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THE LIVER, BILIARY TRACT, AND EXOCRINE PANCREAS

CHAPTER 37

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DEVELOPMENT OF THE HEPATOBILIARY SYSTEM AND PANCREAS

Development of the Hepatic Circulation

In the developed fetus, blood from the umbilical vein flows directly to the caudal vena cava through the ductus venosus, thereby bypassing the liver. By passively responding to changes in the systemic or hepatic circulation, this conduit stabilizes venous return to the fetal heart as the umbilical venous return fluctuates. Functional and morphologic closure of the ductus venosus does not occur simultaneously. In most dogs, functional closure of the ductus gradually occurs during the second and third days after birth. Morphologic closure occurs as the ductus atrophies, leaving behind a thin fibrous band (ligamentum venosum) within the liver. Ductus closure reflects the physiologic response to changes in pressure and resistance across the hepatic vasculature after postnatal obliteration of the umbilical circulation. Normally complete morphologic closure of the ductus is established by 1 to 3 months after birth. Congenital malformations of the intrahepatic and extrahepatic portal circulation and persistence of a functional ductus venosus are well documented in the dog and cat. Anomalous portal circulatory circuits in small breed dogs most commonly involve a single extrahepatic portosystemic vascular anomaly or malformation of the intrahepatic microscopic vasculature (microvascular dysplasia). A persistent or patent ductus venosus is more common in large breed dogs, being particularly notable as a family-associated defect in Irish Wolfhounds and Scottish Deerhounds. Delayed functional closure of the ductus venosus likely explains finding hyperammonemia in some Irish Wolfhound pups (up to 4 to 8 weeks of age) that resolves within several months of age.

Metabolic Functions

Despite early embryogenic differentiation of the liver, many of its metabolic functions are incompletely developed at birth. The fetal liver has reduced capabilities for gluconeogenesis, glycogenolysis, bile acid metabolism, and other biotransformation, detoxification, and elimination processes. Consequently the fetus is susceptible to transplacental and postnatal toxic and infectious challenges that may be inconsequential in adults. During gestation, the functional immaturity of the hepatobiliary system is masked by the maternal placental circulation. However, when maternal support is abruptly severed at birth, certain aspects of hepatobiliary insufficiency may become evident when the neonate is inappetent and exposed to infectious or toxic agents.

Biochemical indicators of hepatic disorders

Normal values for routinely used biochemical indicators reflecting the status of the hepatobiliary system in newborn and growing puppies and kittens are given in Table 37-1.

Blood glucose

Hepatic gluconeogenesis and glycogen storage are the mainstays of blood glucose regulation. Newborns depend on their hepatic glycogen reserves during the first 24 hours, with minimal glucose derivation from gluconeogenic branched chain amino acids. Although the ability to synthesize glycogen develops early, stores of hepatic glycogen accumulate only near term. Hepatic glycogen stores may be low at birth subsequent to intrauterine malnutrition (i.e., multiple pregnancies) or maternal malnutrition. Within 12 hours of birth, hepatic glycogenolysis consumes most glycogen stores, necessitating nutritional intake and gluconeogenesis to maintain euglycemia. It is during this interval that newborns are most susceptible to hypoglycemia. Generally initial blood glucose concentrations in newborn dogs are lower than in adults, although values exceeding 200 mg/dl have been documented. However, puppies deprived of food, especially toy breeds, may develop symptomatic hypoglycemia within 48 hours in contrast to adults, which can fast for days or weeks without becoming hypoglycemic. Comparatively,

TABLE 37-1 **Normal values for routine biochemical indicators of hepatobiliary disorders in young dogs and cats (median [unless otherwise stated] and range)**

Test	Puppy age						Normal adult reference range
	1-3 days ($n = 30$)	2 weeks ($n = 14$)	4 weeks ($n = 7$)	8 weeks ($n = 8$)	8.1-16 weeks ($n = 78$)*	16 weeks-1 year ($n = 78$)*	
BSP% 30 min	<5	<5	<5	<5	<5	<5	(0-5)
Total serum	<15	<15	<15	<15	<15	<15	(0-15)
Bile Acids (βM/L)							
Total bilirubin (mg/dl)	0.5 (0.2-1.0)	0.3 (0.1-0.5)	0 (0-0.1)	0.1 (0.1-0.2)	0.1 (0.-0.1)	0.1 (0-0.1)	(0-0.4)
ALT (U/L)	69 (17-337)	15 (10-21)	21 (20-22)	21 (9-24)	31 (22-48)	37 (29-46)	(12-94)
AST (U/L)	108 (45-194)	20 (10-40)	18 (14-23)	22 (10-32)	27* (15-83)	27* (15-83)	(13-56), (15-83)*
ALP (U/L)	3845 (618-8760)	236 (176-541)	144 (235-301)	158 (144-177)	169 (27-416)	108 (19-285)	(4-107)
GGT (U/L)	1111 (163-3558)	24 (4-77)	3 (2-7)	1 (0-7)	<12 (0-12)	<12 (0-12)	(0-12)
Total protein (g/dl)	4.1 (3.4-5.2)	3.9 (3.6-4.4)	4.1 (3.9-4.2)	4.6 (3.9-4.8)	5.5* (4.4-7.3)	5.68* (4.8-6.7)	(4.0-5.2), (4.4-7.3)*
Albumin (g/dl)	2.1 (1.5-2.8)	1.8 (1.7-2.0)	1.8 (1.0-2.0)	2.5 (2.1-2.7)	2.8* (2.6-4.0)	3.0* (2.6-4.0)	(2.1-2.3), (2.6-4.0)*
Cholesterol (mg/dl)	136 (112-204)	282 (223-344)	328 (266-352)	155 (111-258)	211 (136-279)	211 (136-279)	(150-299), 136-279)*
Glucose (mg/dl)	88 (52-177)	129 (111-146)	109 (86-115)	145 (134-272)	– adult range	– adult range	(65-110)

*Data adapted from Harper et al: Age related variations in hematologic and biochemical test results in Beagles and Labrador Retrievers, *J Am Vet Med Assoc* 223:1436-1442, 2003; mean values.
Kitten data from College of Veterinary Medicine, Cornell University and data adapted from Levy JK, Crawford PC, Werner LL: Effect of age on reference intervals of serum biochemical values in kittens, *J Am Vet Med Assoc* 228:1033-1037, 2006.

TABLE 37-1 **Normal values for routine biochemical indicators of hepatobiliary disorders in young dogs and cats (median [unless otherwise stated] and range)—cont'd**

Test	Kitten age					Normal adult reference range
	1-3 days ($n = 55$)	1 week ($n = 55$)	2 weeks ($n = 79$)	4 Weeks ($n = 62$)	8 weeks ($n = 55$)	
BSP% 30 min	N.D.	N.D.	N.D.	<3	<3	(0-3)
Total serum	<10	<10	<10	<10	<10	(0-10)
Bile Acids (βM/L)						
Total bilirubin (mg/dl)	0.1-1.1	0.1-1.6	0.0-0.7	0.0-0.2	0.0-0.6	(0.0-0.4)
ALT (U/L)	29-77	11-76	10-21	14-55	12-56	(28-91, 10-80)
AST (U/L)	21-126	15-45	14-23	15-31	14-40	(9-42, 5-55)
ALP (U/L)	1348-3715	126-363	116-306	97-274	60-161	(10-77, 10-80)
GGT (U/L)	0-5	0-5	0-4	0-1	0-2	(0-2)
Total protein (g/dl)	2.8-5.2	2.5-4.8	2.7-5.2	4.5-5.6	4.9-6.5	(5.4-8.1)
Albumin (g/dl)	1.9-3.1	2.0-2.5	2.1-2.6	2.4-2.9	2.4-3.0	(2.3-3.0, 2.4-4.1)
Cholesterol (mg/dl)	48-228	119-213	137-443	99-434	124-221	(150-270, 42-170)
Glucose (mg/dl)	52-163	105-145	76-158	99-152	94-143	(63-150)

symptomatic hypoglycemia is uncommon in neonatal cats and may reflect their carnivore-based metabolism. Neonatal dogs have overall poor glycemic regulation compared with adults, with slow recovery from either hypoglycemia or hyperglycemia. This is attributed to a relative insensitivity to endogenous insulin and suboptimal counterregulatory hormone responses (cortisol and epinephrine) in puppies. Consequently puppies can develop prolonged hyperglycemia after supplemental glucose administration.

Neonates have a relative deficiency of alternative energy sources (fat stores, gluconeogenic amino acids) to total body mass compared with adults. Only small amounts of fat are stored in the liver during the last trimester of gestation. Because lactate precedes use of alanine or glutamine for gluconeogenesis in puppies, and because lactate is preferentially used in the brain of hypoglycemic neonatal puppies, there may be an advantage in using lactate-containing fluids in symptomatic hypoglycemic puppies.

Maintaining euglycemia is important for the neonates' neurologic status because they have a brain-to-body mass carbohydrate requirement 2 to 4 times greater than adults. Unfortunately, even though the neonatal brain may preferentially accept lactate as an energy substrate, lactate availability may be insufficient. Ketones, an important alternative fuel during starvation, are insufficiently synthesized in neonates owing to their limited body fat, slow fatty acid mobilization, low ketogenic abilities, and their inability to survive the adaptation interval that precedes effective ketosis.

Although glucose regulation improves with age, puppies and kittens up to 4 months of age should be considered predisposed to hypoglycemia when anorexic or dehydrated. Conditions and clinical signs associated with neonatal/pediatric hypoglycemia are provided in Box 37-1. It is notable that severity of clinical signs increases with age such that hypoglycemia is more easily recognized in older animals. Thus maintaining a high index of suspicion for hypoglycemia is essential to achieve early diagnosis in a neonate. Treatment is aimed at achieving euglycemia, normalizing body temperature and hydration status, avoiding stress, and eliminating underlying causal factors.

Urea cycle function and blood ammonia concentrations

Function of the urea cycle matures at varying stages of fetal and neonatal development in different species. Urea cycle enzymes have not been directly quantified in fetal or neonatal dog or cat liver. Nevertheless, baseline ammonia values in clinically normal dogs and cats as young as 2 months are within the normal adult range, with the exception of some Irish Wolfhounds with apparent delayed closure of the ductus venosus.

Plasma ammonia concentrations can reflect portosystemic shunting caused either by congenital malformations of the portal circulation or secondary to portal hypertension (e.g., hepatic fibrosis, cirrhosis, portal vein thrombosis). Unfortunately because ammonia is labile in blood, immediate analysis is imperative. Samples must be transported from patient to equipment on melting ice, eliminating the routine transport to a commercial laboratory. It is well acknowledged that enzymatic methods for measuring blood ammonia concentrations lack precision. Ammonia is not routinely used in the author's clinical practice because of its unreliability and because there are better test alternatives: measurement of serum bile acids and detection of ammonium urate crystalluria.

BOX 37-1 Signs of hypoglycemia

- Weakness
- Hypothermia
- Dehydration
- Inability to nurse
- Persistent crying
- Bradycardia or tachycardia
- Irregular respiration
- Apnea

Serum bile acids

Serum bile acids (SBAs) are well documented as a reliable method for estimating sufficiency of hepatic function and hepatoportal circulation. Bile acids are synthesized in hepatocytes from cholesterol, conjugated to an amino acid (taurine exclusively in cats; taurine or glycine in dogs), excreted into bile, and then undergo an efficient enterohepatic circulation. In adults, the enterohepatic circulation has 90% to 95% efficiency (each cycle). The utility of the endogenous meal-provoked bile acid challenge for assessment of liver function and perfusion has been fully investigated in neonatal, juvenile, and adult dogs and cats. In our laboratory, SBA concentrations in 1-day-old and 1-, 2-, and 4-week-old puppies and kittens are within the adult reference range. In older puppies and kittens, paired SBA samples (one before and one 2 hours after meal ingestion) concur with the adult reference range. The SBA test is reliable for detection of portal circulatory anomalies when paired samples (premeal and 2 hours postprandially) are evaluated. Random or fasted single samples are ill advised. Normal values may exist in animals with portosystemic vascular anomalies after a prolonged fast owing to circulatory delivery of arterial blood. Approximately 15% to 20% of dogs and 5% to 10% of cats have higher postprandial SBA concentrations relative to premeal values owing to delayed gastric emptying, intestinal transit, or perhaps gallbladder expulsion of bile (physiologic variation). Paired-sample (one before and one 2 hours after meal ingestion) SBA tests are recommended for vigorous routine assessments. Screening puppies for portosystemic vascular anomalies (PSVAs) using single random or fasted SBA concentrations is not recommended. Some animals with PSVA have normal fasting SBA values, and a few demonstrate the "backward" pattern described above. Physiologic variables influencing this test include (1) the gastric emptying rate, (2) the rate of gallbladder contraction and bile expulsion, (3) the rate of intestinal motility, (4) the

functional status of the ileum where active bile acid transporters reside, and (5) the normalcy of the hepatobiliary structures and portal circulation.

Bilirubin metabolism

The fetal, neonate, and juvenile dog's capacity for hepatic uptake, conjugation, and excretion of bilirubin is remarkably mature compared with humans and several nonhuman primates. The fetal dog has substantial concentrations of bilirubin-conjugating enzymes. The capacity of the liver in the fetal, neonatal, and juvenile cat has not been similarly investigated. Some individual puppies have total bilirubin values mildly increased during the first 72 hours of birth, but this resolves within 2 weeks. Some kittens at birth and up to 14 days of age have total bilirubin values as high as 1.0 mg/dl (adult reference range, 0 to 0.2 mg/dl); values normalize by 4 weeks of age. The etiology of such high neonatal bilirubin concentrations remains unclarified.

Liver enzyme activity

Age-appropriate reference intervals for serum liver enzyme activity are essential for interpreting laboratory data in neonatal puppies and kittens. Differences in serum enzyme activities between neonates and adults reflect physiologic adaptations during the transition from fetal and neonatal life stages, trauma associated with birthing, colostrum ingestion, maturation of metabolic pathways, growth effects, differences in volume of distribution and body composition, and nutrition. Activity of serum alkaline phosphatase (ALP), aspartate aminotransferase (AST), creatine kinase (CK), and lactate dehydrogenase (LDH) usually increase greatly during the first 24 hours of life. In kittens, ALP, CK, and LDH activity exceeds adult values through 8 weeks of age, whereas AST increases only transiently after birth. The early increases in AST, CK, and LDH likely reflect muscle trauma associated with birthing, whereas ALP activity reflects bone isoenzyme associated with bone growth. Enteric absorption of colostral macromolecules during the first day of life causes a substantial increase in ALP in puppies and kittens, and of gamma-glutamyltransferase (GGT) in puppies (Figure 37-1, *A* and *B*). This phenomenon is not unique to dogs and cats as it has also been documented in neonatal calves, lambs, pigs, foals, and human infants. Studies also have confirmed significant differences in ALP activities develop between colostrum-deprived and suckling pups and kittens within 24 hours of birth, with a similar change in GGT also observed in puppies. These differences are short lived, resolving within the first 2 weeks, but can be used as a surrogate marker of effective colostrum ingestion. Studies have confirmed that colostrum contains substantially higher GGT and ALP activity than that resident in the serum of the respective dam or queen. For example, colostral or milk GGT in bitches is 100-fold and ALP is tenfold greater than sera until day 10. However, by day 30, GGT and ALP activity in milk is significantly lower than before suckling had commenced. Although a marked influence of colostrum on serum ALP activity in neonatal kittens also occurs, the effect on GGT

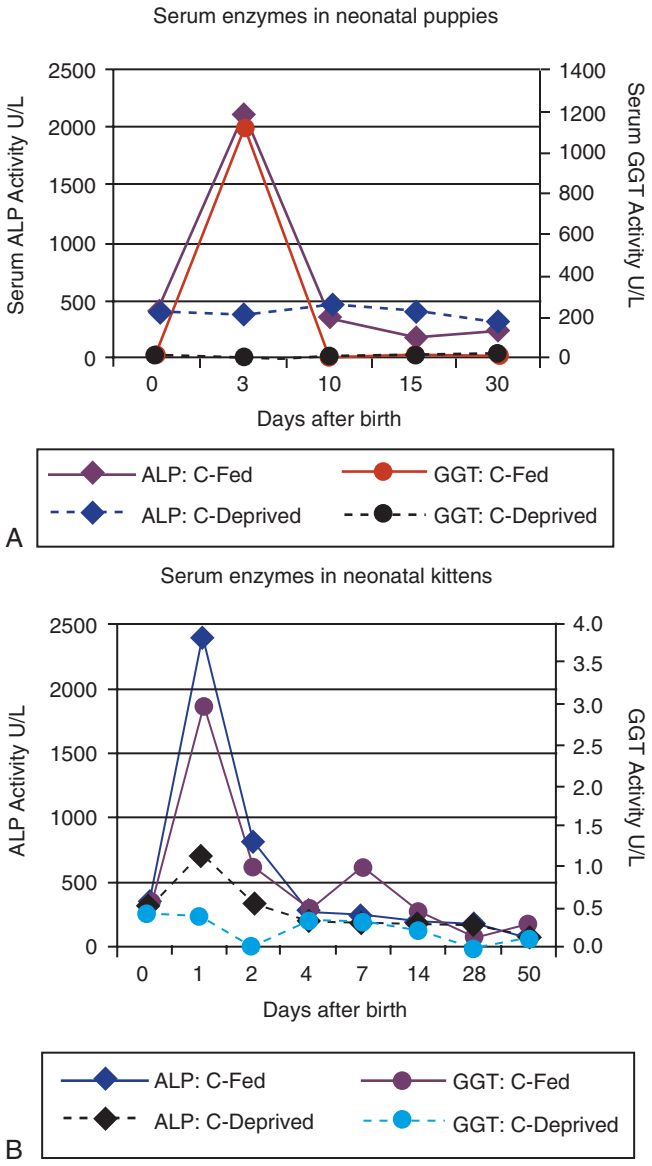

Figure 37-1 Liver enzyme activity in puppies **(A)** and kittens **(B)** immediately after birth showing the influence of colostrum ingestion on associated enzyme concentrations.

is modest compared with that in neonatal puppies. Sustained increases (first 6 to 12 months of life) in serum ALP activity in puppies and kittens (maximally threefold more than high normal adult reference values) reflect the bone ALP isoenzyme derived from osteoblast activity.

Albumin, globulins, coagulation factors, and protein C

Synthesis of albumin, many globulins, most coagulation, and many anticoagulant factors depends on the liver. Total protein and albumin concentrations in young dogs up to 4 weeks of age are below normal limits for adults, whereas protein concentrations in young cats are more variable (see Table 37-1). By 8 weeks of age, puppies have normal adult albumin concentrations, whereas total globulin values increase with age, reflecting cumulative antigenic challenge.

Although coagulation assessments are uncommonly completed in neonatal puppies and kittens, limited observations suggest that values fall within the normal adult ranges for prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen in animals as young as 8 weeks of age. Protein C, recently shown to discriminate normal puppies from puppies with PSVA, is influenced by adequacy of portal venous perfusion. Although liver failure and severe enteric protein loss also can compromise protein C activity, this anticoagulant factor is useful for differentiating PSVA from microvascular dysplasia (MVD) in young dogs.

Cholesterol

Serum cholesterol concentration can reflect hepatic functional and circulatory disturbances. Because cholesterol is synthesized in the liver, synthetic failure can cause marked hypocholesterolemia. Portosystemic shunting, either congenital or acquired, also causes mild to marked hypocholesterolemia. Because cholesterol is excreted into the biliary tree in bile, cholestasis can increase in cholesterol concentrations. A mild to moderate increase in cholesterol is apparent with acute obstructive jaundice and in some animals with acute severe hepatic inflammation (lacking synthetic failure). In 1- to 3-day-old puppies but not kittens, mild hypocholesterolemia is common (see Table 37-1). In puppies and kittens older than 2 to 4 weeks of age, serum cholesterol concentrations are within the adult normal range.

Hepatic hematopoiesis

Extramedullary hematopoiesis can develop in the liver of puppies or kittens through 4 months of age. However, in older juveniles, hematopoietic activity in the liver is usually restricted to disorders associated with a brisk regenerative anemia.

Hepatic mineral storage

Age-related variations in hepatic concentrations of iron, copper, zinc, and selenium (per gram of dry liver weight) have been reported for Beagle dogs from 8 to 193 days of age (Table 37-2). A decrease in hepatic iron concentrations during the first 20 days after birth likely reflects mobilization of iron for hemoglobin synthesis in bone marrow, the relative iron deficiency of a milk diet, and decrease in hepatic extramedullary hematopoiesis. In many species, hepatic copper concentrations are higher in pediatric individuals relative to adults. In dogs, hepatic copper concentrations change little with advancing age unless challenged with a copper-rich diet. In dogs with copper-associated hepatopathy (primary metabolic or copper transport disorder, dietary copper loading, cholestatic liver injury), hepatic copper concentrations significantly increase over time (see later discussion on Copper Storage Hepatopathy).

Hepatobiliary Disorders of the Young Dog and Cat

Survey of young dogs and cats (n = 444; puppies, n = 312 and kittens, n = 132) with liver tissue examined histologically (biopsy or necropsy) over a 12-year interval in the author's hospital is detailed in Table 37-3. Various histologic and definitive diagnoses are represented. Hepatic necrosis, hepatic congestion, and hepatic lipidosis were the three most common histologic features. Hepatic congestion is of uncertain significance as this may represent a terminal or death-related change.

TABLE 37-2 Hepatic mineral concentrations in Beagles (mean ± standard deviation; µg/g dry weight)

Mineral content	8 to 40 days of age (n = 10)	>40 days of age (n = 20)
Iron	1025 ± 882	585 ± 258
Copper	285 ± 75	304 ± 90
Zinc	225 ± 88	143 ± 30
Selenium	2.5 ± 0.4	1.9 ± 0.4

Summarized from Keen CL, Lonnerdal B, Fisher GL: Age-related variations in hepatic iron, copper, zinc, and selenium concentrations in beagles, *Am J Vet Res* 42:1884, 1981.

Congenital Anatomic Malformations

Gallbladder

Congenital malformations of the gallbladder are most common in the cat. Congenital division of the gallbladder is most common and is also referred to as an accessory, cleft, diverticular, or bilobed gallbladder (Figure 37-2). These malformations involve the initial subdivision of the primary cystic diverticulum or a bud from the neck of the embryonic gallbladder. Although such malformations do not cause clinical illness, they can cause confusion when recognized during abdominal ultrasonography as they may be mistaken for a cyst.

Common bile duct diverticulum

A cystic diverticular outpouching of the common bile duct near the sphincter of Oddi has been recognized in some cats. These may become a nidus of infection (rather like the human appendix), eventually leading to septic choledochitis and pancreatitis. Clinical signs are initially vague but may involve inappetence and vomiting. Thereafter, features cannot be differentiated from other causes of hepatobiliary jaundice until gross inspection during exploratory laparotomy. Resection of the cystic diverticulum, often combined with cholecystoenterostomy, and judicious antimicrobial therapy and supportive care are usually curative. Adequate hydration, ursodeoxycholate (7.5 mg/kg orally twice daily with meals) and S-adenosylmethionine (20 mg/kg orally daily 1 to 2 hours before feeding) are used to promote choleresis for several months postoperatively.

Biliary atresia

Congenital maldevelopment of the biliary tree is an unusual anomaly recognized in puppies and kittens. These patients are jaundiced and fail to thrive. There is no treatment.

TABLE 37-3 Hepatobiliary disorders in puppies and kittens less than 4 months of age: gross and histopathologic tissue evaluations

Disorder	Puppies ($n = 312$)	Kittens ($n = 132$)
Infectious hepatopathies	68	18
Parvovirus	30	0
Herpesvirus	7	0
Canine distemper	11	–
Infectious canine hepatitis	4	–
Feline infectious peritonitis	–	17
Parasite migration	4	0
Hepatic abscessation	12	1
Severe hepatic necrosis	54	41
Hepatic congestion	63	25
Hepatic lipidosis	36	16
Extramedullary hematopoiesis	39	10
Cholangitis	9	10
Trauma (hematoma, laceration)	10	6
Nonspecific hepatitis	14	3
Portosystemic vascular anomaly	1	11
Hepatic atrophy	3	2
Vasculitis	1	0
Lymphosarcoma	1	0
Diaphragmatic hernia (liver involvement)	1	0

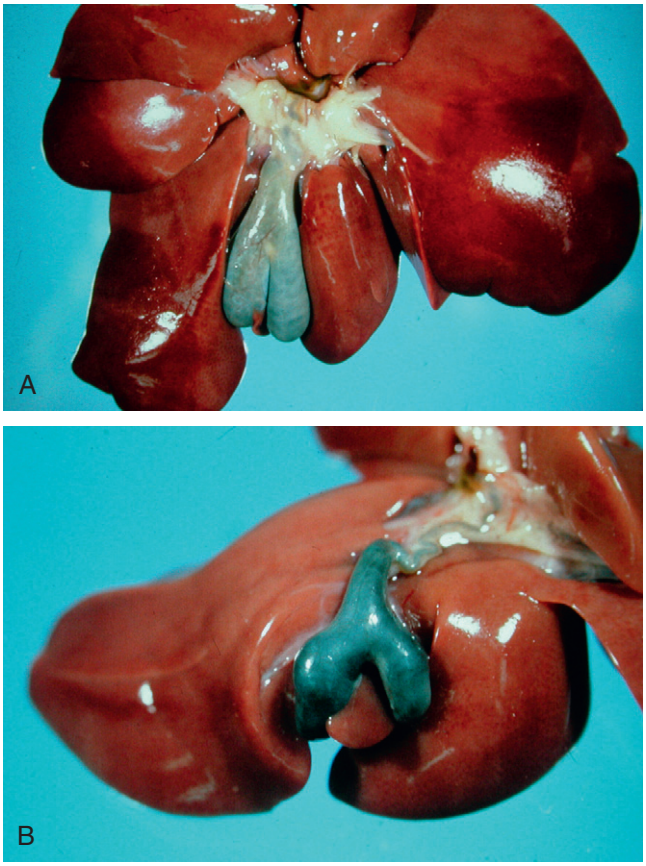

Figure 37-2 Bilobed gallbladders representing developmental anomalies in two cats. (From Hoskins J: *Veterinary pediatrics: dogs and cats from birth to 6 months*, ed 3, Philadelphia, 2001, Saunders, p 201.)

Cystic hepatobiliary lesions

Congenital and acquired hepatic cysts occur in both dogs and cats. Acquired cysts are uncommon in juvenile patients but may develop subsequent to trauma or inflammation and are usually solitary. Congenital or developmental cysts are commonly multiple and variable in size. Polycystic renal and liver lesions have been identified in Cairn Terriers and Persian cats during the first few months of life. Whereas cystic lesions may be parenchymal or ductal in origin, most hepatic cysts are ductal. These arise from primitive bile ducts and lack continuity with the normal biliary tree. If lining epithelium produces fluid, cysts transform into retention cysts. Cysts may be solitary or multiple in the polycystic disorder and vary in size from a few millimeters to several centimeters. Cats with polycystic liver malformations sometimes also have cystic lesions in the kidneys or pancreas. Although hepatic cysts are often asymptomatic, they may become symptomatic when they encroach on normal tissue or organs. Cysts adjacent to the gallbladder are most problematic. In polycystic feline liver disease, prolific production of extracellular matrix surrounding dysplastic ductal structures causes intrahepatic portal hypertension and subsequently development of acquired portosystemic shunts, abdominal effusion, and signs of hepatic encephalopathy.

Clinical illness associated with biliary cystic lesions in juvenile or young adult dogs and cats may be lacking or may remain vague (e.g., inappetence or vomiting caused by cyst compression of the stomach). Diagnosis is accomplished with radiographic or ultrasonographic imaging. Ultrasonography discloses the cystic nature of lesions, as well as the extent of tissue involvement. When abdominal ultrasonography was used to phenotype Persian cats with the polycystic renal mutation, renal cysts were identified at 6 to 7 weeks of age in many cats. Cats lacking cystic lesions at 6 months were deemed unaffected. Although the diagnostic performance of abdominal ultrasonography in detecting the cystic renal lesions was exceptional (specificity, 100%; sensitivity, 75% at <16 weeks of age; and specificity, 100%; sensitivity, 91% at <36 weeks of age), this procedure has not been evaluated for detection of polycystic liver disease.

Cats with cystic liver lesions should be DNA tested for the renal polycystic gene mutation if they are intended for breeding. It remains unclarified if there are variants of this disorder associated with primary liver involvement. DNA testing is done using a cheek swab kit (available from felinegenome@ucdavis.edu). Treatment is usually not indicated for congenital cystic liver lesions unless a large cyst causes abdominal discomfort or fluid accumulation causes pressure effects on adjacent organs or tissues. Periodic aspiration of large problematic cysts has been used to manage some patients. Other alternatives include partial cyst wall

resection, entire cyst excision, or removal of an involved liver lobe. In some Persian cats, the polycystic renal or hepatic involvement is recognized during the first few months of life. In some of these, polycystic kidney disease is rapidly lethal. In others, the disorder is mild, does not cause overt signs, and is recognized incidentally later in life.

Common Vascular Malformations Involving the Liver

Hepatoportal MVD and PSVA are related congenital inherited disorders of hepatic vasculogenesis or angiogenesis. An extensive genotyping project involving nine small dog breeds (in progress by the author) has confirmed the genetic relationship between these disorders with SBA concentrations designating affectation status. Each of these disorders is associated with SBA concentrations greater than 25 µmol/L. However, quantitative SBA values cannot reliably discriminate between these disorders. Current data support an autosomal dominant mode of inheritance with incomplete penetrance or a complicating regulatory element mutation and probable prenatal or perinatal lethality of the most severely affected dogs (PSVA). Pedigree studies suggest that up to 15% of dogs with PSVA remain asymptomatic to knowledgeable breeders and veterinarians. Unfortunately some of these dogs have been outstanding individuals and have been used as foundation stock, propagating the genetic defect. Because the historical, clinical, clinicopathologic, and histologic features of PSVA have saturated the veterinary literature during the past 30 years, most clinicians maintain a high index of suspicion for this disorder when presented with a vaguely ill young dog with high SBA values. However, it is important to acknowledge that the MVD phenotype is far more common than PSVA (10 to 30:1 depending on the breed and the pedigree structure). It is estimated that the frequency of PSVA ranges between 0.1% and 0.6% of the ill patient population in large specialty referral hospitals.

Portal hypoplasia versus portal hypoperfusion

Increased arteriole blood flow is a physiologic response to decreased portal venous perfusion and is a consistent histologic feature of any condition impairing hepatic portal venous perfusion (e.g., thrombi, venous obstruction). This adaptive response is associated with arteriolar tortuosity (coiling) and thickening of the arteriolar smooth muscle. Rather than portal hypoplasia, the functional terminology of *portal hypoperfusion* more accurately depicts the observed perfusion abnormality.

Hepatoportal microvascular dysplasia

MVD was originally well characterized in a family of Cairn Terriers with an increased incidence of PSVA. Extensive studies including organic anion dye clearance, colorectal scintigraphy, hepatic and portal ultrasonography, contrast radiographic portography, and liver biopsy (multiple liver lobes in each dog) confirmed MVD is associated with abnormal microscopic hepatic blood flow and a lack of macroscopic portosystemic shunting. In dogs with PSVA, hepatic ultrasonography detected a subjectively small liver, abnormal portal to systemic vascular communications, and hypovascular intrahepatic portal perfusion. In dogs with MVD, intrahepatic portal vasculature was less well defined than in normal dogs; liver size was subjectively normal; and no large shunting vessels were identified. Radiographic portography confirmed macroscopic shunting only in dogs with PSVA but disclosed inconsistent portal venous perfusion among liver lobes in dogs with MVD. Dogs with only MVD demonstrated contrast retention in some liver lobes, consistent with differential perfusion among liver lobes, and a lack of well-distinguished tertiary portal branches. These findings correspond nicely with scintigraphic features described as portal streamlining in dogs scrutinized for PSVA that lacked a macroscopic shunt. Microscopic features in dogs with only MVD overlap with those observed in dogs with PSVA depending on the liver lobe sampled; lesions are inconsistent among different liver lobes. Cytologic imprints of liver biopsies in dogs with either MVD or PSVA usually demonstrate small binucleate hepatocytes.

Dogs with MVD are typically asymptomatic and do not develop hyperammonemia, ammonium biurate crystalluria, or uroliths. The MVD lesion is irreversible and often accompanies PSVA. Its presence explains why some dogs undergoing surgical PSVA ligation maintain increased SBA concentrations yet lack clinical signs. Definitive diagnosis of MVD from PSVA cannot be made based on the liver biopsy as lesions are similar. Because MVD lesions vary among liver lobes, a minimum of three biopsies from different liver lobes is recommended for definitive diagnosis. Needle biopsies are notoriously poor for ascertaining the presence of either MVD or PSVA because of small sample size and restricted lobe sampling.

The MVD phenotype explains why some dogs suspected of having PSVA based on abnormal liver function (SBA) and hepatic histology lack macroscopic shunting vasculature on contrast radiographic study, colorectal scintigraphy, and surgical inspection. It is important to realize the differences between MVD and PSVA. Dogs with MVD usually remain asymptomatic and do not require special liver diets or therapeutic interventions with lactulose, metronidazole, neomycin, antioxidants, or ursodeoxycholic acid. The typical liver affected with MVD has no necroinflammatory component. High bile acids in these dogs represent the circulatory flux of the enterohepatic bile acid circulation rather than injurious bile acids retained in tissues. Dogs with MVD followed long term (up to 15 years) maintained on a canine maintenance diet without additional therapies do not develop progressive liver injury. Because many small Terrier-type dog breeds have a 30% to 35% incidence of MVD, puppies should be tested using a paired SBA test at 4 months of age before adoption into a pet home. Knowing a dog's SBA status is important for future health care and assessments.

Portosystemic vascular anomaly

Several different types of PSVA have been described in dogs and cats, including but not limited to (1) persistent patent

fetal ductus venosus (large breed dogs especially, inheritable in Irish Wolfhounds and Irish Deerhounds), (2) direct portal vein to caudal vena cava shunt, (3) direct portal vein to azygos vein shunt, (4) combination of portal vein with caudal vena cava into azygos vein shunt, (5) left gastric vein to vena cava shunt (common in cats and many small breed dogs), (6) portal vein hypoplasia or atresia with secondary multiple portosystemic shunts (comparatively rare), and (7) anomalous malformations of the caudal vena cava (rare). Additional subclassifications of PSVA are clinically useful to consider; these involve the different types of vascular malformations (extrahepatic and intrahepatic histologic lesions) in an individual.

Most animals with PSVA are diagnosed at a young age (4 weeks to 2 years), although some dogs have been 13 years of age at first diagnosis. There is no sex predilection. In dogs, Terrier breeds, especially Yorkshire Terriers, Maltese, Cairn Terriers, and several others, are commonly afflicted. Families of dogs have been studied in which a genetic predisposition is obvious (e.g., Yorkshire Terriers, Cairn Terriers, Tibetan Spaniels, Maltese, Havanese, Shih Tzu, Miniature Schnauzers, Irish Wolfhounds, and Scottish Deerhounds).

Although not commonly appreciated, not all dogs with PSVA are symptomatic. Most symptomatic dogs are "unthrifty" in appearance and often are the litter "runt." If not stunted early, most fail to keep up with growth expectations. Neurobehavioral signs (hepatic encephalopathy [HE]) may manifest early during the first few weeks of life owing to hypoglycemia (especially in toy breeds). Signs of HE also may manifest as the puppy or kitten is weaned onto growth-formulated diets from milk or when older animals are cutting teeth and swallowing blood. Failure to demonstrate overt signs of HE in the neonatal period relates to the protein and carbohydrate composition of the milk diet. Signs of HE are episodic and typically associated with meals. However, enteric parasitism can also provoke neurologic signs as a result of enteric inflammation and bleeding. Blood within the intestinal canal is highly encephalogenic in patients prone to HE. Neurobehavioral signs may involve propulsive circling, amaurosis (unexplained transient blindness), dementia (head pressing, staring, vocalizing), aggression (especially in cats), seizure, lethargy, or coma. Gastrointestinal signs may include anorexia, vomiting, constipation (worsens HE), diarrhea, or ptyalism (excessive salivation, in cats especially, often confused with upper respiratory tract infection). Urinary tract signs may include abnormally increased water consumption and increased urine production (polydipsia/polyuria) as a result of the effect of neurologic toxins or dysfunctional hepatic osmostats. Dogs with PSVA often have a markedly increased glomerular filtration rate (GFR) owing to their remarkable water flux. Ammonium biurate urolithiasis may cause stranguria or dysuria and hematuria. Rarely acute abdominal pain reflects ureteroliths. Fever (intermittent) may occur as a result of circulatory bypass of the hepatic reticuloendothelial system that normally provides immune surveillance against infectious material transported from the gut. Intolerance to certain drugs requiring hepatic biotransformation or first-pass elimination may be noted at the time of neutering (general anesthesia) or when anticonvulsant medications are needed to control seizure activity. Animals with PSVA become extraordinarily ill when challenged by infectious disorders (e.g., abscess, puncture wound, rickettsial infections).

Physical findings usually include a small body stature and unthrifty appearance. Abdominal palpation often discloses prominent kidneys. Large kidney size may relate to increased GFR, renal gluconeogenesis, and other designated metabolic functions not normally conducted by the kidney, as well as renal cell hypertrophy induced by high ammonia concentrations. Rarely cystic calculi are palpated. A unique copper-colored iris is observed in non–blue-eyed cats (Figure 37-3); this color is similar to the eye color in Persians and thus must not be interpreted out of context.

Major clinicopathologic features associated with PSVA include poikilocytes in cats (irregularly irregular erythrocytes); red blood cell microcytosis (small cells); low concentrations of blood urea nitrogen, creatinine, cholesterol, and glucose; variable liver enzyme activity and protein concentration; and ammonium urate crystalluria. However, some animals have few or none of these findings. Liver function assessments should include a provocative endogenous SBA challenge and use of the recently described protein C test. The protein C test involves measurement of an anticoagulant protease that depends on the liver and portal circulation for normal regulation. This test can help differentiate MVD from PSVA and thus assists in prioritizing expensive and invasive assessments.

Survey abdominal radiographs usually disclose a small liver and large or prominent kidneys. Urinary calculi usually are not radiodense. Abdominal ultrasonography usually discloses a small homogeneous liver. The anomalous shunting vessel may be identified, depending on operator skill. Color-flow Doppler allows detection of unusual turbulence in the vena cava cranial to the phrenicoabdominal vessels in most extrahepatic PSVAs. Intrahepatic PSVA is most easily visualized. The intrahepatic portal distribution often appears

Figure 37-3 Copper-colored iris of a cat with a portosystemic vascular malformation.

hypovascular in animals with PSVA; however, some patients have partial hepatic perfusion, and these lobes may not appear hypovascular. Renal pelvic and cystic calculi, sand, or overt uroliths (rarely ureteral) may be identified.

Colorectal scintigraphy with a technetium pertechnetate-labeled enema is the least invasive method of documenting portovenous hepatofugal perfusion. A computer-linked gamma-camera records portal distribution of isotope either to the heart (shunt) or liver (no shunt present) within 3 minutes. This noninvasive technique usually confirms PSVA macroscopic shunting. Unfortunately it is unable to describe anatomic shunt location, to verify multiple (acquired shunts) versus single congenital shunts, and may miss shunts in very petite patients, splenic vein to azygos vein shunts, and shunts occluded by visceral compression while the patient is in lateral recumbency. Radiographic contrast portovenography is the "gold standard" for PSVA confirmation (Figure 37-4). Various methods have been described, including (1) mesenteric vein cannulation (requires surgery), (2) splenic vein cannulation (surgery or ultrasound guided), (3) splenic pulp injection (percutaneous, ultrasound guided, or surgical; may cause infarcts/infection/hemorrhage), (4) arteriography via cannulation of the anterior mesenteric artery through the femoral artery (fluoroscopy directed, contrast dilution impairs strong shunt visualization), and (5) nonselective venography by rapid bolus jugular vein injection of contrast (useful only in very petite patients as contrast dilution is a problem). Mesenteric vein cannulation during exploratory laparotomy is most commonly used. Both right and left lateral recumbency portograms and a ventrodorsal portogram are used to verify that a PSVA has not been missed (Figure 37-5). Many extrahepatic PSVAs are better visualized on a single lateral projection; the side of best imaging is inconsistent. Left gastric vein shunts can resemble the

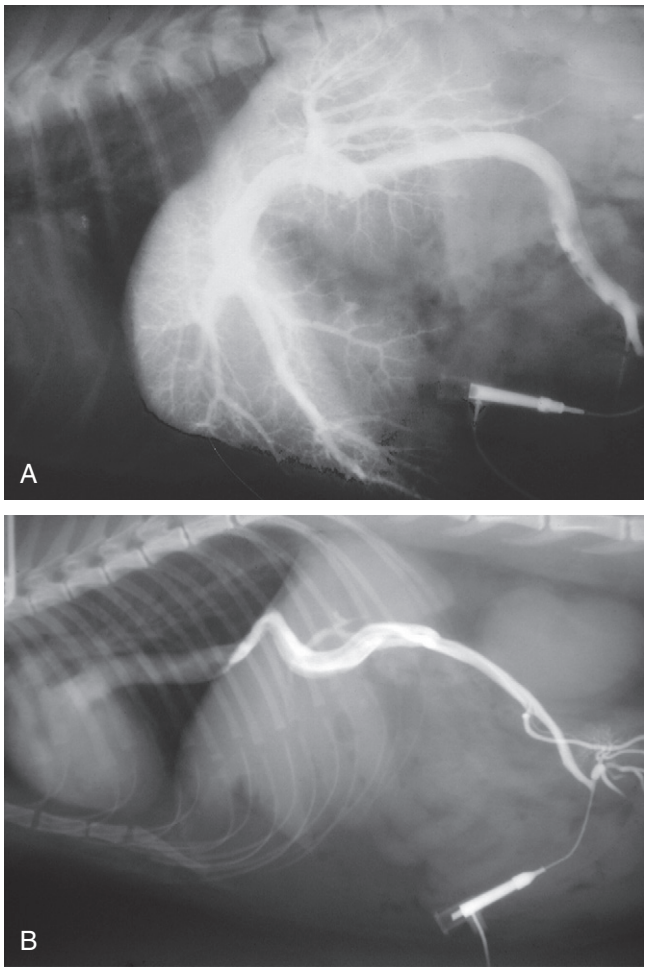

Figure 37-4 **A,** Portogram completed in a healthy dog with normal bile acid values. **B,** Mesenteric portogram in a cat with a left gastric vein shunt. Note the absence of contrast in the hepatic portal vasculature.

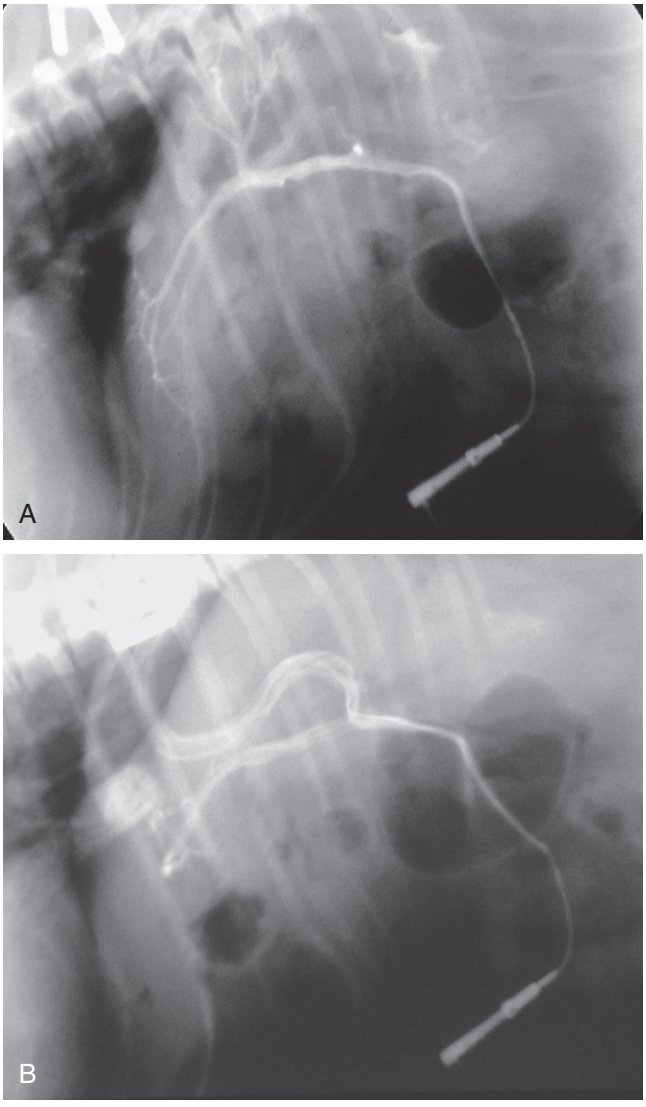

Figure 37-5 Positive contrast portograms of the same dog with a portosystemic vascular anomaly in right and left lateral recumbency. This study demonstrates how single-sided recumbency can fail to demonstrate shunting vasculature. So-called "portal streaming" or simply shunt compression by visceral structures explains these findings. **A,** Right side down. **B,** Left side down.

shape of a ductus venosus on lateral radiographs, each having an S or Z shape. A helpful but imperfect general rule is that intrahepatic PSVA can be differentiated from extrahepatic PSVA by location relative to the thoracolumbar spine. Most intrahepatic PSVAs have their caudal extent cranial to T13, whereas most extrahepatic PSVAs have their caudal extent caudal to T13.

Contrast multisector computed tomographic portograms provide the most informative studies for distinguishing aberrant portal vasculature. Equipment is costly and at present limited to large specialty facilities.

Generally these patients are referred for ligation of a PSVA, which is the definitive treatment for dogs demonstrating clinical signs. However, based on findings in the large genotyping study previously cited, clinical experience with dogs serendipitously discovered to have a PSVA at more than 9 years of age (asymptomatic dogs) and dogs managed medically long term (8 years), it is clear that not every dog with PSVA requires surgery. Furthermore, some dogs undergoing PSVA ligation cannot accommodate increased hepatic portal perfusion and develop multiple acquired shunts. A scheme explaining surgical outcomes relative to PSVA/MVD malformations is summarized in Table 37-4. Extrahepatic PSVAs are more amenable to surgical attenuation than many intrahepatic PSVAs (right divisional are more accessible than left divisional). Intravenous coils for occlusion of ductus venosus offer a new treatment option for intrahepatic PSVA. Success of PSVA surgical attenuation in cats is lower than in dogs. Placement of ameroid constrictors in cats is contraindicated because of the dismal response to full PSVA ligation. The general discussion that follows applies wholly to dogs.

Excellent outcome was found in 80%, good outcome in 14% (15/108;13 requiring a protein restricted diet, 1 requiring long term antimicrobials for HE, and 1 with grand mal seizures), and poor outcome in 7/108 dogs (6%, 6 dogs died of PSVA, 1 dog failed to improve clinical signs).

Medical management of PSVA is aimed at minimizing signs of HE and encompasses manipulation of dietary protein, modification of enteric flora, and avoidance of medications or substances augmenting or inducing encephalopathic signs. Careful regulation of dietary protein intake is critical. For dogs, a restricted protein diet (2.2 to 2.5 gm protein/kg body weight) derived chiefly from dairy and soy protein sources is best. Some dogs also tolerate chicken (white meat). Commercial diets formulated for dogs with hepatic insufficiency are convenient and function well in dogs with PSVA. Supplementation of such diets with additional cheese or cottage cheese to increase protein intake by 0.5 gm protein/kg body weight can be used to individually titrate protein intake to response. Diets can be modified with assistance from the free Nutritional Analysis Tools and System website (http://nat.crgq.com/mainnat.html). Meals should be frequent and small to maximize digestion and absorption. Minimizing colonic residue is helpful as colonic anaerobes degrade nitrogenous compounds to ammonia. Dogs with inoperable PSVA (severe MVD causing intrahepatic portal atresia or extrahepatic portal atresia) have been managed for more than 3 years in the author's home without incident using commercial diets formulated for hepatic insufficiency. It is certain that dietary modification alone may be sufficient to abate clinical signs in dogs with PSVA. However, dogs with persistent ammonium biurate crystalluria or neuroencephalopathic signs should adjunctively receive lactulose dosed to achieve multiple soft stools per day (0.25 to 1 ml per 4.5 kg orally daily) and/or metronidazole (7.5 mg/kg body weight orally twice daily) or amoxicillin (especially cats, 2.5 mg/kg orally twice daily). Neomycin is the least desirable treatment for enteric flora modification. A small percentage of oral neomycin is absorbed and may result in renal injury or hearing loss with long-term administration. Milk can be used as an alternative for lactulose in some dogs and cats (lactose intolerance). Lactulose, a synthetic disaccharide indigestible by mammals, is fermented in the enteric canal to organic acids that acidify luminal contents. Colonic acidification promotes ammonium ion trapping, which reduces ammonia uptake into the portal circulation. Colonic acidification also inhibits enteric urease and protease activities. Organic acids promote bacterial nitrogen fixation and impose an osmotic catharsis (frequent soft stools) that promotes colonic evaluation of toxic substrates and products. If a commercial diet formulated for dogs or cats with hepatic insufficiency is used, additional vitamin supplements are not urgent. If a homemade diet is used, additional vitamins are recommended, taking care to avoid methionine supplements. Most dogs with PSVA have subnormal liver zinc concentrations, suggesting systemic zinc insufficiency. Zinc supplementation (1 to 2.5 mg elemental zinc/kg body weight/day) is recommended because zinc is essential for certain metalloenzymes (e.g., urea cycle). Zinc acetate is most commonly used (31% elemental zinc of formula weight) and can be compounded from Galzin (Gate Pharmaceuticals, North Wales, PA).

Medical and surgical management of minimally symptomatic patients is usually good. However, dogs with degenerative and nonsuppurative inflammatory lesions involving the hepatic venule may develop a progressive hepatopathy whether or not they undergo surgical treatment. Dogs with continued portosystemic shunting have increased susceptibility to systemic infections because of reduced function of hepatic macrophages. Thus prompt treatment must be provided for small wounds, cutaneous infections, and urinary tract infections. Attention also must be given to avoid conditions that can promote HE; these promiscuously expose patients to endogenous systemic or enteric toxins, nitrogen challenge, or promote dehydration and azotemia. Constipation must be avoided as colonic contents are an important toxin source contributing to HE. Management of acute severe HE requires mechanical cleansing of the colon with warm polyionic fluids until fecal debris is clear. Thereafter, instillation of a retention enema is used to modify enteric pH, flora, urease, and protease activities. Lactulose is the preferred retention enema solution. Dehydration, hypoglycemia, and electrolyte aberrations must be corrected.

TABLE 37-4 Malformations associated with extrahepatic and intrahepatic portosystemic vascular anomalies

	Single aberrant extrahepatic portosystemic communication	Two aberrant portosystemic shunts	MVD: attenuated intrahepatic portal tributaries (variably reduced flow to full atresia)	MVD: abnormal location and flow through hepatic venule: lobule outflow obstruction	Poorly developed extrahepatic portal vein (porta hepatis): extrahepatic portal hypoplasia	No extrahepatic portal vein in porta hepatis: portal atresia	Acquired portosystemic shunts	Ductus venosus, right or left divisional branch	Projected outcome: with successful surgical ligation*
Type 1	+	+/–	–	–	–	–	–	–	1
Type 2	+	+/–	+	–	–	–	– (possible with ligation)	–	2 or 3
Type 3	+	+/–	+	+	–	–	+/– (+ with ligation)	–	2, 3, or 4
Type 4	+	+/–	+	–	+	–	+/– (+ with ligation)	–	3, 4, 5
Type 5	+	+/–	+/–	–	–	+	+	–	4, 5
Type 6	–	–	–	–	–	–	–	+	1
Type 7	–	–	+	–	–	–	–	+	2 or 3
Type 8	–	–	+	–	–	–	+	+	4, 5

*"Cured" = 1; improved but retains high SBA = 2; requires medical Rx, retains high SBA = 3; no change = 4; worsened = 5.

Intrahepatic arteriovenous fistula

Congenital intrahepatic arterioportal fistulae unite a branch of the hepatic artery and portal vein and are uncommon malformations in the dog and cat. These vascular aberrations represent abnormal differentiation of the embryologic capillary plexus into arteries (sprouting) and veins (pruning). Arteriolarization of the portal venous system results in portal hypertension, development of multiple acquired portosystemic shunts, and commonly development of a transudative abdominal effusion. Nonhepatic systemic arteriovenous (AV) fistulae create a short circuit of arterial blood to the heart causing cardiac failure, effects analogous to the physiologic sequela of a chronic patent ductus arteriosus. However, when located in the liver, hepatic sinusoids impose hemodynamic resistance, blocking direct circulatory return of shunted arterial blood. Such patients do not develop cardiac sequela, but rather present with gastrointestinal signs (vomiting, diarrhea, melena) and HE. Age at initial diagnosis is usually within the first 2 years.

With the exception of abdominal effusion, historical, physical, and clinicopathologic findings resemble those affiliated with PSVA. All animals demonstrate high SBA concentrations and ammonium biurate crystalluria (examine three or more urine specimens). Abdominal ultrasonography equipped with color-flow Doppler rapidly identifies these malformations, AV admixture, and hepatofugal portal circulation. Liver lobes directly involved with the AV malformation are normal to large in size, and those distant to the malformation are atrophied. Contrast radiographic imaging of hepatic AV malformations requires injection into the anterior mesenteric or hepatic artery or into the jugular vein in very small patients. On inspection, affected liver lobes are prominent and may have numerous pulsating surface vessels. A continuous murmur accentuated during systole may be auscultated near the lesion. Palpation of the area may reveal a thrill.

Treatment of an intrahepatic AV fistula requires ligation of the nutrient artery and/or obliteration of the aberrant AV communication(s). Traditionally this has been accomplished by surgical resection of large malformations by hepatic lobectomy, ligating involved vessels, and/or establishing normal circulatory communications by vascular anastomosis. Caval banding, attempted in some dogs with intrahepatic AV fistula to rectify portosystemic shunting, provides no benefit and should not be done. Outcome to surgical interventions is poor, with many dogs dying during surgery or shortly thereafter; several dogs have developed portal venous or mesenteric thrombi. A small number of dogs have markedly improved with surgical procedure, which may reflect the nature of their AV malformations (location, distribution). It is common for survivors to manifest continued portosystemic shunting, recurrent abdominal effusion, and episodic HE. Medical management may require diuretics (furosemide combined with spironolactone) in conjunction with dietary sodium restriction to manage ascites and protein restriction (commercial diet for hepatic insufficiency) for episodic HE. Recent review of 22 dogs with hepatoportal AV fistula (treated surgically, with cyanoacrylate embolization, or both) had a dismal 25% good long-term outcome; 75% required continued diuretic therapy and/or dietary management for HE.

Neonatal Jaundice

There are no well-documented cases of inborn errors of bilirubin metabolism in dogs or cats causing neonatal jaundice. However, neonatal puppies have UDP-glucuronyl transferase activity (enzyme essential for bilirubin catabolism) lower than adult dogs. Activity of this enzyme matures within 28 to 42 days of age. Neonatal jaundice has been reported as a result of immunohemolytic anemia in puppies and kittens and in kittens with a hemolytic syndrome associated with neonatal isoerythrolysis. Neonatal isoerythrolysis may occur when kittens of type A or AB receive colostrally delivered anti-A alloantibodies from a type B dam.

Congenital Metabolic Abnormalities

Congenital disorders affecting the function or availability of lysosomal enzymes or effector proteins (activatory or protector proteins) necessary for catabolism of glycoproteins, glycolipids, glycosaminoglycans (mucopolysaccharides), gangliosides, and glycogen have been identified in humans and animal species, including the dog and cat. Such disorders cause tissue accumulation of undegraded storage products that impair organ or tissue structure and function with progressive clinical signs first emerging at a young age. Hepatomegaly is associated with some of these disorders when storage material accumulates in hepatocytes and/or Kupffer cells (fixed macrophages). A brief description of lysosomal storage disorders that may involve the liver, recognized in dogs and cats, is summarized here (Table 37-5).

Mannosidosis (deficiency in acid mannosidase) causes hepatomegaly, neurologic dysfunction (tremors, ataxia, hypermetria, and weakness), growth retardation, facial dysmorphia, and early death. Hepatic vacuolation is associated with membrane-bound mannose containing pentasaccharide. Demonstration of reduced intracellular alpha-mannosidase is diagnostic.

The mucopolysaccharidoses (MPS) are lysosomal enzyme defects impairing degradation of various glycosaminoglycans (connective tissue matrix components including dermatan sulfate, heparan sulfate, or keratan sulfate). Clinical features vary with the specific enzyme deficiency. Clinical features vary with different disorders and may include facial dysmorphia (rounded broad forehead, small ears, and dished face), corneal opacity, bone lesions (odontoid hypoplasia, vertebral exostoses, osteoporosis, coxofemoral luxation, lytic lesions in long bones and vertebrae), intervertebral disk degeneration, degenerative joint disease causing joint effusions and lameness, cardiac murmurs, growth retardation, neurologic abnormalities (i.e., cervical or thoracolumbar myelopathy, mental retardation), and early death. Metachromatic granules in leukocytes may also be recognized. Presumptive diagnosis of MPS is made based on a positive urine toluidine blue spot test, but definitive diagnosis is only confirmed on measurement of specific enzymes in fresh plasma, cultured

TABLE 37-5 Hepatic storage of glycosaminoglycans in feline and canine models of mucopolysaccharidoses I, VI, and VII

Disorder	Species	Deficiency	Hepatomegaly	Hepatocyte change	Other tissues affected
Mannosidosis	Cat	Alpha-mannosidase	Yes	Vacuolation of hepatocytes with mannose containing pentasaccharide storage material	Neurons; severe neurologic signs
Mucopolysaccharidosis (MPS) I	Dog (Plott Hound, other single cases), DSH Cat	Alpha-*L*-iduronidase	Yes	Vacuolation of hepatocytes and Kupffer cells with MPS storage material	Facial dysmorphia, corneal opacity, osseous lesions, vertebral exostoses, intervertebral disk degeneration, degenerative joint disease, stunted growth, metachromatic granules in WBC, neurologic abnormalities, early death
MPS II: Hunter syndrome	Labrador Retriever	Iduronate sulfatase	Yes	Vacuolation of hepatocytes, biliary epithelium, sinusoidal lining cells, and hepatic macrophages with MPS storage material	Similar facial deformity but lack of bone effects as in MPSI; very slowly progressive neurologic syndrome (5 years)
MPS IIIa, San Filippo syndrome	Wirehair Dachshund, Huntaway Dog	Heparan *N*-sulfatase		Fine foamy vacuolation of hepatocytes with discrete membrane bound material, similar vacuolation in macrophages	Progressive neurologic syndrome
MPS IIIb	Schipperke	α-*N*-acetylglucosaminidase	Yes	Vacuolation of hepatocytes and Kupffer cells and many other tissues with MPS storage	Lethargy, mental dullness, gradual onset neurologic signs (tremors, vestibular signs), lack of bone effects
MPS VI	Siamese, DSH cats, Miniature Pinscher, Welsh Corgi, Chesapeake Bay Retriever, Miniature Schnauzer	*N*-acetyl glucosamine 4-sulfatase, (arylsulfatase B)		Vacuolation of hepatic macrophages	Facial dysmorphia, short stature, reduced bone growth, arthritis, corneal clouding, but variable clinical signs with different mutations
MPS VII	DSH Cat, German Shepherd Dog	B-Glucuronidase			
Glycogen storage disease (GSD) Ia (von Gierke disease)	Maltese	Glucose-6-phosphatase	Yes	Vacuolation of hepatocytes with glycogen and lipid	Early onset clinical signs with neuroglycopenia causing failure to thrive, collapse, and seizures
GSD II (Pompe disease)	Swedish Lapland dogs	Lysosomal alpha-glucosidase	No	None described	
GSD III, Cori disease	German Shepherd Dog, Curly-Coated Retriever	Glycogen debranching enzyme	Yes	Hepatocyte vacuolation due to glycogen accumulation	

Hepatic storage of glycosaminoglycans in feline and canine models of mucopolysaccharidoses I, VI, and VII, *Vet Pathol* 29(2):112-119, 1992.

dermal fibroblasts, or leukocytes. Practically, only symptomatic treatment for bone pain caused by skeletal deformities can be offered.

Gangliosidosis, caused by the lysosomal accumulation of incompletely catabolized gangliosides or glycolipids, has been documented in both dogs and cats. Affected animals develop neurologic signs as early as 2 to 3 months of age (progressive fine generalized muscle tremors, ataxia, and paresis) associated with ganglioside accumulation in the central nervous system. Visceral organs, including the liver, also accumulate membrane-bound cytoplasmic bodies microscopically characterized as multilamellar spherical cytoplasmic inclusions.

Glycogen storage disorders (GSDs) have been diagnosed in Maltese dogs (type Ia, defective glucose-6-phosphatase, von Gierke disease), Swedish Lapland dogs (lysosomal acid α-glucosidase deficiency, GSD II, Pompe disease), German Shepherd Dogs and Curly-Coated Retrievers (glycogen debranching enzyme, GSD III, Cori disease); and English Springer Spaniels (phosphofructokinase deficiency, GSD VII, Tarui disease). Only the GSD I and GSD III syndromes cause symptomatic hypoglycemia and profound hepatocyte engorgement with glycogen.

In Maltese dogs with GSD Ia (autosomal recessive trait), puppies have abdominal distention as a result of profound hepatomegaly at birth. Clinical signs attributable to symptomatic hypoglycemia develop within a few days (weakness, failure to nurse, mental dullness, and seizures). Puppies surviving beyond several weeks have poor growth rates, delayed development of neurological reflexes, and are difficult to wean to solid food. Abdominal ultrasonography reveals a diffuse hyperechoic hepatic parenchyma as a result of accumulation of glycogen and fat in hepatocytes. Clinicopathologic features include hypoglycemia, hyperlactacidemia, hypercholesterolemia, and hypertriglyceridemia. At death, the liver is grossly large and pale. Histologically, hepatocytes are markedly distended by vacuolar retention of glycogen and fat. A specific genetic defect has been characterized; carriers (heterozygotes) manifest no clinical effects.

Curly-Coated Retrievers with deficiency of glycogen debranching enzyme (GSD III, autosomal recessive trait) are identified at 6 to 9 months of age based on increased liver enzyme (alanine transaminase [ALT], AST, ALP) and inconsistently on CK activity. Fasting and postmeal serum bile acids, cholesterol, and triglyceride concentrations are normal. Clinical signs are mild in the first year of life but become overt with age and include lethargy, exercise intolerance, and episodic hypoglycemia (collapse and unresponsiveness). Grossly livers are friable, large, dark red, and have a finely irregular surface. Liver lesions include a diffuse vacuolar hepatopathy (hepatocyte glycogen retention). There are no fatty vacuoles nor necroinflammatory or fibrotic lesions. Carriers manifest no clinical effects. A specific genetic defect has been characterized, and a polymerase chain reaction (PCR)-based DNA test is available.

Canine GSD IIIa (glycogen debranching enzyme deficiency) reported in a family of German Shepherd Dogs was more severe than the disorder characterized in Curly-Coated Retrievers, with illness manifesting in puppies (lethargy, muscle weakness, hepatomegaly, and growth retardation). Disease severity limited survival to 15 months of age. Accumulated glycogen caused hepatomegaly and dysfunction in skeletal, cardiac muscle, smooth muscle, and the central nervous system (glia and neurons). Although the genetic defect has not been characterized, it is speculated to totally abrogate glycogen debranching enzyme function.

Copper Storage Hepatopathy

Bedlington Terriers have an autosomal recessive mutation causing an age-related accumulation of hepatic copper that causes a progressive hepatopathy and liver failure. A 13-kilobase pair deletion in the *COMMD1* gene (chromosome 10) has been verified in European dogs, and a PCR diagnostic test has been developed. Other *COMMD1* mutations exist in some affected Bedlington Terriers. Other chronic hepatopathies in dogs also may be associated with excess liver copper retention; these generally do not manifest in dogs less than 1 year of age, and it is not clear that copper retention in these dogs is an epiphenomenon of hepatocyte injury, relates to excessive dietary copper intake, or is a causal factor (West Highland White Terrier, Dalmatian, Labrador Retriever, Doberman Pinscher).

Copper, an essential component of certain metalloenzymes, is absorbed from food, circulates bound to plasma proteins, and is taken up into the liver. A complex hepatocellular copper transport system (chaperones, binding proteins, membrane transporters) disperses copper to essential storage sites and excretes excess copper into canalicular bile. In health, these mechanisms ensure a neutral copper balance with reasonable copper ingestion. Excess hepatic copper retention is easily identified in liver biopsies with copper-specific stains (e.g., rhodanine, rubeanic acid). However, hepatocellular copper excess must be verified by reconciliation of copper-specific stains and quantitative tissue copper measurements (expressed on a dry weight basis). Excessive hepatocellular copper leads to organelle and cell membrane oxidative injury and lysosomal degranulation causing cell necrosis, and a progressive hepatopathy. Initial injury occurs in zone 3 (centrilobular, periacinar). Dogs homozygous for the mutation develop a progressive hepatopathy that may become evident during the first year of life (high serum ALT activity). However, most affected dogs develop a progressive diffuse hepatopathy evident after several years of life. Homozygous normal and heterozygous carrier dogs usually have hepatic copper concentrations in the normal range (≤400 μg/g dry weight liver), whereas homozygous affected dogs develop increased hepatic copper concentrations during the first year. Hepatic copper concentrations greater than 2000 μg/g dry tissue are consistently associated with morphologic and functional evidence of a progressive hepatopathy that may proceed to cirrhosis without treatment. Older affected animals may develop hepatic copper concentrations greater than 10,000 μg/g dry tissue. Many affected dogs can be identified as early as 6 months of age based on hepatic biopsy

(copper granule accumulation) and metal quantification before histologic evidence of hepatocellular injury. Some dogs require as long as 1 year before accumulating excessive hepatic copper. Although affected Bedlington Terriers may have evidence of increased hepatic copper as early as 8 to 12 weeks of age, biopsy at this age is unreliable for discriminating affectation status.

Copper-associated hepatopathy in Bedlington Terriers should be suspected in any individual with persistently high ALT activity. Although definitive diagnosis requires liver biopsy, genetic testing is useful in families with the characterized mutation. Measurement of serum or urine copper or ceruloplasmin (copper transport protein) concentrations does not have diagnostic value. In dogs with chronic copper-induced liver injury, hepatic mass replacement with fibrous tissue and regenerative nodules decreases the concentration of copper measured in sampled liver.

Life-long treatment with a copper chelator such as D-penicillamine or with zinc acetate that blocks enteric copper uptake is necessary for homozygous affected dogs. D-Penicillamine chelates copper within the circulation, promotes cupruresis, and provides antiinflammatory effects. A recommended dosage of D-penicillamine is 10 to 15 mg/kg body weight given orally every 12 hours 30 minutes before feeding. The most common adverse effects are vomiting and anorexia mitigated by initial dose reduction and gradual retitration and dose administration with food. If D-penicillamine is not tolerated, 2,2,2 tetramine may be used as an alternative chelator; 5 to 7 mg/kg is given orally every 12 hours 30 minutes before feeding. Vitamin C is contraindicated in liver disease associated with transition metal accumulation (copper, iron) because it may enhance oxidative injury. Pyridoxine supplementation (5 to 25 mg/day) is recommended with long-term D-penicillamine therapy. Vitamin E (10 IU/kg body weight/day) and S-adenosylmethionine (20 mg/kg body weight/day given orally on an empty stomach) are recommended antioxidants for dogs with excess hepatic copper storage. Prednisolone administration is not advised unless a dog is suffering a necrolytic or hemolytic copper crisis or an immune-mediated inflammatory process coexists. Dietary copper intake should be restricted to less than 5.0 ppm (dry matter basis) or no greater than 0.4 mg copper/day for a Bedlington Terrier. The amount of copper in commercial dog foods is variable, and the manufacturer should be contacted for specific information. Copper in the drinking water should not exceed 0.2 ppm (0.2 µg/L), especially if chelation therapy is the mainstay of therapy. It is prudent to avoid domestically softened water passing through copper pipes as this may contribute copper during initial flushing each day. Vitamin supplements should be investigated to determine their copper content before daily use. Nutritional support using home-cooked copper-restricted diets (e.g., avoiding organ meats, nuts, shrimp, and legumes) and commercial diets manufactured for dogs with liver disease have been successfully used in affected Bedlington Terriers. The reader is referred to the U.S. Department of Agriculture (USDA) food tables to ascertain copper content in basic foods (http://www.nutritiondata.com/ or http://www.nal.usda.gov/fnic/foodcomp/Data/SR18/nutrlist/sr18w312.pdf). Dietary adjustments (energy, protein content) can be made using the NAT 2 freeware at the University of Illinois (also linked to the USDA food tables) at http://nat.crgq.com/mainnat.html.

Abnormal Urate Catabolism in Dalmatians

Dalmatians are predisposed to urate urolith formation as a breed-specific genetic disorder associated with hyperuricemia and hyperuricuria. Whereas normal dogs metabolize uric acid, a product of purine degradation, to water-soluble allantoin via hepatic uricase, all Dalmatians have an autosomal recessive defect in purine metabolism resulting in hyperuricosuria (ten- to twentyfold greater than other pure or cross-breed dogs). Defective membrane transport of urate compromises hepatocyte and renal tubular epithelium to uptake urate. The Dalmatian defect involves abnormal urate transport across cellular membranes. Although the molecular basis for the disorder is unresolved, the trait is linked (microsatellite linkage studies) to chromosome 3 (CFA03). The current hypothesis is that a promoter of urate membrane transport, made in the liver, is dysfunctional or absent.

Urinary excretion of uric acid in Dalmatians ranges between 400 and 600 mg/24 hours versus 10 to 60 mg/24 hours in non-Dalmatian dogs. Urinary uric acid/creatinine ratios range between 0.3 to 0.6 for normal puppies and 1.3 to 4.6 for Dalmatian puppies at 3 to 7 weeks of age and between 0.2 to 0.4 for normal dogs and 0.6 to 1.5 for adult Dalmatians. Although not all Dalmatians develop symptomatic urolithiasis, males have greater risk owing to their urogenital anatomy. Urate stones in Dalmatians often involve hundreds of very small stones that act as a conglomerate obstructing the penile urethra.

Treatment of dogs with symptomatic urate urolithiasis includes increasing their daily water intake (wet food), urinary alkalinization (increases urate solubility, goal pH between 6.5 and 7.0), dietary modification (reducing intake of urate precursors), titrated dosing with allopurinol (dosing based on uric acid urinary excretion), and scrotal urethrostomy (for males with recurrent obstruction despite medical strategies). Dietary modification involves selection of foodstuffs low in purines rather than focusing on protein restriction. Foods low in purines include bread and cereal (except whole grains), most vegetables excluding cauliflower, spinach, peas, mushrooms, and legumes (kidney beans, navy beans, lima beans, and lentils), fruit (avoid acidic citrus), nuts, pasta, eggs, cheese, milk, and butter. Foods with moderate purine content or risk include most poultry (chicken, turkey), fish and shellfish (except mussels and scallops), lamb, pork, and beef, oats and oatmeal, wheat germ and bran, and whole grain breads. Foods with high purine or risk include those noted above and organ meats (kidneys, liver, brains, hearts), game meats (venison, duck, goose), high purine seafoods such as sardines and mackerel, yeast (including brewer's yeast), and gravies made from organ meats. There are few

prescription manufactured diets restrictive enough in purines to be appropriate for stone dissolution (Hills U/D); however, this diet is not an appropriate growth food for puppies. Thus affected puppies should have surgical removal of their stones as medical stone dissolution can take months (3 to 4 months is common). Allopurinol is used to inhibit xanthine oxidase, the enzyme transforming hypoxanthine to uric acid. Initial starting dose is 15 mg/kg body weight given orally every 12 hours. It is important to titrate the dose of allopurinol against the urinary uric acid concentration because inhibition of xanthine oxidase causes high urine concentrations of hypoxanthine and xanthine. Unfortunately excess urine xanthine concentrations can lead to xanthine urolithiasis. A 24-hour uric acid production test is used to titrate allopurinol dosing. All urine produced over a 12-hour interval is collected, mixed well, and an aliquot is submitted for measurement of uric acid. Optimal uric acid elimination approximates 300 mg/kg body weight/day. If output is much lower, the allopurinol dose is reduced; if output is much higher, the allopurinol dose is increased. However, scrutiny of dietary intake also is essential before recommending dose adjustments.

Hepatic Lipidosis

In a survey of histologically diagnosed liver disorders in puppies and kittens younger than 4 months of age (n = 444; see Table 37-1), hepatic lipidosis was diagnosed in 9.0%. Because most animals were evaluated for primary conditions in other organ systems or for infectious disorders, it is likely that hepatic lipidosis in this population represents a sequela of acquired nutritional inadequacies. A variety of metabolic disorders can disturb mobilization of triglycerides from the liver or enhance mobilization of peripheral fat stores to the liver. Whenever intrahepatic lipid synthesis or hepatocellular uptake of fat exceeds hepatic triglyceride dispersal, hepatic lipidosis ensues. It is well documented that the metabolic balance in juveniles is fragile. Studies have confirmed excess hepatic triglyceride accumulation in puppies born to undernourished bitches and in semistarved puppies fed only glucose at a rate of 60 kcal/kg body weight/day for 10 days. Two-month-old puppies completely starved for 24 hours also develop significantly greater hepatic triglyceride stores than normally fed control puppies. It is well established that cats have higher susceptibility to diffuse hepatic lipidosis compared with dogs. Any serious medical condition in the cat that induces anorexia can lead to diffuse severe hepatic lipid accumulation. Cytoplasmic hepatocellular vacuolation with triglycerides adversely influences hepatic function, leading to metabolic failure in affected cats. Nutritional support ensuring adequate intake of energy and protein, as well as providing essential amino acids, fatty acids, and water-soluble vitamins, is the major focus of treatment. Forced enteral feeding by gentle syringe alimentation, nasogastric intubation, or esophagostomy tube (especially cats) is necessary in most patients. Supplementation of cobalamin in B_{12}-deficient cats is essential. Oral supplementation with L-carnitine (250 mg/day, medical grade), taurine (250 to 500 mg/day), thiamine (50 to 100 mg/day), S-adenosylmethionine (190 mg/day on an empty stomach), and vitamin E (10 U/kg body weight/day) is recommended.

Selected Infectious Disorders Affecting the Hepatobiliary System

Hepatic Abscessation

Hepatic abscesses are more common in young puppies than in kittens. Hematogenous, omphalogenic, biliary, and peritoneal extension are reported sources of infecting organisms; postpartum umbilical infection is most common. After onset of clinical illness, health status deteriorates rapidly, culminating in death within 2 to 4 weeks. Occasionally seemingly healthy puppies die unexpectedly with the cause discovered on postmortem examination. Affected puppies usually range between 3 and 70 days of age and are from large litters. Although there is no evidence that individual bitches recurrently whelp litters with affected puppies, poor sanitation may be a predisposing factor. In kennels with recurrent puppy or kitten losses associated with omphalitis and liver abscessation, kennel sanitation may be the underlying cause. Isolated organisms include *Staphylococcus*, *Streptococcus*, *Salmonella*, and *Escherichia coli*. Affected neonates are usually stunted, emaciated, dehydrated, and may have abdominal distention as a result of hepatomegaly and peritonitis. Liver lobes may be adhered to one another and to adjacent viscera; there is no liver lobe predisposition. Unaffected lobes often have randomly distributed multiple foci of microabscesses and necrosis.

Liver Flukes

Hepatic trematode infection has been diagnosed in kittens as young as 4 months of age. The most common liver fluke in cats in North America is *Platynosomum concinnum*. Other species of flukes that may infect cats include *Amphimerus pseudofelineus*, *Opisthorchis tenuicollis*, *Metorchis albidus*, and *Metorchis conjunctus*. The life cycle of *P. concinnum* requires a tropical to semitropical climate and two intermediate hosts: a land snail (*Subulina octona*) and a lizard or marine toad. Cats acquire infection by ingestion of the second intermediate host. Once ingested, the parasite migrates up the common bile duct into the gallbladder, bile ducts, and pancreas. In 8 to 12 weeks, adult flukes produce embryonated eggs that are passed in feces. Recognition of fluke eggs in feces (fecal sedimentation) is the basis of definitive diagnosis. Clinical signs of liver injury are apparent by 7 to 16 weeks after infection and may include lethargy, inappetence, weight loss, emaciation, hepatomegaly, mucoid diarrhea, vomiting, and abdominal tenderness. The severity of clinical signs varies with the degree of the fluke infection; many naturally infected cats show no clinical signs. In experimentally infected cats, 62% returned to normal clinical health in 24 weeks without treatment. In heavily infected cats, clinical signs may develop before fecal shedding of ova. Circulating eosinophilia may develop and peak at 4 to 5 months after infection. Transient increases in serum AST and ALT

activity develop during fluke migration through the liver. Serum ALP and GGT activities may remain normal or may increase depending on the numbers of developing flukes and the extent of invasion and obstruction of biliary structures. Cats with heavy fluke infection may become jaundiced, albeit some only transiently, as a result of biliary tree obstruction. Flukes within the gallbladder can be visualized ultrasonographically as hypoechoic foci. Histologic lesions in hepatic parenchyma and biliary structures include leukocyte infiltration, adenomatous hyperplasia of biliary structures, and periportal and periductal fibrosis. Chronic fluke infestation and bile duct obstruction may result in biliary cirrhosis. On postmortem examination, gross lesions may be absent; when apparent, enlargement of the gallbladder and bile ducts is found. Adult flukes and eggs are demonstrable in bile and within biliary structures. Treatment with praziquantel (20 to 40 mg/kg daily for 3 days) eradicates fluke infestation.

Canine Herpesvirus

Infection with canine herpesvirus causes an acute, rapidly fatal illness associated with hepatic necrosis. Puppies may have predisposition as a result of their poor thermoregulation and inability to mount a febrile response. Herpesvirus is not stable in the environment and must be acquired from a persistently infected carrier. Infection can be acquired in utero, during passage through the birth canal, by exposure to infected littermates, from oronasal secretions of the dam, or by fomite transmission. Abortions and stillbirths may follow in utero infections. Generalized, fatal infections develop in puppies exposed when less than 1 week of age. Puppies exposed when older than 2 weeks are comparatively resistant and often develop mild or inapparent infection. Diffuse necrotizing vasculitis and spread of virus into parenchymal organs, including the adrenal glands, kidneys, lungs, spleen, and liver, result in multifocal organ necrosis. Thrombocytopenia develops associated with disseminated intravascular coagulation as a result of the vasculitis and/or immune-mediated mechanisms. Meningoencephalitis is common, although puppies infected at less than 1 week of age usually die before neurologic signs develop. Survivors that had neurologic signs may have permanent neurologic deficits, most commonly cerebellar vestibular deficiencies. Ocular involvement may cause panuveitis, cataracts, keratitis, retinitis, and subsequent blindness.

Clinical signs of herpesvirus infection in puppies may include lethargy, decreased suckling, persistent crying, yellow-green diarrhea, rhinitis, abdominal pain, and incoordination. A distinct feature is the absence of fever. Petechial hemorrhages may be notable on mucous membranes and provide testimony to the thrombocytopenia and vasculitis associated with viremia. Death frequently occurs within 24 to 48 hours after onset of clinical signs in puppies less than 3 weeks of age. Puppies older than 3 to 5 weeks of age at exposure may develop only mild or inapparent infections. Passage of maternal protective antibodies or lymphocytes in colostrum can prevent illness in neonates.

Definitive diagnosis is made based on history, clinical signs, pathologic changes, and virus isolation. Hematologic and biochemical abnormalities are nonspecific and variable. Gross pathologic findings include disseminated multifocal 1- to 2-mm hemorrhages and areas of necrosis that are distinctly circumscribed in the liver, kidney, and lungs (Figure 37-6). Wedge-shaped renal infarcts develop subsequent to fibrinoid necrosis of interlobular arteries. Hepatomegaly, splenomegaly, and lymphadenopathy are common. Further information on systemic manifestations and treatment of herpesvirus infections can be found in Chapter 16.

Canine and Feline Parvovirus

Focal hepatitis and hepatic cord disorganization may develop in puppies and kittens infected with parvovirus. Twofold to fivefold increases in serum activity of ALT and AST may develop. In some cases, hepatic involvement is progressive, resulting in jaundice. Whether signs of hepatobiliary involvement are the result of parenchymal injury from viral infection, thromboembolic complications resulting from vascular lesions, or secondary to bacterial infection or endotoxemia (from breakdown of the gastrointestinal mucosal barrier) is unresolved. Seemingly, a poor prognosis is warranted when hepatic involvement becomes clinical (see Chapter 16).

Feline Infectious Peritonitis

Infection with feline coronavirus causing feline infectious peritonitis (FIP; herein referred to as FIPV) most often affects kittens and cats between 6 months and 5 years of age housed in a multiple-cat population. FIPV reflects a progressive and lethal coronavirus infection causing immune-mediated tissue injury. Tissue lesions are initiated by virus or viral antigen and host antiviral antibodies and complement. Humoral antibody responses increase virus pathogenicity, and cell-mediated immune responses play a decisive protective role. Effusive FIPV is thought to represent acute disease,

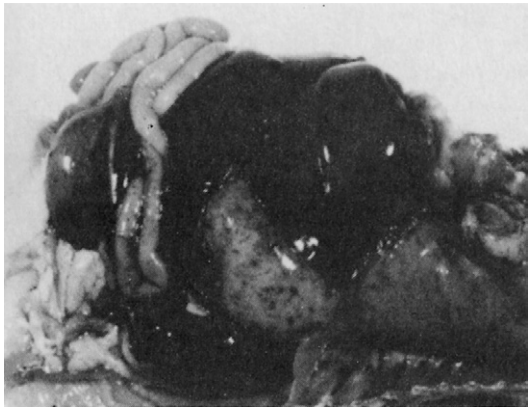

Figure 37-6 Photograph of petechial hemorrhages on visceral surfaces in a puppy with canine herpesvirus infection. Note hepatomegaly and diffusely mottled appearance of the liver associated with multifocal hepatic necrosis. (From Hoskins J: *Veterinary pediatrics: dogs and cats from birth to 6 months*, ed 3, Philadelphia, 2001, Saunders, p 217.)

occurring 4 to 8 weeks after infection or a stress-imposing event. The less common dry form of FIPV is considered to reflect a chronic form of infection. In dry FIPV, a 2- to 12-week interval of vague illness precedes initial presentation. Clinical signs include chronic undulant fever, inappetence, and weight loss. Plasma protein concentrations increase as a result of variable increases in globulins associated with an acute phase response. Coagulopathy reflects diffuse vascular injury and occurs in cats with severe inflammatory lesions or diffuse severe hepatic involvement. Coagulopathies and thrombocytopenia are more common in cats with effusive FIPV, and their presence portends a grave prognosis. Clinical signs of either syndrome ultimately depend on involved target organs. The clinical syndromes associated with FIPV are described in Chapter 16 on Viral Infections. Necrotizing hepatitis reflects immune complex–facilitated tissue injury, and lesions are associated with inflammatory perivascular cuffing. Animals with FIPV hepatitis may demonstrate anterior abdominal pain and hepatomegaly, with a subset becoming jaundiced. Serum ALT and AST activities are variably increased, ranging from twofold to tenfold normal values.

At present, diagnosis of FIPV is based on history, clinical signs, feline leukemia virus (FeLV) status, and, most importantly, histologic lesions and immunohistochemical demonstration of virus in tissue lesions or macrophages. Kittens with signs of hepatic involvement are poor candidates for immunosuppressive therapy.

Feline Leukemia Virus

Infection of kittens with FeLV may occur by vertical or horizontal transmission. By virtue of its oncogenic potential and ability to immunologically compromise its host, FeLV may be associated with neoplastic conditions and infectious disorders involving the liver of both pediatric and adult patients (e.g., see Toxoplasmosis below). Lymphosarcoma and myeloproliferative disease can develop in infected cats within weeks or months of virus exposure. Cats with hepatic neoplastic infiltrates often demonstrate nonpainful hepatomegaly. Jaundice indicates diffuse hepatic involvement or periportal infiltrates but less commonly signals impingement or infiltration of the common bile duct. Abdominal ultrasonography may or may not disclose mass lesions or foci of infiltrated regions involving hepatobiliary structures. Hematologic abnormalities may include a moderate to severe nonregenerative anemia and atypical cytology consistent with a myeloproliferative disorder or lymphosarcoma. Serum biochemical abnormalities are variable depending on the extent of hepatic involvement. Definitive diagnosis of FeLV infection is made by enzyme-linked immunosorbent assay for viral antigen or indirect fluorescent antibody labeling of infected cells. See Chapter 16 on Viral Infections.

Bordetella bronchiseptica

Accidental subcutaneous administration of attenuated live intranasal *Bordetella bronchiseptica* vaccine induces fever (within 2 days), a local inflammatory reaction at the injection site, and acute, nonseptic hepatocellular degeneration and necrosis. Chronic sustained liver injury has also been reported. Anecdotally, this accident has occurred several times in different veterinary facilities; in some cases dogs have succumbed to liver failure. Treatment with doxycycline for 3 weeks is advised. Some animals have required intravenous fluids and extended hospitalizations.

Virulent Systemic Calicivirus

Recently a highly infectious, vaccination-resistant, and virulent form of feline calicivirus (FCV) causing systemic disease and death has been described. Time from exposure to first clinical signs ranges from 1 to 12 days (median, 4 days). Affected cats show varying degrees of pyrexia, cutaneous edema, ulcerative mucositis and dermatitis, anorexia, facial and limb edema, lameness, upper respiratory signs, pulmonary edema and pleural effusion causing dyspnea, and jaundice. See Chapter 16 on Viral Infections. In one outbreak where biochemistry panels were available for 10 cats, 6 of 10 had hyperbilirubinemia (range, 0.6 to 3.9 mg/dl), and 5 of 10 had hypoalbuminemia (range, 1.1 to 2.1 g/dl). High serum enzyme activities included AST (3 of 10), ALT (2 of 10), and CK (5 of 10). Hepatic lesions include disruption of hepatic cords with hepatocyte individualization and zone 3 (centrilobular, periacinar) foci of necrosis associated with small accumulations of intrasinusoidal neutrophils and scattered intrasinusoidal fibrin deposits. Multifocal, peracute, pancreatic necrosis with adjacent fat saponification has been observed in some cats. Many clinical features and histologic lesions are associated with virus-induced vascular damage (e.g., edema, microthrombi, intrasinusoidal fibrin accumulation). Immunohistochemistry of liver tissue with anti-FCV antibody can confirm a definitive diagnosis. However, viral antigen was not discernable in hepatocytes in the initial report of virulent systemic FCV.

Strains of FCV causing virulent systemic FCV are genetically distinct from one another yet still cause similar clinical disease. Because these FCV strains are resistant to routine FCV vaccinations, cats with suspected infection should be handled with strict hygienic precautions.

Salmonellosis

Along with *Salmonella* spp., other enteric microorganisms such as *E. coli* also can be a source of hepatic parenchymal and biliary tract infection in young dogs that resembles the syndrome caused by *Salmonella*. *Salmonella* infection is associated with environmental or food or water contamination. Certain individuals are predisposed to infection by immunocompromising circumstances, such as malnutrition, parvoviral (vaccinal or field isolates) or FeLV infections, neoplasia, inherited immunoincompetence syndromes, glucocorticoid therapy, systemic or environmental stress, or neonatal life. Feeding of uncooked contaminated meat products (e.g., BARF diet), other forms of food contamination, and environmental transfer of bacteria by fomites are responsible for most infections. Puppies and kittens less than 1 year of age are more susceptible to infection and clinical illness than

adults. Neonates may acquire infection from infected secretions from their dam (e.g., vaginal discharges, placentas, meconia). In utero infection may result in fetal death, abortion, or birth of weak "fading" puppies or kittens.

Salmonella spp. may exist in dogs and cats as a part of their normal enteric flora. Positive *Salmonella* fecal cultures occur in 1% to 36% of clinically healthy dogs and 0% to 18% of clinically healthy cats. Consequently isolation from feces does not confirm pathogenic infection without serotyping. Jaundice may reflect hepatic endotoxemia, hepatic infarction (development of disseminated intravascular coagulation), or bacterial colonization of hepatic parenchyma. Very young animals manifest the most severe clinical signs; puppies and kittens less than 7 weeks of age may not have a fever despite bacteremia and endotoxemia. Biochemical evidence of liver involvement includes increased serum activity of ALT, AST, and ALP and in some cases hyperbilirubinemia and hypoglycemia. Hypoglycemia also may reflect endotoxemia. Coagulopathy reflecting disseminated intravascular coagulation develops in animals with severe systemic or hepatic infection.

Hepatic necrosis has been documented in puppies with lethal infection. In these, multifocal foci of necrosis are the most common histologic lesion. Affected livers are grossly enlarged and have a mottled appearance. Bacterial organisms may be microscopically evident on routinely stained tissue sections. Hepatic colonization can follow either a clinical or subclinical infection. Suppurative meningitis also may develop in puppies or kittens. Definitive diagnosis of salmonellosis as the cause of illness relies on bacterial culture from involved tissues or body fluids that are normally sterile. Positive culture of fecal specimens cannot confirm a causal relationship with clinical disease.

Tyzzer's Disease

Clostridium piliforme (previously *Bacillus piliformis*) is a gram-negative spore-forming obligate intracellular bacterium that can cause enteric and hepatic infection in dogs and cats. Infection is precipitated by stress (e.g., crowding, unsanitary husbandry, weaning, or transportation), irradiation, and immunosuppression (e.g., glucocorticoid therapy). All species subject to infection develop necrotizing ileitis and colitis and multifocal hepatitis. Spontaneous infections in dogs and cats are believed to follow ingestion of bacterial spores passed in rodent feces. It is undetermined whether this organism also is an enteric commensal of the dog or cat. Most infections have been observed in laboratory-reared pediatric animals at the time of weaning. Infections are facilitated by stress or factors impairing immunocompetency. Clinical disease follows proliferation of organisms in enterocytes. Infected cells degenerate and slough, causing ulcer formation that permits mucosal translocation of bacteria into the portal circulation. Wide dispersal of organisms into the liver causes multifocal bacterial hepatitis. Presenting signs of natural infection in pediatric puppies and kittens include sudden onset of lethargy, anorexia, diarrhea (small amounts), abdominal tenderness, and rarely jaundice (cats). Within 24 to 48 hours of clinical illness, hepatomegaly and abdominal distention are followed by hypothermia. Animals become nonresponsive and die shortly thereafter. Marked increases in serum ALT precede death.

Owing to the rapidly fatal course of infection, diagnosis is often made based on gross findings at necropsy. Inspection of the liver reveals many white-gray hemorrhagic 1- to 2-mm foci on the capsule and cut surfaces, with similar lesions on other viscera. The terminal ileum and proximal colon appear inflamed and thickened and contain foamy, dark-brown feces. Mesenteric lymphadenopathy is common. Definitive diagnosis is easily accomplished by histologic examination of liver sections. A multifocal periportal hepatic necrosis is associated with mononuclear cells and neutrophils at the margins of necrotic lesions. Clostridial organisms are easily identified within phagocytes in these areas in tissue sections with special stains (Giemsa, Warthin-Starry, or Gomori's methenamine-silver stains) or in fresh tissue imprints stained with methylene-blue or Diff-Quik. Organisms are not easily identified with routine hematoxylin and eosin staining of tissue sections. Treatment of Tyzzer's disease has not been successful owing to its rapid progression after realization that an animal is ill. Thus antibiotic efficacy is undetermined.

Toxoplasmosis

Toxoplasma gondii is a protozoal organism that can infect young dogs and cats, as well as many other young vertebrates. Cats can serve as either an intermediate or definitive host and are the only definitive host. Clinical signs associated with *Toxoplasma* infections vary depending on the chronicity of infection, host immune status, mode of infection, and target organs. *Toxoplasma* behaves as a pathogenic opportunist. Prenatal or lactationally acquired toxoplasmosis is generally more severe than postnatal infections. In utero infection can lead to stillbirths or acute severe neonatal illness or death from a fading puppy or kitten syndrome. Systemically infected puppies and kittens can appear normal at birth and continue to nurse but insidiously become lethargic, inappetent, and dyspneic and may demonstrate mucopurulent oculonasal discharge and develop progressive neurologic abnormalities with illness, culminating in death. Dissemination to multiple organs usually involves the liver and leads to jaundice, hepatomegaly, and abdominal effusion. Lesions may include multifocal necrotizing hepatitis or cholangiohepatitis.

Acute postnatal infection can develop in seemingly normal individuals following ingestion of large numbers of sporulated oocysts or bradyzoites. Again multiple organ dissemination is the rule, with clinical signs including inappetence, dyspnea, coughing, vomiting, diarrhea, hematemesis, enlarged tonsils and peripheral lymph nodes, splenomegaly, and hepatomegaly. Hepatic inflammation may be associated with anterior abdominal pain and peritoneal effusion and usually is associated with vomiting, diarrhea, and inappetence. Animals may become jaundiced as a result of diffuse hepatic necrosis or cholangiohepatitis. A survey of 100 cats with histologically confirmed toxoplasmosis

confirmed clinical syndromes involving the liver in 93% of cats. Generalized systemic infections with toxoplasmosis are more common in dogs and cats less than 1 year of age.

Biochemical abnormalities indicating hepatic involvement include marked increases in serum ALT, AST, and ALP activities and hyperbilirubinemia. Diagnosis of toxoplasmosis is definitively confirmed by finding tachyzoites in histologic or cytologic specimens.

Clindamycin is the drug of choice for treating clinical toxoplasmosis in dogs and cats and also is recommended for pregnant animals. Oral and parenteral dosing is similar, 10 to 20 mg/kg body weight given orally or intramuscularly every 12 hours for 4 weeks. Clinical response is usually evident as early as 48 hours. Treatment response requires an adequately functioning immune system that can eliminate *Toxoplasma* organisms.

The zoonotic potential of fecal oocyst shedding must be considered when dealing with infected cats. Because cats only shed large numbers of oocysts during the first several weeks of infections, those with chronic infections (sustained IgG antibody titers) impose a smaller zoonotic risk.

Ascariasis

Hepatobiliary lesions produced by ascarid larval migration (*Toxocara* spp.) are commonly observed during necropsy of young dogs and cats. Most animals do not manifest clinical signs or laboratory abnormalities. However, severe hepatic and peritoneal migration, gallbladder rupture, and bile peritonitis have been observed in puppies.

Pregnant and lactating bitches reactivate larval forms encysted in tissues, leading to intestinal infection and the shedding of eggs into the newborn pups' environment. Therefore ascarid infection of neonates may occur by environmental contamination and egg ingestion or by transplacental or transmammary larval infection. After egg ingestion, larval forms of *Toxocara canis* and *Toxocara cati* penetrate the intestines and pass into the lymphatic system or portal circulation and travel to the liver. Larvae migrate through hepatic tissue and gain access to the lungs via the caudal vena cava, heart, and pulmonary arteries. Ascarids may also migrate from the gastrointestinal tract directly through the peritoneal cavity to the liver, causing transient abdominal discomfort and liver enzyme activity.

EXOCRINE PANCREAS

An important anatomic difference between the anatomy of the pancreas in the dog and cat is the fusion of the feline major pancreatic duct with the common bile duct. This difference may predispose the cat to intraductal pancreatic inflammation secondary to biliary obstruction or microbial infections. The pancreas possesses both exocrine (digestive) and endocrine (hormonal) functions. The islets of Langerhans (0.1- to 0.2-mm-sized islets comprise <1% of the adult pancreas, higher percentage at birth) and acini (approximately 80% of the pancreas) are derived from endoderm. Islet composition includes β cells (insulin producing, 68%), α cells (glucagon producing, 20%), δ cells (somatostatin producing, suppress release of insulin and glucagon, 10%), and pancreatic polypeptide-secreting cells (2%). Rare cells include those producing vasoactive intestinal polypeptide (VIP; induces glycogenolysis and hyperglycemia, stimulates intestinal fluid secretion, can rarely cause secretory diarrhea) and enterochromaffin cells (synthesize serotonin, rarely can produce a "carcinoid syndrome"). Acinar cells are microscopically basophilic as a result of their prominent endoplasmic reticulum and Golgi structures and provide an apical oriented secretory complex transporting zymogen granules (inactivated digestive enzymes, periodic acid Schiff "+") to their apical plasma membrane. In health, the pancreas produces a bicarbonate-rich fluid containing digestive enzymes with secretions regulated by neural-humoral stimuli (vagus nerve, secretin, and cholecystokinin). Secretin, a peptide hormone produced in the duodenum in response to gastric acid and luminal fatty acids, stimulates water and bicarbonate release from pancreatic duct cells. Cholecystokinin, also a peptide hormone released from the duodenum in response to fatty acids, peptides, and amino acids, initiates discharge of digestive enzymes from acinar complexes. The repertoire of pancreatic enzymes includes trypsin, chymotrypsin, aminopeptidases, elastase, amylases, lipase, phospholipases, and nucleases. Trypsin, the major catalytic activator of the other enzymes, is initially activated by enterically produced enterokinase. Intrapancreatic control of enzyme activation is maintained by their storage in inactivated forms (zymogens) and colocalization with enzyme inhibitors. Certain systemic antiproteases also protect against inappropriate tissue enzyme activation (e.g., α1-antitrypsin, α1-macroglobulin).

Inflammatory disease of the pancreas primarily affects the exocrine portions and is uncommon in juvenile animals. However, pediatric pancreatitis has been associated with abdominal trauma, systemic infectious disease, and iatrogenic pancreatic injury during ovariohysterectomy (spearing with a spay hook or excessive manipulation of the pancreas). Infectious agents occasionally initiate pancreatic inflammation. In cats, pancreatitis has been associated with effusive FIP. Toxoplasmosis can directly invade pancreatic tissue. Ascarid migration (dogs, cats) and fluke migration in cats can damage pancreatic tissue or obstruct pancreatic ducts, leading to pancreatic inflammation. In cats, cystic duct malformations and development of choleliths also can compromise patency of the common bile duct, leading to pancreatic injury and inflammation.

Although seldom warranted in neonates or pediatric patients, laboratory confirmation of inflammatory pancreatic disease includes a complete blood cell count, serum chemistry profile, serum amylase and lipase, species-specific pancreatic lipase activity, survey abdominal radiographs, and abdominal ultrasonography. Definitive diagnosis of pancreatic inflammation requires reconciliation of test findings (particularly abdominal palpation, ultrasonography, and pancreatic lipase activity). Treatment of pancreatitis is supportive and managed similarly to that for an adult animal.

Pancreatic Exocrine Insufficiency

Exocrine pancreatic enzymes provide essential digestive functions such that loss of 90% of this capacity leads to maldigestion and exocrine pancreatic insufficiency (EPI) syndrome. Subclinical and clinical EPI syndromes have been characterized in dogs and are relatively rare in cats. Dogs with subclinical EPI have clinical signs masked by continued small-volume pancreatic enzyme secretion or digestion facilitated by alternative mechanisms (lingual or gastric lipases, gastric pepsins, intestinal mucosal esterases, and peptidases). Causes of canine EPI include pancreatic acinar atrophy (PAA; an apparent autoimmune lymphocytic inflammatory disorder), chronic pancreatitis, and pancreatic neoplasia. By far, PAA is most common and can affect dogs within the first year of life, although it usually becomes overt within the first 3 years. Long considered a hypoplastic pancreatic disorder, longitudinal studies have proven that PAA is the culmination of a lymphocytic immune-mediated inflammatory process.

Inherited PAA is not rare and has been intensively studied in German Shepherd Dogs and Rough-Coated Collie dogs in Finland, where 70% of dogs with EPI are German Shepherd Dogs and 20% are Rough-Coated Collies. A breed prevalence rate of 1% is reported. Although an autosomal recessive mode of inheritance has been proposed in German Shepherd Dogs, the trait may be polygenic or have incomplete penetrance. Accurate recognition of PAA as a syndrome requires acknowledgment that it also can represent the end result of pancreatic duct obstruction, ischemic tissue injury, toxicity, various nutritional deficiencies or imbalances, or defective secretory or trophic stimuli.

Clinical signs of PAA are variable but largely dominated by polyphagia, weight loss, excessive flatulence and borborygmi, and frequent, soft voluminous feces. However, some dogs vomit, some are inappetent, some are overweight, and rarely some dogs are hyperexcitable or aggressive. Progression of subclinical to clinical PAA varies widely; some dogs progress to full clinical disease within weeks, and others have slow progressive disease that never matures. At end-stage PAA, the pancreas is grossly diminished in size, thin, and transparent, with obvious ducts. Owing to the lymphocytic inflammatory lesion, the disorder has been more precisely labeled atrophic lymphocytic pancreatitis. Immunophenotyping has confirmed that CD3-positive T lymphocytes are involved with acinar destruction; histologic features mirror those associated with lymphocytic thyroiditis.

Routine clinical pathologic tests are not informative in most dogs with EPI. Serum ALT may be mild to moderately increased, reflecting uptake of noxious material from the small intestinal tract. Total lipid and cholesterol concentrations are usually low, whereas total protein, albumin, and globulin concentrations are usually normal. Serum activity of amylase and lipase is not informative. Serum canine trypsin-like immunoreactivity (cTLI) is the distinguishing test for EPI; the test is species- and pancreas-specific, measuring only pancreatic trypsin and trypsinogen that have entered the bloodstream directly from the pancreas. Healthy dogs have cTLI activity greater than 5.0 µg/L, whereas values less than 2.5 µg/L are diagnostic for EPI. Assessment of fasting cTLI values is recommended because even a transient postprandial increase of serum trypsinogen concentration can confuse test interpretation. Renal dysfunction also can obfuscate test interpretation because trypsinogen is eliminated by glomerular filtration. Low serum cTLI concentrations (<5.0 µg/L) on repeated tests can be used to detect subclinical PAA before overt EPI maldigestion can be recognized. Some dogs with minimal clinical signs have cTLI activity as low as others with end-stage PAA. Repeated cTLI measurements may be necessary to confirm subclinical PAA; the lower the cTLI value, the more certain the diagnosis. Notably, some dogs developing PAA have borderline low normal cTLI values. Although pancreatic biopsies can be safely collected, they are not recommended for early diagnosis of PAA because the pathologic process is unevenly distributed. Ultrasonographic diagnosis of PAA also is unreliable.

Treatment of clinical EPI requires pancreatic enzyme supplementation for the life of the patient. Most clinicians prefer powdered enzymes (pancrelipase) that are easily mixed with food: 3 g/meal for a 20- to 35-kg dog. Efficacy of enteric-coated enzyme tablets remains unsubstantiated; some studies suggest lower response rates and others no difference from powdered enzymes. However, tablet efficacy may be compromised by gastric retention. Rapid response to enzyme supplementation is usually evident during the first few weeks (weight gain, improved fecal consistency, and reduced flatulence and steatorrhea). Preincubation of digestive enzymes in food before feeding and supplementation with bile salts or antacids have no proven efficacy. Inhibition of gastric acid secretion with H_2 blockers remains controversial and is only recommended when response to enzyme therapy is suboptimal or inconsistent. Titrating the amount of supplemental enzymes mixed in food has been advocated by some clinicians but remains controversial. Too large a dose of powdered enzymes in food has been associated with oral bleeding that resolves on dose reduction.

Although diet modifications including low fat, high fiber, and low residue formulations have been recommended for dogs with EPI, studies have demonstrated wide variability in clinical responses among dogs. A highly digestible, low fiber, and moderate/low fat maintenance diet is recommended as the initial choice. Focus on individual patient needs and response to dietary changes and avoidance of radical dietary recommendations are prudent. The goal of diet modification coupled with responsible enzyme supplementation is reduced flatulence, borborygmi, fecal volume, and defecation frequency. Although a low fat diet may be useful during initial treatment, no long-term benefit has been demonstrated.

Dogs with subclinical PAA do not require treatment. However, dogs with partial PAA showing chronic intermittent gastrointestinal signs should receive a clinical trial of supplemental enzyme therapy. Patients with clinical PAA showing persistent signs despite enzyme replacement require

a full diagnostic evaluation for inflammatory bowel disease or treatment for small intestinal bacterial overgrowth (SIBO). It is well acknowledged that EPI may be associated with secondary problems including SIBO, low cobalamin concentrations, and coexistent inflammatory bowel disease. Genesis of SIBO is attributed to loss of bacteriostatic factors normally supplied by pancreatic secretions and to greater availability of undigested enteric substrates that allow development of SIBO. Some evidence suggests that pancreatic enzyme replacement alone or administration of tylosin can abate SIBO. In SIBO, low cobalamin concentrations are proposed to reflect bacterial vitamin sequestration or failure to degrade nonintrinsic factor proteins (R proteins) that bind luminal cobalamin. Low cobalamin concentrations also may reflect deficient production of pancreatic intrinsic factor as a result of acinar atrophy. In one study of dogs with EPI, cobalamin concentrations were low in 82%; a smaller subset had severe hypocobalaminemia (<100 ng/L), which seemingly functioned as a negative prognostic indicator (i.e., shortened survival). Parenteral cobalamin administration is necessary in dogs with subnormal cobalamin concentrations; such treatment is inexpensive and safe, and a good response can be expected in 60% of treated dogs (one study). High folate concentrations, consistent with enteric microbial folate synthesis, have been documented in 37% of dogs with EPI (one study). Although SIBO has been anecdotally linked with EPI, this syndrome remains controversial, and neither high serum folate nor low serum cobalamin concentrations can accurately confirm its presence. Suspected SIBO does not predict favorable response to antibacterial therapy.

Testing for PAA using low serum trypsin–like immunoreactivity (sTLI) as a defining marker has permitted early diagnosis of dogs with subclinical disease. Nevertheless, immunomodulation during this stage cannot be advocated because of the slow onset of full PAA in some dogs and because some dogs with PAA remain asymptomatic for their lifetime. Because dietary sensitivities may complicate EPI, hypoallergenic diets may benefit some dogs during early treatment. Although some clinicians have used medium-chain triglycerides to increase the energy value of foods fed to undernourished EPI patients, benefit of this strategy remains unproven. The typical gastrointestinal signs of EPI are almost completely eliminated in nearly 50% of treated dogs. Poor responses are realized in approximately 20% of dogs (continued diarrhea, unthrifty appearance, and flatulence), and many of these are euthanized during the first year of diagnosis. Dogs failing to respond to treatment do not make good house pets. Unfortunately the high cost of enzyme supplements also has led to euthanasia of some dogs. At present, there is no evidence that combinations of antimicrobials, H_2 blockers, or powder versus tablet enzyme formulations improve response and/or survival in symptomatic dogs. Generally the long-term prognosis is good for dogs that survive the initial treatment interval. Although mesenteric torsion has been noted as a severe complication of EPI in German Shepherd Dogs, this complication has decreased in frequency with improved treatment regimens and enzyme preparations.

SUGGESTED READINGS

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