Several hepatobiliary disorders have in the last few years come under increased recognition and interest in dogs. Understanding these conditions is essential in the diagnosis and management of canine liver disease.

**Vacular hepatopathies**

Hepatic vacular change is a common histological diagnosis in dogs but not cats. When we reviewed 150 consecutive liver biopsies performed at Colorado State University approximately 12% of the cases had predominately a vacular hepatopathy (VH) as the major histological finding. By definition according to the WSAYA Liver Standardization Group VH refers to a reversible parenchymal change that is characterized by swollen hepatocytes with clear cytoplasm due to glycogen without displacement of the nucleus from the center. The distribution and the extent of the lesion can vary being either diffuse, zonal, or involve individual cells. VH is a relatively easy histological diagnosis to make however Periodic acid Schiff (PAS) staining with or without diastase can be used to demonstrate glycogen accumulation. Vacuolated hepatocytes can also result from fat accumulation secondary to abnormal fat metabolism and is referred to as hepatic steatosis or lipodisosis. Hepatic steatosis is a distinct histological vacuolar classification associated with abnormal fat metabolism and will not be discussed in this chapter.

VH in dogs is most often associated with hyperadrenocorticism (HAC). The dog is particularly sensitive the effects of glucocorticoids that both induce serum alkaline phosphatase (ALP) steroid isoenzyme activity and causes hepatic glycogen accumulation. (see chapter Evaluation of Elevated Alkaline Phosphatase in Evolve). Congenital glycogen storage disorders, breed specific disorders, hepatic nodular hyperplasia and a variety of stress-associated secondary diseases are conditions that can cause this typical hepatic vacular changes. In a large study of 336 histological liver specimens having VH (defined as making up greater than 25% of the hepatocytes) were retrospectively reviewed for an underlying etiology (Hill et al., 2006). The authors report 55% of the cases were associated with either endogenous or exogenous glucocorticoids with the remaining 45% having no known glucocorticoid exposure. Most all of the dogs with no glucocorticoid exposure had other identifiable concurrent illness. Conditions such as renal, immune-mediated, cardiac, hepatic, gastrointestinal disease, or neoplasia accounted for many cases. The author’s hypothesis was that stress-induced hypercortisolemia associated with acute or chronic illness likely contributed to the development of the VH. A second in vivo study showed that by experimentally inducing a chronic four to five-fold elevations in plasma cortisol concentrations to simulate a stress-like state in normal dogs inhibited non-hepatic glucose utilization and increased hepatic glucoseogenesis and glycogen formation through enhanced substrate delivery to the liver.

**Idiopathic vacular hepatopathy**

There is a subset of dogs having elevations in serum alkaline phosphatase and excessive hepatic glycogen accumulation that do not have evidence of either a stress induced illness, evidence of HAC based on cortisol testing, a history of recent glucocorticoid administration or have a specific hepatic disease. These dogs are referred to as having an idiopathic vacular hepatopathy (IVH). They generally have no clinical signs and are usually identified during investigation of unexplained elevations in serum alkaline phosphatase (ALP) found on a routine health screen. Several theories have been put forward as to the cause of IVH. Some believe adrenal progestagens; most likely increases in 17-hydroxyprogesterone and progesterone are responsible as these changes as they are frequently identified to be abnormal when a commercial adrenal steroid panel is performed. However, critical evaluation and validation of the adrenal steroid panel (17-hydroxyprogesterone, progesterone, estradiol, testosterone and androstenedione) is as yet still lacking and a direct association has not been made. Because the VH changes are typical of glucocorticoid excess it is entirely possible that a yet to be identified adrenal steroid could be responsible for the VH. Obviously future research is necessary to delineate this syndrome and the relationship to adrenal steroids.

Scottish terriers are also reported to have a breed-specific syndrome associated with a VH and elevated serum ALP. These affected dogs generally have no clinical signs. The authors found that the elevated ALP was predominately the corticosteroid isoform and following ACTH stimulation test in conjunction with an adrenal steroid panel found increases in one or more non-cortisol steroid hormones. The authors conclude that affected Scottish terriers have a type of hyperadrenocorticism on the basis of exaggerated adrenal hormone response. We have also observed similar non-cortisol steroid hormone increases in Scottish terriers but also in Scottish terriers without VH or increases in ALP adding more confusion to this syndrome. The reader should refer to Chapter 51, Occult hyperadrenocorticism: Is It Real? for further information concerning adrenal steroids.

Dogs with IVH generally have no clinical signs. They are usually identified serendipitously on a biochemical profile identifying elevations in serum ALP concentrations that subsequently initiates a diagnostic work-up. Most affected dogs are middle-aged or older at the time of diagnosis. There does not appear to be a breed or sex predisposition other than the syndrome described above in the Scottish terrier. A small percent of dogs may have reported polyuria and polydipsia (PU/PD) but the other signs typical of HAC are generally absent. The work up of the asymptomatic dog having an IVH usually begins after the identification of an elevation in serum
than 10 years of age. Laboratory findings include an ALP increase (mean ALP ~ 600 IU/L), but some may have mild increases in chronic hepatitis or neoplasia. The etiology is unknown but appears to be an aging change in dogs; most of those affected are greater hepatic nodules containing vacuolated hepatocytes. Liver function remains unchanged. Grossly, the appearance may be suggestive of This is a benign process causing an increase in hepatic values and histomorphologic changes that include macroscopic or microscopic hepatic nodular hyperplasia

Liver support therapy using products such as s-adenosylmethionine (SAMe), the milk thistle products, or other antioxidants may have some beneficial effects. One study showed dogs given glucocorticoids and treated with SAMe failed to show a decrease in serum ALP or amount of VH but did have improvement in hepatocyte oxidative status through increased glutathione concentrations. The above products are generally safe for liver support but will unlikely have any effect in the resolution of IVH.

Hepatic nodular hyperplasia

This is a benign process causing an increase in hepatic values and histomorphologic changes that include macroscopic or microscopic hepatic nodules containing vacuolated hepatocytes. Liver function remains unchanged. Grossly, the appearance may be suggestive of chronic hepatitis or neoplasia. The etiology is unknown but appears to be an aging change in dogs; most of those affected are greater than 10 years of age. Laboratory findings include an ALP increase (mean ALP ~ 600 IU/L), but some may have mild increases in ALT and AST concentrations as well. Ultrasound may be normal or may demonstrate larger nodules (many can be only microscopic and not observed on ultrasound). Biopsy confirms the diagnosis, however a wedge section is preferred. A needle aspirate or needle
biopsy may only demonstrate show a vacuolar hepatopathy. There is no specific therapy and it does not progress to a neoplastic process.

**Gallbladder mucocele**

To date greater than 130 cases of gallbladder mucocele have been documented in the literature. A gallbladder mucocele is a condition that is described as an enlarged gallbladder with immobile stellate or finely striated patterns of mucoid material within the gallbladder lumen detected with ultrasound. The changes described can result in biliary obstruction or gallbladder perforation and peritonitis. Smaller breeds and older dogs are overrepresented. Shetland sheepdogs and Cocker Spaniels are most commonly affected. Most dogs are presented for nonspecific clinical signs such as vomiting, anorexia and lethargy. Abdominal pain, icterus and hyperthermia are common findings on physical examination in advanced cases. Most have serum elevations in bilirubin, ALP, GGT and variable ALT although some dogs are asymptomatic and a mucocele is diagnosed as an incidental finding on abdominal ultrasound. The Shetland sheepdogs tend to have hyperlipidemia and were first thought to have a genetic defect in the ABCB4 hepatobiliary transporter gene involved phosphocholine transport into the bile. That theory is now questioned in a reported second larger study. Risk factors identified in mucocele cases include endocrine disease (hypothyroidism, Cushing’s disease) and idiopathic vacuolar hepatopathy, hyperlipidemia and dogs on high fat diets. Gallbladder mucoceles appear ultrasonographically as an immobile accumulation of anechoic-to-hypoechoic material characterized by the appearance of stellate or finely striated bile patterns (wagon wheel or kiwi fruit appearance). This should be differentiated from biliary sludge ( bile sludge can be found in normal animals), by the absence of gravity dependent bile movement while the mucocele is non-movable. The gallbladder wall thickness and wall appearance are variable and nonspecific. The cystic, hepatic or common bile duct may be normal size or dilated suggesting biliary obstruction. Gallbladder wall discontinuity on ultrasound indicates rupture whereas neither of the bile patterns predicted the likelihood of gallbladder rupture.

Cholecystectomy is the treatment of choice for biliary mucoceles. Following cholecystectomy and recovery of postoperative period the prognosis is excellent especially when the liver enzymes are normal. Mortality rates have been reported to be in the 20% range and some may persist in having liver disease with elevated liver enzymes. There are reports of resolution of some mucoceles using ursodeoxycholic acid (ursodiol) and a low fat diet but this should only be attempted in the healthy patient and with careful monitoring. Ursodeoxycholic acid is thought to up-regulate biliary excretion of phospholipids and increase bile salt dependent flow. On histopathology the gallbladder demonstrates cystic mucinous hyperplasia. The pathophysiology of this condition is unknown. It is possible biliary stasis and abnormal bile composition or lack of solubility results in gallbladder mucosal irritation and subsequent mucinous hyperplasia. Infection does not appear to be a factor in this condition. A mucocele is reported the most common cause of a gallbladder perforation.

**Portal vein hypoplasia**

Portal vein hypoplasia (PVH), also referred to as microvascular dysplasia (MVD), is a common syndrome in the dog associated with abnormal microscopic hepatic portal circulation. It is thought that PVH is 15 to 30 times more common that a congenital portosystemic shunt (PSS). Hepatic PVH has been suggested as the terminology by the WSAVA Liver Standardization Group that may better reflect the etiology of this condition although MVD is ingrained in the veterinary literature. It is believed that the primary defect in affected dogs is the result of hypoplastic small intrahepatic portal veins. This condition is thought to be a defect in embryologic development of the portal veins. With paucity in size or number of portal veins there is a resultant increased arterial blood flow in attempt to maintain hepatic sinusoidal blood flow. The hepatic arteries become torturous and abundant in the triad. Sinusoidal hypertension occurs under this high pressure system. Lymphatic dilation results and it is thought that this opens up of embryologic sinusoidal vessels to reduce pressure and thus acquired shunts develop to transport some (but not all) of the blood to the central vein thus by-passing the sinusoidal hepatocytes. This results in abnormal hepatic parenchymal perfusion and lack of normal trophic factors bathing the sinusoids causing hepatic atrophy. With portal shunting of blood increased iron uptake also occurs that results in hepatic iron granuloma formation. Ascites or portal hypertension generally do not occur in this condition.

Because similar histological changes occur in dogs having PVH and PSS (i.e., hepatic hypoperfusion) the diagnosis can be confusing. If an intrahepatic or extrahepatic macroscopic shunt is not observed then PVH becomes the probable diagnosis. Angiography or transcolonic portal scintigraphy fails to demonstrate macroscopic shunting in this condition. Often a needle biopsy is not sufficient to provide enough portal areas to make the diagnosis, and consequently a wedge or laparoscopic biopsy may be necessary. The condition that was first described in Cairn terriers and now is felt to occur in other breeds of dogs. Yorkshire Terriers and Maltese may be over represented. Animals show no outward clinical signs and are usually identified because of elevated liver enzymes (ALT). All patients have abnormal serum bile acid concentrations (usually moderate elevations) but generally they are less than 100 µmole/L. It is reported PVH dogs have normal protein c concentrations while PSS dogs have concentrations less than 70% normal. There is no specific therapy. Some suggest antioxidants (i.e., SAMe, milk thistle etc.). The long-term prognosis is uncertain because of lack of experience with this relative new disease. There may be a small number of dogs developing portal hypertension over time.