory ascites characterized as a sterile inflammatory exudate in most cases. Ileus is also present and contributes to abdominal distention. It is not uncommon for these dogs to be prostrate upon initial examination reflecting their grave status.

Clinicopathologic Features

There is nothing in the clinicopathologic profile that distinguishes pancreatic abscess from necrotizing pancreatitis.[3,5,7,9,11] In Anderson’s review, anemia occurred in nine of 36 dogs and was likely associated with the anemia of inflammation.[9] Leukocytosis occurred in 25 of 36 dogs and this was likely caused by the systemic inflammatory response. Of these, 25% had increased circulating immature white blood cells. The leukopenia that was reported in three dogs should be seen as a grave sign associated with either insufficient bone marrow production, sequestration of white blood cells in the area of severe inflammation, or both.

Coagulation testing will yield variable responses. Acute pancreatitis itself may cause platelet consumption and thrombocytopenia in some patients. This was seen in 10 of 36 cases in Anderson’s review.[9] Prolongations in the PT and activated partial thromboplastin times can occur in severe cases of acute pancreatitis often times reflecting DIC. This latter complication is thought to be an ominous sign if the parameters do not normalize after intense treatment.

Serum chemistry abnormalities accompanying pancreatic abscess cannot be distinguished from those reported in dogs with acute pancreatitis. Reported abnormalities include hypoproteinemia associated with plasma protein leakage into the abdominal cavity (“third spacing”); hyperglycemia (with or without ketoacidosis) as a result of relative insulin insufficiency; hypoglycemia secondary to sepsis or endotoxemia; hypocalcemia associated with hypoalbuminemia and saponification; elevated liver enzymes with or without hyperbilirubinemia occurring as a result of cholestasis; and normal or below normal concentrations of serum sodium and potassium. Increases in renal parameters (BUN and serum creatinine) reflect a more guarded prognosis if acute renal failure has occurred.

Increases in the serum amylase and lipase concentrations can be present in some cases, but neither of these tests are sensitive or specific for this condition. They might even be normal by the time a pancreatic abscess has formed because of the failure of a damaged pancreas to produce digestive enzymes. Canine and feline pancreatic-specific lipase (cPLI, fPLI) tests have not proved useful in the diagnosis of pancreatic abscess. More discussion about clinicopathologic changes may be found in the section on pancreatic phlegmon.

Abdominal fluid is commonly present in hemorrhagic and necrotizing acute pancreatitis. The fluid is usually exudative but sterile.[12] Pancreatic infection occurs more commonly in humans than in dogs and cats, and in humans it is associated with a guarded to grave prognosis. Sterile cultures in dogs and cats might result from prior treatment with antibiotics. In Anderson's study,[9] two of 13 cases of necrotic pancreatitis were positive for bacterial (*Staphylococcus saprophyticus* and *Klebsiella pneumoniae*) infection while cultures of the abdominal fluid of 12 dogs were positive for bacteria in seven animals (*E. coli*, *Enterococcus*, *Pseudomonas*, *Streptococcus*, and *Bacteroides*). Johnson's review of 15 dogs detected *Staphylococcus epidermidis* in three dogs, but these were interpreted as contaminants.[7] Salisbury's review of six cases makes no mention of bacterial isolation.[5]

Diagnostic Imaging

Radiographic and ultrasonographic pancreatic abnormalities have been reported in dogs with pancreatic abscess, but there are no distinctive features for pancreatic abscess formation when compared with other forms of severe acute pancreatitis. Abdominal radiographs will show an increased fluid pattern in the anterior abdomen that can be diffuse or more localized to the upper right abdomen. This will cause a loss of serosal detail and occasionally a mass effect with organ displacement.

Chest radiographs are usually normal or they might show a pleural effusion consistent with migration of pancreatic fluid into the thoracic cavity and development of serositis. Acute pancreatitis is one cause of the acute respiratory distress syndrome that appears as a diffuse "whiteout" caused by diffuse alveolar infiltrates.

Abdominal ultrasonography usually reveals cavitation of a pancreatic abscess, but it is not readily distinguished from pancreatic pseudocyst or pancreatic phlegmon. In the Anderson study, only one dog had a nondiagnostic study while 26 of 27 dogs had abnormal pancreatic appearance described as hypoechoic, hyperechoic, or mixed echoic patterns (Figure 60-30). Fourteen of the 26 dogs had a "mass effect." Although the mass effect can be caused by an abscess, the same can be described for pancreatic phlegmon or any other combined effects caused by inflammation and adhesions. Abdominal ultrasound does give the radiologist an opportunity to do a transabdominal fine-needle aspiration biopsy of any abnormal abdominal tissue and tissue fluid for bacterial culture and cytology.

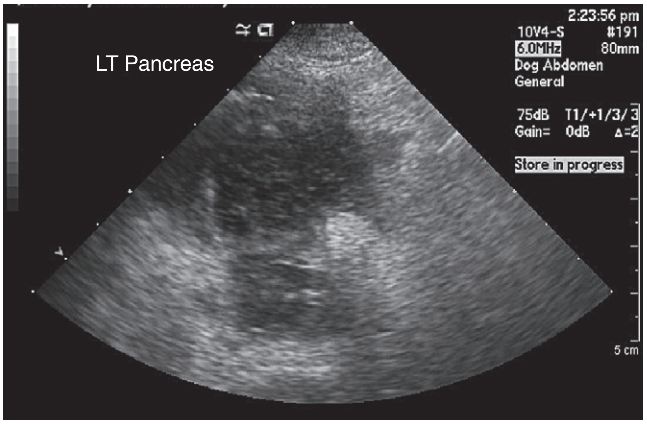

Figure 60-30 Abdominal ultrasound examination showing pancreatic abscess.

Treatment

Most patients will have been treated medically in intensive care for 7 to 14 days before any decision for surgery is made. The extent of sophisticated patient monitoring will be individualized according to the particular facility, the skill of the attending clinician, and the financial restrictions imposed by the pet owner. The medical treatment of many acute pancreatitis patients will require an intensive care setting because it entails meticulous parenteral fluid therapy, analgesics, plasma transfusions, and continuous patient monitoring. Pressor drugs might be necessary to stabilize the hypotensive patient that does not respond well to parenteral fluid therapy. Antibiotics are often administered because of concern about infection caused by transcolonic bacterial migration or the demonstration of bacteria on cytologic examination of a sample of the abdominal fluid.[13] Today, however, the routine use of antibiotics for severe ANP without the demonstration of sepsis is not recommended in human medicine because of a lack of influence on outcome between treated and untreated patient populations.[14-17] Glucocorticoid drugs might be of theoretical benefit because of their antiinflammatory effects, but they might predispose the patient to secondary infection that could have catastrophic effects. Antiemetic agents should be used in those patients that have multiple vomiting episodes per day, but attention to side effects should be made along with the necessary dosage adjustments. Many patients lack nutrition support for the first several days, and eventually require either total parenteral nutrition or jejunostomy tube feedings. The patient with pancreatic abscess and severe necrotizing pancreatitis frequently shows few signs of clinical improvement during the first week. A repeated abdominal ultrasound examination at that time will show the same or worsened abdominal abnormalities. In humans, the decision for abdominal surgery is made on the basis of continuing worsening clinical condition, the need for jejunostomy tube placement, the need to grossly assess the degree of pathology within the abdomen, the demonstration of infected pancreatitis.[18,19]

The accepted principles of surgical management of necrotizing pancreatitis are the removal of the necrotic pancreatic and peripancreatic tissue (necrosectomy), as well as providing drainage of ascites from the peritoneal cavity[2,7,9,11,18,19] Conventional drainage involves necrosectomy with placement of standard surgical drains and reoperation as required. Open or semiopen management involves necrosectomy and either scheduled repeated laparotomies or open packing, which leaves the abdominal wound exposed for frequent changes of dressing. Closed management involves necrosectomy with extensive intraoperative lavage of the pancreatic bed. The abdomen is closed over large-bore drains for continuous high-volume postoperative lavage.[20] Most surgeons in human medicine have abandoned the conventional surgical approach to debridement, as inadequately removed necrotic tissue becomes or remains infected, resulting in significant mortality as high as 40%.[21]

Johnson et al. compared the treatment of pancreatic abscesses via surgical omentalization with abdominal closure versus open peritoneal drainage in 15 dogs.[7] Five of the eight dogs treated with omentalization survived while only one of four dogs treated with open peritoneal drainage survived. The other three dogs either died or were euthanized.

All 36 dogs with pancreatic abscess in the Anderson study went to surgery. The pancreas was debrided in 13 dogs and partial pancreatectomies were performed in three others. Duodenostomy tubes were placed in three dogs, and seven dogs received jejunostomy tubes. Sump-Penrose drains were placed in three dogs, and 11 were managed with open peritoneal drainage. Overall, 23 of the 36 dogs had one surgery and 13 of 36 had multiple surgeries. Multiple surgical procedures did not influence outcome nor was there any difference in outcome between dogs managed with open abdominal drainage or Sump-Penrose drainage and those managed with primary closure.[9]

Conclusion

The diagnosis of pancreatic abscess will usually not be made until the patient goes to surgery. This particular patient will be one that does not respond well to the standard of care for treating acute pancreatitis and may have evidence of a mass effect on abdominal imaging. The length of hospitalization is substantial, the risks of surgery rather daunting, the cost to the pet owner is often staggering, and the prognosis is fair to grave.

Pancreatic Pseudocyst

Definition and Incidence

A pancreatic pseudocyst is a collection of enzyme-rich pancreatic fluid containing variable amounts of tissue debris and blood. It results from autodigestion and liquefaction of pancreatic tissue during severe pancreatitis and is highly associated with necrosis and hemorrhage. A pseudocyst is not a true cyst in that it is lined by inflammatory tissue instead of epithelium.[3] It is an uncommon sequel to acute pancreatitis in humans, and is rare in the dog and cat.[22] In humans, a pancreatic pseudocyst can resolve spontaneously or it can rupture into the abdominal cavity with potentially life-threatening consequences. Complications in humans include infection, rupture into the peritoneal cavity, and acute hemorrhage. There are only a few case reports of this condition in the dog[22-25] and one in the cat.[26]

History and Physical Examination

Because this condition is a sequel to acute pancreatitis, the initial signs will represent the primary illness and be characterized by any combination of signs including vomiting, anorexia, fever, dehydration, abdominal tenderness, lethargy, mental depression, and occasionally diarrhea.[22] The acute pancreatitis can resolve uneventfully, or it can culminate in a pseudocyst over a period of a weeks. A small cyst might not cause any clinical signs, but a large mass will cause abdominal discomfort and displacement of abdominal organs. Additional signs reported in the literature include vomiting, diarrhea, anorexia, abdominal pain, and a palpable abdominal mass.[23,24]

Clinicopathologic Findings

The laboratory features of pancreatic pseudocyst will vary from normal to those similar to acute pancreatitis. Normal or minimally abnormal test results will depend on the time proximity to the most recent bout of pancreatitis. Minimal abnormalities will be present if the pseudocyst forms after the inflammatory phase has ceased. This trend would also pertain to serum pancreatic enzyme activities (amylase, lipase) or concentrations (cPLI).

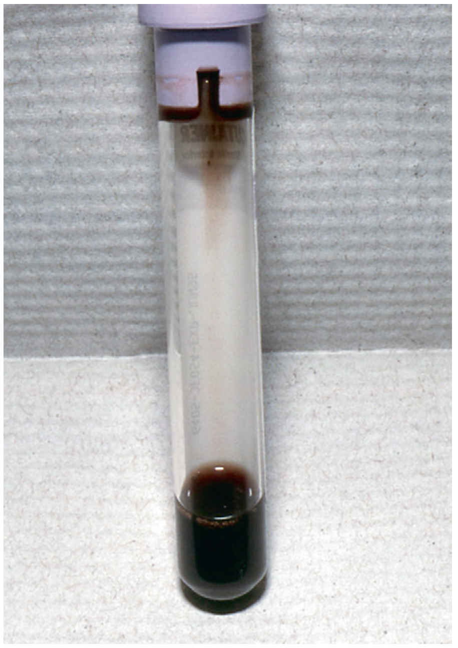

Figure 60-31 Pancreatic pseudocyst fluid containing amorphous debris.

A sample of the cystic fluid can be obtained by ultrasound-guided fine-needle aspiration. The character of the fluid will vary, especially if it is infected. Sterile cyst fluid can vary from being thin to viscous depending on the amount of necrotic debris present (Figure 60-31). In humans, the cyst can contain high concentrations of amylase and lipase, especially if the cyst is connected to the pancreatic duct. The cyst fluid from the canine case reported by Smith et al. contained high concentrations of amylase, lipase, and TLI.[22] This finding has been reported in other canine cases.[27] The cytologic features of the pancreatic cyst fluid can range from minimal cellularity to that of increased cellularity that reflects an inflammatory component. The latter finding in a clinically ill patient with fever might prompt a more aggressive treatment strategy including laparotomy.

Diagnostic Imaging

Pancreatic pseudocyst might have the radiographic appearance of a mass with fluid density in the area of pancreas. Large cysts will displace adjacent abdominal viscera. Radiographs will not distinguish pseudocyst from the inflammation pattern typical of acute pancreatitis. Abdominal ultrasonography has greatly facilitated this diagnosis in humans, and it will probably accomplish the same in veterinary medicine once the technology and the accompanying necessary skills become more widely available. The sonographic appearance of pseudocyst will likely be indistinguishable from other types of pancreatic masses such as pancreatic abscess or cystic neoplasia until a sample of the cyst fluid or the tissue itself is analyzed. Using this technique, it will appear as a hypoechoic mass containing hyperechoic sediment (Figure 60-32). One report showed that the size of the pseudocyst ranged from 2×2 to 7×6 cm,[27] and that the fine-needle aspiration procedure was a practical and efficient way to make this diagnosis, and in some cases to expedite its medical treatment.[11,28]

CT provides an excellent visualization of pancreatic pseudocyst. This technique is more commonly used in humans for general abdominal diagnostic evaluations, but abdominal ultrasound might be more feasible for veterinarians because of its availability, lesser cost, and high degree of diagnostic accuracy.

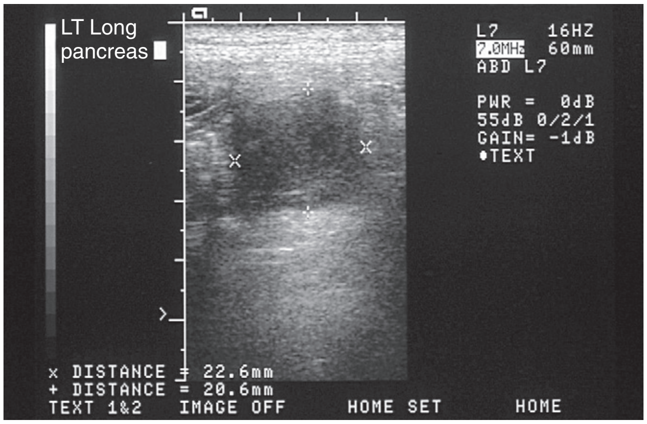

Figure 60-32 An abdominal ultrasound showing pancreatic pseudocyst.

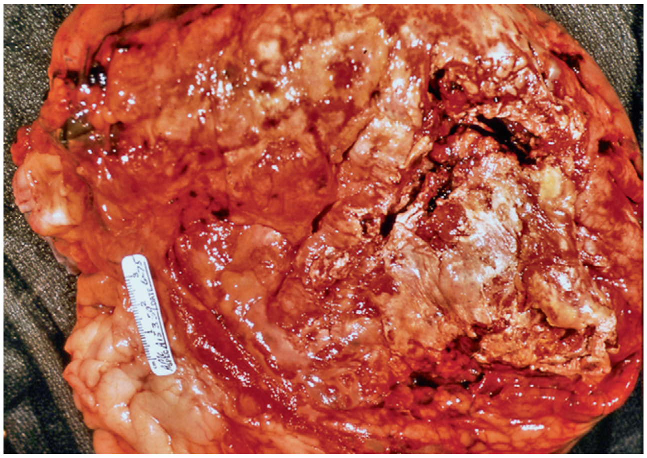

Figure 60-33 Pancreatic phlegmon at postmortem.

Treatment

Physicians will monitor human pancreatic pseudocyst for several weeks so long as they are not infected, not causing pressure on nearby structures, and not showing evidence of spontaneous rupture. In many cases, the cyst will resolve spontaneously.[3,11,28] The incidence of spontaneous resolution in small animals is not known either because of the rarity of the condition or its infrequency of diagnosis. It would seem prudent to conservatively monitor a small cyst for spontaneous resolution if it is of no immediate threat to the patient.

Transabdominal fine-needle aspiration of the cyst contents is commonly performed in humans and this technique has been reported in dogs.[11,23,27] The procedure is performed selectively on those patients who are clinically stable and who do not show signs of a surgical abdomen (fever, prostration, palpable tenderness, cytologic evidence of abdominal sepsis). Potential complications include leakage of cyst fluid into the peritoneal cavity, hemorrhage, and introduction of infection. Patients treated with this technique should be clinically reevaluated for 2 weeks. Other treatment techniques that are used in humans include percutaneous cystogastrostomy, and endoscopic cystogastrostomy, and duodenostomy. Surgical resection is done if the less-invasive techniques fail to resolve the problem or if bacterial infection is present.[3,8,22,26] Procedures include anastomosis of the cyst to an adjacent hollow viscus, Roux-en-Y anastomosis, and external drainage with creation of a pancreatic fistula to the skin.[3,20]

Conclusion

Pancreatic pseudocyst formation occurs as a sequel to acute pancreatitis. Small pseudocysts might be clinically asymptomatic and resolve spontaneously over a few weeks. Large cysts can cause a range of clinical signs related to their physical size, the possibility of secondary infection, or because of spontaneous rupture into the abdominal cavity. Treatment of large intact cysts can be accomplished by transabdominal ultrasound-guided fine-needle aspiration. Surgery is indicated for infected cysts and those that rupture.

Pancreatic Phlegmon

Definition

Adler and Barkin describe pancreatic phlegmon as a mass that results from acute intrapancreatic inflammation with fat necrosis and pancreatic parenchymal necrosis. They are usually found in association with necrotizing pancreatitis and are characterized by necrotic pancreatic and peripancreatic tissue.[11] "Pancreatic ascites" commonly accompanies this condition because of the substantial peritonitis that occurs with this condition. It is characterized as a sterile exudate in the absence of infection.[2] The largest number of reported cases describes this condition in seven dogs.[6] Because of the overlap in defining pancreatic necrosis and pancreatic phlegmon, Edwards et al. use the description provided by Warshaw where pancreatic phlegmon is a solid mass of indurated pancreas and adjacent tissue resulting from edema, inflammatory cells, and some tissue necrosis (Figure 60-33).[29] A fluid pocket is not present. Phlegmon develops within days after a severe bout of pancreatitis and is characterized by the presence of a palpable or radiographic abdominal mass and prolonged leukocytosis. Persistent fever and abdominal tenderness frequently are present. The terms *pancreatic necrosis* and *phlegmonous pancreatic slough* refer to the condition where glandular tissue becomes devitalized. These masses involve peripancreatic tissue more extensively than a phlegmon and can be associated with fluid-filled pockets produced by liquefaction necrosis.[6,30]

Incidence, History, and Physical Examination

There is nothing in particular that distinguishes one particular patient with pancreatic necrosis from another that has pancreatic phlegmon except for the eventual mass-like lesion that develops with phlegmon within 5 to 7 days of severe clinical illness. Edwards et al. reporting on seven dogs described all of them as seriously ill and showing signs typical of severe pancreatitis.[6] The ages ranged from 4 to 12 years (mean: 7.8 years) with a majority (five) in obese female dogs. All seven had signs of anorexia, lethargy or depression, and vomiting, which were present for a few hours to 3 days prior to being seen by a veterinarian. Five were admitted to the teaching hospital within 2 days of onset of clinical signs of acute pancreatitis while two were referred 9 to 10 days after the initial signs of pancreatitis. Fever occurred in five, abdominal pain in three, and diarrhea in two. All of the initial imaging and clinical pathology results were typical of most dogs affected with pancreatitis. One dog had a palpable abdominal mass that resolved, and this dog was discharged after 8 days of hospitalization. Because the pancreas was not grossly visualized in this dog, the diagnosis of a phlegmon was tentative based on imaging and laboratory results. The other six dogs were diagnosed at surgery, which was done after a protracted hospital stay that ranged from to 8 to14 days after initial signs of pancreatitis. The clinical course in some of these dogs fluctuated with varying degrees of illness, but they were persistently ill.

Clinicopathologic Findings

It is important to note that there are no laboratory tests to distinguish between severe acute pancreatitis, pancreatic necrosis, pancreatic abscess, and pancreatic phlegmon. They can all have the same clinicopathologic findings from normal to highly abnormal. All of these conditions cause a leukocytosis, many of which also have toxic changes in the white blood cells. Many cases have a lowered platelet count that is attributable to consumption of platelets because of inflammation. DIC can occur in any patient with severe acute pancreatitis as a result of the systemic inflammatory response or secondary sepsis. Patients with phlegmon usually have elevated serum liver enzyme concentrations and hyperbilirubinemia. Icterus can occur from either cholestasis or secondary to an obstruction of the common bile duct. Serum proteins might be increased initially but then decrease because of "third spacing" of plasma proteins in the peritoneal space because of increased vascular permeability associated with the marked inflammatory response. BUN and serum creatinine concentrations can increase as a result of prerenal effects from hypovolemia and renal hypoperfusion. Acute renal failure can occur as an ominous secondary complication because of acute tubular necrosis, antibody–antigen accumulation at the glomerulus, secondary to drug toxicity, and pathologic thrombi formation at the glomerulus.[20,31,32]

Diagnostic Imaging

The detection of an abdominal mass using diagnostic imaging is the main sign that suggests pancreatic phlegmon formation. In Edwards' review, pancreatic (anterior abdominal) masses were detected by radiography in five cases, with ultrasonography in two cases, and with abdominal palpation in one case. Today we expect a large majority of cases to be discovered using abdominal ultrasonography. The main radiographic abnormalities include a mottled appearance in the peritoneal cavity with a loss of serosal detail. The majority had a mass effect in the pancreatic region that often displaced the pylorus or ascending proximal transverse colon. The main ultrasonographic features were a hyperechoic mass in the pancreatic region containing hypoechoic and anechoic areas.[6]

Treatment

The treatment for pancreatic phlegmon and sterile necrosis can range from purely medical to those that require major surgery. When surgery is selected, it is essential to be aware that the procedure begins on a severely ill patient that might be near death prior to surgery, and that the postoperative outcome could be disastrous. This is evidenced in Edwards' report showing that all six patients that underwent surgery either died or were euthanized.[6] Perhaps part of the reason for this outcome might be the protracted care that was needed in each of those cases. In humans, the decision to operate is controversial, each based on valid opinions, but the one unanimous decision in favor of surgery is the presence of infected necrosis.

Infected necrosis is a serious and potentially lethal complication in humans.[18] Overall, the rate of mortality is 20% to 30%, and in some cases even higher, especially if the condition goes unrecognized until the postmortem examination. Surgery is essential for treating this condition where debridement is carried out by gentle finger dissection of necrotic material which consists of necrotic fat and pancreatic parenchyma. As discussed for pancreatic abscess, the various types of surgical drainage include necrosectomy with closed peritoneal lavage, necrosectomy with wide peripancreatic drainage, necrosectomy with staged reexploration, and necrosectomy with open packing.[20] These same procedures can be done in veterinary patients. Regardless of the species, one of the most important factors regarding surgery is to not delay the surgery while the patient continues to worsen because of sequestered necrosis. The postoperative morbidity in all of these procedures is substantial, and all are associated with a long postoperative stay.

The treatment of sterile necrosis is controversial when considering the option for surgery.[2,18,33] In such cases, intense medical treatment is done before surgery is considered. In humans, most patients found to have sterile necrosis heal successfully without debridement. However there are exceptions to this that usually involve patients who continue to deteriorate despite adequate medical support.

Infected Pancreatitis

Overview

The veterinary literature suggests that cultures of pancreatic tissue are usually negative.[5-7] In Anderson's review of 36 dogs with pancreatic abscess, only two of 13 cultures yielded bacterial growth.[9] However, 12 of the 36 dogs had peritoneal fluid cultured, and seven of these had positive bacterial growth. The results of Anderson's study population raises the possibility of the presence of an undiagnosed peritonitis in the face of ongoing sterile pancreatic necrosis. There is also the question of bacterial isolation from necrotic tissue which might not be conducive to pancreatic growth. It is possible that antibiotics administered to the pancreatitis patient could favor negative bacterial isolation on samples taken several days after the antibiotics have had a chance to take effect. Perhaps veterinary patients might show a higher incidence of infected pancreatitis if tissue and/or abdominal fluid samples were obtained initially by fine-needle aspiration prior to administering antibiotics. The remaining question regarding the indication for antibiotic treatment is also one with answers that have changed over time. Because there is experimental evidence for transcolonic migration of bacteria during acute pancreatitis, there are some clinicians who will administer broad-spectrum antibiotics in the hope of reducing the incidence of pancreatic and peripancreatic infections even though the benefits of doing so have not been proved.[33,34] In a recent study involving 100 human patients with severe necrotizing pancreatitis, using antibiotic treated and untreated controls, there was no statistically significant difference between the antibiotic treated groups and the untreated group for pancreatic or peripancreatic infection, mortality, or the requirement for surgical intervention therefore concluding that early prophylactic antimicrobial use provided no distinct advantage in human patients.[14]

Regardless of its rare occurrence, infected pancreatitis should be suspected in every case of pancreatic necrosis or phlegmon. Diagnosis is established by demonstrating bacteria with fine-needle aspiration of any abdominal fluid or parenchymal tissue samples (Figure 60-34). Treatment should begin with a broad-spectrum antibiotic(s) while the results of culture and sensitivity are pending.

INSUFFICIENCY

Maria Wiberg

Exocrine Pancreatic Insufficiency in Dogs

Exocrine pancreatic function may be diminished by chronic diseases leading to inadequate production of digestive enzymes and classic signs of maldigestion. EPI is a functional diagnosis based on

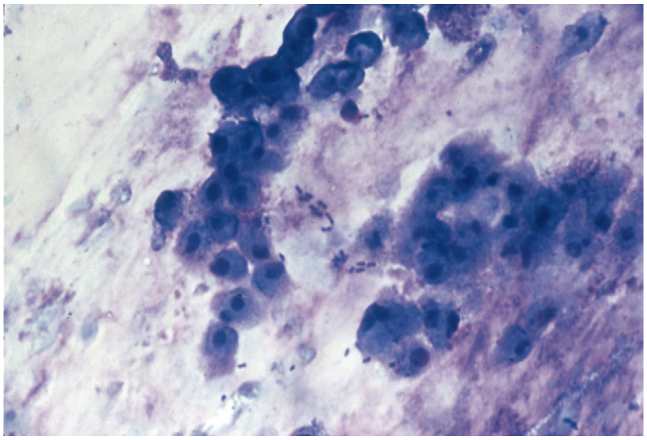

Figure 60-34 Bacteria detected on a fine-needle aspiration cytology sample from a dog with an infected pancreatic phlegmon that was confirmed at surgery.

measuring decreased pancreatic secretion capacity by pancreatic function test. The exocrine pancreas has a large reserve secretory capacity, and maldigestion signs are usually not seen until 90% of the secretory capacity is lost. Exocrine pancreatic diseases that may result in clinical signs of EPI include pancreatic acinar atrophy (PAA; dogs), chronic pancreatitis (dogs, cats), and very rarely reported pancreatic neoplasia (dogs, cats).[1-6]

Etiopathogenesis

EPI has been reported in many different breeds, but some breeds appear to be more predisposed than others. EPI is most commonly found in German Shepherds, followed by Rough-Coated Collies, Chow Chows, and Cavalier King Charles Spaniels.[3,5,7-10] Female association with EPI has been reported.[10] The prevalence of the various pancreatic diseases causing clinical signs of EPI is difficult to assess, because pancreatic morphologic examination is needed for the specific diagnosis. However, PAA is reported to be by far the most common cause of severe EPI in young adult dogs. Of all dogs diagnosed with EPI, approximately 50% to 70% were German Shepherds, and in Finland 20% of the cases are found in Rough-Coated Collies.[3,9,10] With German Shepherds and Rough-Coated Collies, the underlying cause for EPI is PAA. The estimated prevalence of the disease within these two breeds is approximately 1%.[3,8] Similar etiopathogenesis with PAA may also be suspected in other breeds with early onset EPI, such as the Chow Chow and Eurasian dog breeds.[10,11] In contrast, dogs that develop clinical signs of EPI later in life more likely have chronic pancreatitis as the underlying pathogenesis.[10]

Pancreatic Acinar Atrophy

The characteristic of PAA is a selective destruction of the digestive enzyme, producing acinar cells. Loss of acinar tissue leads to inadequate secretion of pancreatic enzymes and to signs of maldigestion typical of EPI. The endocrine function of the pancreas is usually spared in this process.[1,2,5,12] Canine PAA is a unique disease compared with other species. In humans, PAA has been reported, but in association with multiorgan diseases such as Sjögren and Shwachman-Diamond syndromes.[13] Congenital isolated deficiencies in pancreatic enzymes are reported in humans[13] but not in dogs. Experimental studies show that acinar atrophy can be an end result of multiple pathogenetic processes involving the exocrine pancreas, such as pancreatic duct obstruction, ischemia, toxicity, nutritional deficiencies or imbalances, and defective secretory and/or trophic stimuli.[6] That said, there is no evidence to support the involvement of these factors in naturally occurring PAA in dogs.[6,14] Congenital exocrine or compound exocrine and endocrine pancreatic hypoplasia in young puppies is sometimes found.[15-17] Westermarck et al.[18] followed the morphologic changes in the pancreas of a German Shepherd puppy bred from parents with PAA. The puppy was born with a grossly and histologically normal pancreas, but developed EPI later in life. This finding supports the hypothesis that PAA in this breed is neither hypoplastic nor congenital, but rather a progressive disease.

The clinical signs of EPI caused by PAA are usually seen in young adults, 1 to 4 years of age, although sometimes the clinical disease may develop later in life.[19] The hereditary nature of PAA has been demonstrated in German Shepherds, Rough-Coated Collies, and recently with Eurasian dogs. Pedigree analyses suggest that the disease in these three breeds is heritable by an autosomal recessive trait.[7,8,11,20,21] Preliminary results of a test mating between two German Shepherds with PAA showed that only two of the six offspring were affected, thus suggesting that EPI is not a single-gene disease but rather a polygenic disease (unpublished data). To date, two studies have attempted to identify the candidate genes for PAA. In German Shepherds, the gene for glycoprotein 25L, located at CFA3, is downregulated by 500-fold in affected pancreata. However, there were no mutations found in the coding sequence (that segregates with PAA).[22] In Eurasian dogs, linkage analysis of CFA3 and CFA23 as canine orthologs of the human cholecystokinin and cholecystokinin A receptor genes excluded them as candidates for PAA.[11] Therefore, additional studies are necessary to identify the molecular defect responsible for PAA in these breeds.

Recent etiopathogenetic studies showed that PAA has some features of autoimmune disease in German Shepherds and Rough-Coated Collies.[23,24] These features include genetic susceptibility to disease and characteristic morphologic and immunologic findings during progression of disease. The ability to diagnose PAA prior to development of total acinar atrophy and manifestation of clinical maldigestion signs, permits the progression to atrophy to be closely monitored.[9] The progression of PAA was divided into a subclinical phase characterized by partial acinar atrophy and a clinical phase with severe end-stage atrophy. In the subclinical phase, both atrophied and normal acinar parenchyma were found. Grossly, the normal pancreatic mass was diminished and scattered areas of atrophied tissue were found among the normal tissue. No hemorrhagic or fibrotic tissue was observed. The histologic findings during the progression of atrophy were typical for an autoimmune disease showing marked lymphocytic inflammation into the partially atrophied acinar parenchyma. The gradual destruction of the acinar structure was found in association with the inflammatory reaction. Lymphocytic inflammation was most extensive in the border zones of the normal and affected acinar parenchyma, and lymphocytes spread into the normal acinar parenchyma and intraacinar areas. As tissue destruction progressed, the findings became more typical of end-stage PAA.[23]

The clinical signs appear in the end stages of PAA. The gross pathologic findings are typical, showing thin and transparent pancreas with no signs of fibrosis. The normal glandular structure is hardly recognizable and the pancreatic ducts are clearly visible. Histologically, no normal acinar tissue is left in the end stages, or if normal tissue is present, it is found in small isolated lobuli. The normal acinar parenchyma is replaced by atypical tissue, and ductal structures are prominent. Fibrous tissue is not generally increased, and in some cases the normal tissue is replaced by adipose tissue.

Inflammatory cells, lymphocytes, and plasma cells may be found, but in general inflammation is less prominent than in the subclinical phase. The endocrine part of the pancreas in dogs with PAA is usually well preserved.[1,5,12,25]

Further immunologic studies with dogs with partial PAA have suggested that both cellular and humoral immune responses play a role in the pathogenesis of acinar atrophy, although tissue destruction appears to be largely mediated by cellular immune mechanisms.[24] Immunohistochemical analysis showed that at the onset of acinar cell destruction, the majority of the infiltrating lymphocytes were T cells, with an almost equal number of CD4+ T-helper and CD8+ cytotoxic T-lymphocytes. Cytotoxic T cells predominated in sections where the gradual destruction of the acinar parenchyma was present.[24] The role of the humoral immune response was previously studied, in which serum pancreatic-specific antibodies in dogs with clinical signs of EPI were compared with those of healthy controls, but the study found no differences between these two groups.[26] A recent study showed that serum autoantibodies reacting at low intensity with pancreatic acinar cells were found in some dogs with partial and end-stage PAA, but not in healthy control dogs, suggesting that the humoral immune response was also activated.[24]

As lymphocytic pancreatitis with active destruction of acinar structures preceded the end-stage atrophy, the term *autoimmune-mediated atrophic lymphocytic pancreatitis* has been suggested to describe the pathologic findings.[23,24] The rate of progression of the atrophy from the subclinical to the clinical phase is variable, and the factors affecting it are not yet identified. Long-term followup of dogs with partial PAA shows that they may remain in the subclinical phase for years or sometimes for life. No diagnostic markers predicting which dogs will develop clinical disease have been found.[27] Autoimmune diseases are often multifactorial. Genetic susceptibility, environmental factors, and immunologic abnormalities are all involved in this pathogenesis. Environmental factors, either microbial or nonmicrobial, are usually needed to initiate a clinical autoimmune disease in genetically susceptible individuals.[28] The possible contribution of various environmental factors, such as feeding, housing, training, stress, and viruses, in the pathogenesis of PAA has been proposed, but there are no comprehensive studies available on their roles. A survey failed to show any common triggering environmental factors in the histories of dogs with EPI.[19]

Chronic Pancreatitis

Chronic pancreatitis is probably an underestimated reason for EPI, because there has been lack of sufficient histologic data. Recent studies show that chronic pancreatitis may be more common in dogs than clinically suspected.[29,30] Unlike the situation in autoimmune atrophic pancreatitis, there is usually a progressive destruction of both exocrine and endocrine pancreas in chronic pancreatitis. Clinical history usually shows more nonspecific GI signs, or the signs of EPI also can develop later in dogs with previous diabetes mellitus. The pathologic findings in chronic pancreatitis are clearly different from those of PAA. Macroscopically, the pancreas is usually hard, shrunken, and nodular, and there may be adhesions. The characteristic histologic findings in chronic pancreatitis involve an increase in interlobular and intralobular fibrosis and disorganized acinar lobuli, with or without inflammatory cells in the interstitium.[1,2,5,29]

Clinical Signs

The typical clinical signs of EPI include increased fecal volume and defecation frequency, yellowish feces, weight loss, and flatulence. Other common signs are polyphagia, poorly digested, loose and pulpy feces, and coprophagia. Nervousness or aggressiveness may occur and these are suspected to result from abdominal discomfort because of increased intestinal gas. Severe watery diarrhea is usually only temporary. Skin disorders have also been reported. Although these signs of EPI are typical, they are not pathognomonic for the disease, as small intestinal diseases may show similar maldigestive or malabsorptive signs.[6,19]

Diagnosis

The diagnosis of exocrine pancreatic dysfunction is based on typical findings in clinical histories and clinical signs and is confirmed with a pancreatic function test. Complete blood cell count and routine serum biochemistry often show unremarkable changes. Serum amylase and lipase activities are not useful in the diagnosis of EPI. Various pancreatic function tests, which measure pancreatic enzyme concentrations in the blood and feces, have been used to diagnose canine EPI. The diagnostic value of these tests lies in their ability to distinguish whether the maldigestion signs are caused by exocrine pancreatic or small intestinal disease, as well as in their practicality. When needed to verify the underlying pathologic process causing the clinical signs, morphologic examination of the pancreas may be performed.[31]

The measurement of canine serum TLI has become one of the most commonly used pancreatic function tests in the diagnosis of canine EPI.[32] Serum TLI measurement is species- and pancreas-specific. The new reference ranges for cTLI in healthy dogs are 5.7 to 45.2 μg/L (Texas A&M, Gastrointestinal Lab, College Station, TX). Abnormally low serum cTLI concentrations (<2.5 μg/L), with the typical clinical signs of maldigestion, are considered highly diagnostic for severe EPI and indicate severe loss of the digestive enzyme-producing acinar cells.[32] Interpretation of the cTLI values is not always straightforward. The pathologic processes affecting exocrine pancreatic function are progressive, and cTLI levels can vary from normal to abnormal depending on the degree of pancreatic tissue lost. Overlapping results between normal and affected dogs can be expected, and a normal cTLI greater than 5.7 μg/L does not necessarily exclude mild to moderate pancreatic dysfunction.[9] In general, the lower the cTLI value, the more valuable a single measurement is in assessing pancreatic dysfunction. When the cTLI value is in a subnormal range (2.5 to 5.7 μg/L), further diagnostic procedures with repeat cTLI measurement are recommended.[9] In German Shepherds and Rough-Coated Collies, breeds predisposed to autoimmune atrophic pancreatitis, it was shown that repeatedly subnormal cTLI values (2.5 to 5.0 μg/L) in dogs showing no typical signs of EPI indicated subclinical EPI and suggested partial atrophy.[9,23]

Fecal proteolytic activity measurement has been used historically for the diagnosis of EPI. The reliability of the different tests varies, and a common problem with these tests is that sometimes normal dogs also showed decreased proteolytic activity.[6,33,34] To avoid this problem, fecal proteolytic activity was measured from repeated fecal samples and after using pancreatic stimulation by giving raw soybeans in the food during the test period.[34] A recent study showed that in dogs with protein-losing enteropathy, increased fecal loss of α_1-proteinase inhibitor is associated with a decrease in fecal proteolytic activity and may result in a false diagnosis of EPI.[35]

A new fecal test for diagnosing exocrine pancreatic dysfunction is the ELISA determination of fecal elastase. Canine fecal elastase is species- and pancreas-specific test with high sensitivity, but relatively low specificity. A single fecal elastase concentration greater than 20 μg/g can be used to exclude EPI in dogs with chronic diarrhea. Values less than 20 μg/g in association with typical clinical signs of EPI are suggestive of severe pancreatic dysfunction.[36-38] For diagnosing subclinical EPI and partial PAA the fecal elastase measurement was not sufficiently sensitive enough.[39]

Treatment

Enzyme Replacement Therapy

When signs of maldigestion secondary to EPI appear, enzyme replacement therapy is indicated. The basic treatment includes supplementation of the dog's ordinary food with pancreatic enzyme extracts. Various pancreatic enzyme extracts are available in different countries. In dogs, the highest enzyme activity in the duodenum was achieved using nonenteric-coated supplements, such as powdered enzymes or raw chopped porcine pancreas, and these supplements are equally effective in controlling clinical signs.[40,41] The choice among preparations is based on practical properties, availability, and costs. In many countries the use of raw porcine pancreas is not permitted because of possible zoonotic disease. The maintenance dosage for the powdered enzyme is dependent on the preparation used (Viokase-V, Fort Dodge, Fort Dodge, KS, 1 tsp/meal). Raw frozen pancreas has been fed at 50 to 100 g/meal for dogs that weigh 20 to 35 kg.[6,40,41] The value of enteric-coated supplements is limited in dogs as a result of delayed gastric emptying of the preparations.[42] Despite accurate enzyme therapy the digestive capacity does not return to normal, because orally administered enzymes are largely destroyed by gastric acid. Sometimes the increase in enzyme dosage or change to another nonenteric-coated supplement may be beneficial. Inhibition of gastric acid secretion by H_2-histamine receptor antagonists has shown some positive effects. Even if routine use of H_2-histamine receptor antagonists is not needed, they may be indicated when the response to enzyme treatment alone is poor and especially when vomiting or inappetence appear.[6,41,43] A rare complication with oral enzyme powder supplementation is gingivitis and oral bleeding, which is treated either by decreasing the enzyme dose or by changing the supplement or preincubation enzyme in the food prior to feeding.[44,45]

Supportive Treatments

Supportive treatments should be considered when the treatment response to enzyme replacement therapy alone is not satisfactory. EPI also may be associated with secondary problems that may worsen the clinical signs. These include small intestinal bacterial overgrowth or antibiotic-responsive diarrhea, malabsorption of cobalamin, and the coexistence of small intestinal disease.

The most commonly used adjunctive medications in the treatment of EPI are antibiotics. An increased amount of substrates for bacteria in the small intestine, a lack of bacteriostatic factors in the pancreatic fluid, and changes in intestinal motility and immune functions are possible reasons for the accumulation of bacteria in the small intestine of dogs with EPI.[46-48] Antibiotics have been used during the initial treatment when clinical signs, such as diarrhea, increased intestinal gas, and flatulence have not resolved with enzyme therapy, or when these signs have recurred during long-term treatment. Antibiotics reported to be effective include tylosin (10 to 20 mg/kg BID) or metronidazole (10 to 15 mg/kg BID) for 1 to 3 weeks.[6,41]

Clinical feeding studies during long-term treatment of EPI show that the need for special diets is minimal and that dogs may continue to be fed their original diet. Radical dietary changes should be avoided and special attention should be focused on individual needs, since the response to different diets varies among dogs.[41,49-51] In those dogs that do not show satisfactory treatment response, dietary modification may be useful. The severity of some clinical signs of EPI can be decreased with dietary modification. A highly digestible, low-fiber and moderate-fat diet can alleviate clinical signs such as defecation frequency, increased fecal volume, and flatulence.[49] Highly digestible diets may be of particular value in the initial treatment until the nutritional status has improved and possible mucosal damage has been repaired. A low-fat diet was recommended, because enzyme supplements alone are unable to restore normal fat absorption.[52] Lipase is most easily destroyed by exposure to gastric acid during gastric transit. Fat absorption may also be affected by bacterial deconjugation of bile salts in small intestinal disease, producing metabolites, which, in turn, may result in diarrhea. However, feeding the low-fat diet did not significantly alleviate the clinical signs during the long-term treatment.[50] Dietary sensitivities may be a consequence of EPI, and therefore hypoallergenic diets may benefit some dogs, especially those with concurrent skin problems. No obvious clinical benefits were demonstrated by adding medium-chain triglycerides to food.[53]

Cobalamin deficiency in dogs with EPI is partly a result of increased uptake of cobalamin by the intestinal bacteria and partly to the lack of pancreatic intrinsic factor, shown to play a major role in the absorption of cobalamin. Enzyme treatment alone is not helpful for increasing serum cobalamin levels.[54-56] Because cobalamin deficiency is common in canine EPI, serum cobalamin should be measured in dogs that are clinically suspected of having EPI or that do not respond satisfactorily to enzyme treatment. Cobalamin is given subcutaneously and the dose currently recommended is 250 to 1000 μg, depending of the size of the dog.[57] The treatment should be repeated based on serum concentrations.

Although malabsorption of fat-soluble vitamins may be expected with EPI, the clinical importance of vitamins A, D, E, and K deficiency in this syndrome has not been reported. When the treatment response to enzymes and supportive therapies is still unsatisfactory, concomitant small intestinal disease should be suspected, and further diagnostic studies and treatment should be performed.[6]

Treatment of Atypical Cases

The diagnosis and treatment of EPI can be more complicated in dogs with pancreatic dysfunction as a result of chronic pancreatitis or with dogs having only partial PAA. These dogs may show nonspecific chronic or intermittent GI signs associated with serum TLI concentration in the subnormal area of 2.5 to 5.7 μg/L.[9] GI signs may be a result of subnormal pancreatic function or underlying small intestinal disease or a combination of both. The diagnostic workup and treatment for possible concurrent small intestinal disease is recommended (see Chapter 57), and serum TLI measurement should be repeated in 1 to 2 months. If no underlying small intestinal disorder is identified, a trial treatment with pancreatic enzymes should be initiated. Those dogs with diagnosed partial PAA caused by autoimmune pancreatitis, but showing no clinical signs of EPI, need no treatment. The value of early immunosuppressive treatment with azathioprine in slowing the progression of the autoimmune-mediated tissue destruction was shown to be questionable, and is thus not recommended.[27]

Prognosis

When the clinical signs of EPI appear, the loss of pancreatic tissue is already almost totally complete. Changes are considered to be irreversible, and lifelong enzyme replacement therapy is usually required. The response to enzyme treatment is usually seen during the first weeks of treatment, with weight gain, cessation of diarrhea, and decrease in fecal volume.[6,43]

The level of treatment response achieved during the initial treatment period remains fairly stable.[41] Although some dogs show short relapses of clinical signs, the permanent deterioration of the clinical condition during long-term treatment is uncommon. During long-term treatment with nonenteric-coated enzyme supplements, the GI signs considered typical for dogs with EPI were almost completely controlled in half of the dogs. Although it was not always possible to eliminate all the signs, good resolution was found especially in the more serious signs. Those signs most commonly remaining were increased fecal volume, yellow and pulpy feces, and flatulence. Poor response to treatment was observed in 20% of the dogs, despite similar treatment regimens.[41]

Another study showed similar results, with favorable initial treatment response in 60% of dogs, partial in 17%, and poor in 23%.[58] Severe cobalamin deficiency was associated with shorter survival. Other predictors, such as breed, sex, age, clinical signs at the time of diagnosis, dietary modification, and fat-restricted diet did not affect the favorable initial treatment response or long-term survival. Interestingly, no difference in the treatment response or survival was found between enteric-coated and nonenteric coated supplements. This was clearly a different result than that previously reported[40] and thus should be further investigated.

Approximately 20% of dogs diagnosed with EPI were euthanized during the first year.[41,58] The most common reason for euthanasia was poor treatment response; another reason for euthanasia was owner reluctance for expensive and lifelong treatment. A rare, but severe, complication of EPI is mesenteric torsion.[59] Today mesenteric torsion is more seldom seen, probably because of more efficient enzyme preparations.

Exocrine Pancreatic Insufficiency in Cats

EPI in cats is rare. End-stage chronic pancreatitis is considered to be the most common cause of exocrine pancreatic dysfunction and clinical signs of maldigestion in the cat. Adenocarcinomas of the exocrine pancreas may cause obstruction of the pancreatic duct and thus decreased production of digestive enzymes.[60,61]

Clinical Signs

The clinical signs are similar to those of dogs, including loose and voluminous stools, weight loss, poor body condition, and polyphagia. Cats with EPI may have greasy, wet-looking hair coats, especially in the perineal region. The GI signs are often similar to those of small intestinal IBD and cobalamin deficiency. Other differential diagnoses to be considered are hyperthyroidism and intestinal neoplasia. Because chronic pancreatitis affects both the endocrine and exocrine pancreas, diabetes mellitus is commonly associated with EPI in cats.[60,61]

Diagnosis

The results of routine laboratory tests, abdominal radiography, and ultrasound are generally unremarkable, unless subtle changes of chronic pancreatitis can be recognized. The diagnosis of exocrine pancreatic dysfunction should be based on species-specific measurement of feline serum TLI. The reference ranges for fTLI are 12 to 82 μg/L (Texas A&M, Gastrointestinal Lab, College Station, TX). A severely decreased fTLI concentration equal to or less than 8 μg/L is considered diagnostic for EPI.[62] Fecal proteolytic activity tests can also be used for fEPI diagnosis, but in comparison to fTLI measurement these tests are impractical.[31,60]

Treatment

The basic treatment of feline EPI is pancreatic enzyme supplementation. Powdered formulations are the most effective in cats. With powdered enzyme extracts the initial dose is 0.5 tsp/meal. When possible, raw frozen pancreas can also be used. Tablets or enteric-coated supplements are usually less effective and thus not recommended. Dietary modification is not usually needed, and most cats with EPI can be fed with regular maintenance diets.[31,60] In cats with EPI, serum cobalamin concentrations are often severely decreased, and therefore serum cobalamin should be routinely measured in cats with suspected EPI and also during treatment of EPI in case of poor response to enzyme replacement alone. Some cats do not respond satisfactorily to enzyme treatment until cobalamin is also supplemented. The recommended dose for parenteral cobalamin is 250 μg subcutaneously weekly for 4 to 6 weeks, and thereafter based on the measurement of serum cobalamin concentrations.[31,60,63] EPI can also be associated with small intestinal disease, and in these cases treatment with oral prednisolone and/or antibiotics (oral metronidazole) may be needed.[31]

NEOPLASIA

Sandra Axiak and Kevin Hahn

Cats

Two types of feline exocrine pancreatic neoplasia are described: adenomas, which are usually incidental and benign, and adenocarcinomas. Adenocarcinomas are rare and can be diffuse throughout the pancreas,[1] although some reports show greater incidence in the head of the pancreas than the tail.[2] Age at presentation ranges from 4 to 20 years. Metastasis to the liver is common and less-common sites of metastatic spread include the lungs, lymph nodes, small intestine, and heart. Adenocarcinoma is also associated with diabetes mellitus and hyperadrenocorticism. Diabetes mellitus is thought to be secondary to compression of the islet cells, tumor-derived cortisol inducing β-cell degeneration, or decreased carbohydrate metabolism.[1]

Clinical Examination

Presenting clinical signs are anorexia, vomiting, abdominal pain, weight loss with a normal appetite, and icterus. Physical examination findings include icterus and cranial abdominal mass. Duration of signs is bimodal with 50% of cats having signs for less than 7 days and 50% having signs for more the 1 month.[1]

A rare paraneoplastic syndrome has been described in cats with pancreatic adenocarcinoma. It consists of nonpruritic, symmetrical alopecia of the face, ventral body, and medial limbs. Skin is glistening, but not fragile, and crusty lesions can be seen on the footpads. This syndrome is also reported in cats with bile duct carcinoma. Histopathologically, it is characterized by loss of the stratum corneum and severe follicular atrophy with miniaturized hair bulbs.[3] In one case report, the syndrome resolved following surgical excision of the pancreatic adenocarcinoma, but recurred when metastatic disease became evident, 18 weeks after surgery.[3]

Diagnosis

A CBC may show neutrophilia and serum biochemistry may reveal increased liver enzymes (alkaline phosphatase, alanine aminotransferase) and mild hyperglycemia. Chest radiographs may show pleural effusion indicative of metastasis.[1] Abdominal radiographs may show loss of serosal detail with or without a cranial abdominal mass. A pancreatic mass can be found on abdominal ultrasound. Definitive diagnosis requires fine-needle aspiration and cytology or exploratory laparotomy with biopsies and histopathology.[1]

Treatment and Prognosis

Supportive care is generally ineffective.[1] Surgical excision has been reported in one cat.[3] The prognosis is poor and most cats are euthanized within 7 days of diagnosis because of disease progression.[1] The cat in which surgical excision was reported did well for 18 weeks until euthanized for progressive disease.[3]

Dogs

The etiology of most canine exocrine pancreatic tumors is unknown and no predisposing factors have been identified. However, experimentally intraductal administration of *N*-ethyl-*N*′-nitro-*N*-nitrosoguanidine can induce pancreatic adenocarcinoma.[4]

Pancreatic exocrine tumors are derived from duct or acinar epithelium. Four types of pancreatic carcinoma have been described in the dog: adenocarcinoma, anaplastic carcinoma, alveolar carcinoma, and endocrine-like carcinoma.[5] An additional subset, hyalinizing pancreatic adenocarcinoma, has recently been described in a group of six dogs.[5a] There is no sex predilection, and breeds at higher risk include Airedales, Boxers, Labrador Retrievers, and Cocker Spaniels.[4] The overall incidence of exocrine pancreatic carcinoma is less than 1%, with an incidence of 12% in dogs with pancreatic disease.[5] Unlike the cat, benign neoplasms of the pancreas are not reported in the dog, although hyperplastic nodules are common in older dogs.[5] Location varies and grossly the tumor can appear singular, nodular, or diffuse. Hemorrhage and necrosis are common (Figure 60-35). Metastasis occurs early and affects the liver, omentum, and mesentery most frequently. Other sites of metastasis reported are lungs, thyroid gland, heart, duodenum, and subcutaneous tissue.[5] Histologically, there is extreme variation in cellular structure and central necrosis is common. Reduction in exocrine secretion does occur, however complete pancreatic insufficiency in dogs due to neoplasia has not been observed.[5]

Multifocal necrotizing steatitis has been reported in association with pancreatic carcinomas in three dogs.[6] In these cases, the presenting complaint was of panniculitis. Lesions ranged from ill-defined nondraining soft-tissue swellings to localized subcutaneous lesions with a purulent discharge. The mechanism of steatitis with pancreatic carcinoma is unknown, but is postulated to be a result of systemic release of lipase.[6] Panniculitis with polyarthritis and osteomyelitis also has been reported in two dogs, one with exocrine pancreatic adenoma, and the other with pancreatic adenocarcinoma.[7]

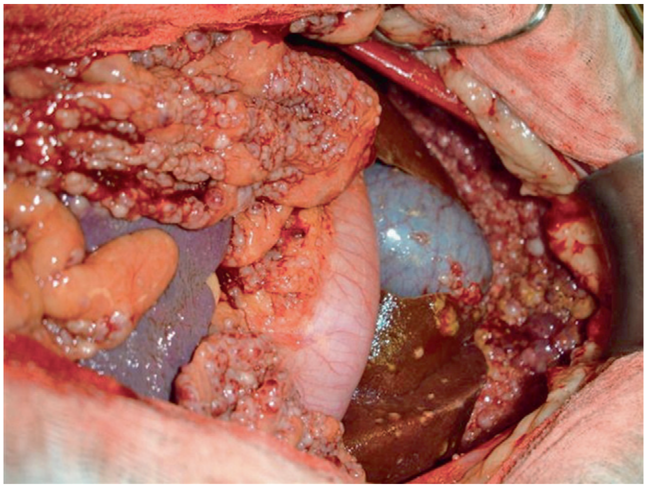

Figure 60-35 Carcinomatosis in a dog with pancreatic adenocarcinoma at surgery.

Clinical Examination

Clinical signs are nonspecific and bimodal, with duration of less than 1 month or of 2 to 4 months.[5] Most patients have a history of weight loss, anorexia, and vomiting. Other less-common signs include depression and weakness.[4] On physical examination, ascites, cranial abdominal mass, or icterus may be noted.[5]

Diagnosis

A CBC may reveal mature neutrophilia, while serum biochemistry may show increased alkaline phosphatase, lipase, or amylase. The increased lipase may occur from associated pancreatitis or from tumor production of lipase.[8] Chest radiographs are usually normal, whereas abdominal radiographs may show a loss of abdominal detail or cranial abdominal mass. Abdominal ultrasound may reveal a pancreatic mass, and can also be used to guide fine-needle aspiration and cytology. Cytology of abdominal fluid, if present, may also provide a diagnosis. Definitive diagnosis is based on ultrasound guided fine-needle aspiration and cytology (diagnostic in eight of 10 cases) or exploratory laparotomy and histopathology.[4] Immunocytochemical labeling for amylase and carboxypeptidase may be of value in diagnosing the primary tumor or metastasis.[9]

Treatment and Prognosis

Treatment is aimed at surgical removal of the pancreatic mass, however disease is usually advanced at the time of diagnosis.[10] One exception may be hyalinizing pancreatic adenocarcinoma, which may progress more slowly than other subtypes of exocrine pancreatic cancer. In one case series of six dogs, two lived greater than 15 months, one dog with no treatment and another with surgical excision. The other four dogs in this series died of complications related to concurrent disease or partial pancreatectomy.[5a] In general, chemotherapy and radiation therapy are ineffective.[10] Overall prognosis is poor as a result of location of the tumor and early onset of metastasis.[10]

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