Throughout much of recorded history there was a belief that the liver was the center of life. As we learn more of the complexity of the liver with all of its metabolic functions, we have to acknowledge that there is a lot of truth in those early thoughts. Liver disease can result from many different insults, metabolic derangements, and genetic abnormalities, and liver damage can occur in many different ways. To this end, if clinicians are to understand liver disease, they must simply understand all of medicine. The detection of liver disease requires an accurate history, a thorough physical examination, and biochemical testing. The identification of abnormal liver enzymes usually indicates liver damage but rarely provides a diagnosis or etiology. Abnormal liver enzymes are common, and in a study of 1,022 blood samples taken from both healthy and sick dogs and cats, one diagnostic laboratory found that 39% had ALP increases and 17% had ALT increases (Comazzi et al. 2004). The identification of liver biochemical abnormalities in conjunction with the clinical findings suggests certain diagnostic possibilities and will indicate further steps into the investigation of possible liver disease. This presentation will cover what I consider to be five of the most common clinical conditions the veterinarian encounters when dealing with liver disease. These situations include the normal dog with abnormal liver enzymes, the sick dog with abnormal liver enzymes, and the icteric dog. The first section will provide a brief review of liver enzymes and tests involving liver function; we will then proceed to a clinical case discussion.

Laboratory Tests
Liver biochemical enzymes can be insensitive or nonspecific for primary liver disease, and in addition, some of the enzymes can have isoenzymes from other tissues not associated with the liver. An understanding of liver biochemical tests is essential when evaluating patients. Liver biochemical test abnormalities are categorized into groups that reflect: (1) hepatocellular injury, (2) cholestasis, or (3) tests of impaired metabolic function or synthetic capacity.

Tests of Hepatocellular Injury
Increases in either alanine aminotransferase (ALT) or aspartate aminotransferase (AST) activity indicate hepatocellular membrane damage and leakage of the enzymes. Canine and feline hepatocyte cytoplasm is rich in ALT and contains lesser amounts of AST. Altered permeability of the hepatocellular membrane caused by injury or a metabolic disturbance results in a release of this soluble enzyme. Conceptually, ALT and AST should be thought of as hepatocellular “leakage” enzymes. Subsequent to an acute, diffuse injury, the magnitude of increase crudely reflects the number of affected hepatocytes. It is, however, neither specific for the cause of liver disease nor predictive of the outcome. The plasma half-life of ALT activity is 60 hours in dogs; however, ALT concentrations may take days to weeks to decrease following an acute insult. Persistent increases of ALT are characteristic of chronic hepatitis in the dog. I believe ALT increases should be investigated when they are greater than twice the norm or persistently abnormal.

A variety of tissues, notably skeletal muscle and liver tissue, contains high AST activity. Hepatic AST is located predominately in hepatocyte mitochondria (80%), but is also soluble in the cytoplasm. Skeletal muscle inflammation invariably causes a serum AST increase (and an ALT increase, to a much lesser extent) that exceeds the serum ALT activity and that can be further defined as muscular in origin by the measurement of serum creatine kinase (CK), a specific muscle enzyme. Clinical experience in veterinary medicine indicates that there is value in the interpretation of the serum activities of ALT and AST for liver disease. The half-life for ALT is 2.5 days. Following an acute injury resulting in a moderate to marked increase in the serum ALT and AST concentrations, the serum AST will return to normal more rapidly (hours to days) than the serum ALT (days), due to their difference in plasma half-life and cellular location (Brovida and Rothuizen 2010). By determining these values every few days following an acute insult, one can obtain a sequential “biochemical picture” indicative of resolution or persistent pathology.

Tests of Cholestasis and Drug Induction
Alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) show minimal activity in normal hepatic tissue but can become increased in the serum subsequent to increased enzyme production stimulated by impaired bile flow or drug induction. These enzymes have a membrane-bound location at the canalicular surface. ALP is associated more with the canalicular membrane and GGT is associated more with epithelial cells of the bile ductular system (Center et al. 1992). With cholestasis, the surface tension in the canaliculi and bile ductules increases, and these surface enzymes are then upregulated into production.
Alkaline phosphatase is also present in a number of tissues, but the only two that are diagnostically important are the bone and liver. The plasma half-life for hepatic ALP in the dog is 66 hours, in contrast to 6 hours for the cat, and the magnitude of enzyme increase (presumably a reflection of the synthetic capacity) is greater for the dog than for the cat. Bone source arises from osteoblastic activity and is elevated in young growing dogs before their epiphysial plates close or in some bone tumors or lytic lesions. In the adult without bone disease, increased serum ALP activity is usually of hepatobiliary origin. One study identified some dogs with osteogenic bone tumors to have increased ALP concentrations (Bunch 2003). The ALP increase in those dogs tended to indicate a poorer prognosis, probably from diffuse bone metastasis. A minor bone source of ALP could result from osteomyelitis and secondary renal hyperparathyroidism.

An increase in the serum ALP and GGT activity can be induced by glucocorticoids (endogenous, topical, or systemic), anticonvulsant medications, and possibly other drugs or herbs. There is remarkable individual variation in the magnitude of these increases, and there is no concomitant hyperbilirubinemia. A moderate to marked increase in serum ALP activity without concurrent hyperbilirubinemia is most compatible with drug induction and warrants a review of the patient’s history (topical or systemic glucocorticoids) or evaluation of adrenal function. The increased ALP has long been attributed to a glucocorticoid-stimulated production of a novel ALP isoenzyme in the dog that can be distinguished from the cholestasis-induced hepatic ALP isoenzyme by several procedures. It was initially thought that the glucocorticoid-associated isoenzyme could be used as a marker of exogenously administered corticosteroids or increased production of endogenous glucocorticoids. Unfortunately, the glucocorticoid-associated isoenzyme is associated with hepatic disease as well, and differentiation of steroid from liver ALP is rarely helpful.

Hepatic GGT is located predominately on the hepatocyte and bile ductular canalicular membrane. In dogs, GGT has a lower sensitivity (50%) but higher specificity (87%) for hepatobiliary disease than total ALP. If there is an elevated ALP with a concurrent increase in serum GGT, specificity for liver disease increases to 94% (Webster and Cooper 2008). The most marked elevations in GGT result from diseases of the biliary epithelium, such as bile-duct obstruction, cholangiohepatitis, cholecystitis, and glucocorticoid administration in the dog (Center et al. 1992). Bone does not contain GGT, and the administration of anticonvulsant medications to dogs does not cause an increase in the serum GGT activity. Colostrum and milk have high GGT activity, and nursing animals have increased serum GGT activity.

Tests Involving Liver Function

On a routine biochemical profile, it is important to note the liver function tests, including bilirubin, albumin, glucose, BUN, and cholesterol. Albumin is exclusively made in the liver, and if not lost from the body (GI or renal), sequestered, or diluted, a low concentration would suggest significant hepatic dysfunction. It may take greater than 60% hepatic dysfunction for albumin concentrations to decline and 75% or greater liver dysfunction for glucose to drop. Major clotting factors are also made in the liver (except factor 8), and therefore prolonged clotting time suggests hepatic dysfunction. Liver disease and abnormal function tests suggest hepatic failure and a guarded prognosis.

The most sensitive function test that is readily available in small animals is for serum bile acids. The fasting total serum bile acid (FSBA) concentration is a reflection of the efficiency and integrity of the enterohepatic circulation (Anwer and Meyer 1995). Pathology of the hepatobiliary system or portal circulation results in an increased FSBA prior to the development of hyperbilirubinemia, negating its usefulness in the icteric patient. An increase is not specific for a particular type of pathologic process but is associated with a variety of hepatic insults and abnormalities of the portal circulation.

The current suggestion for the determination of the FSBA is to differentiate between congenital portal vascular anomalies and liver insufficiency prior to the development of jaundice. The determination of FSBA can contribute to the decision to obtain histological support for the diagnosis of this last group of hepatic diseases. When the fasting value is greater than 25 µmol/L for the dog or cat, there is a high probability that the histology findings will define a lesion. When the FSBA concentration is normal or in the “gray zone,” the FSBA should be followed by a 2-hour postprandial serum total bile acid (PPSBA), looking for an increase greater than 25 µmol/L (Center et al. 1985). The diagnostic value of determining PPSBA concentration is increased sensitivity for the detection of hepatic disease and congenital portal vascular anomalies. In dogs, the specificity of fasting and postprandial bile acids for hepatobiliary disease is 95% and 100% when cutoff values greater than 15 µmol/L and 25 µmol/L are used,
respectively. When using these guidelines, it is prudent to recognize that a small number of healthy dogs have been reported with PPSBA values above 25 µmol/L.

Occasionally, the FSBA value is greater than the PPSBA value. The reason for this is unclear but the cause is probably multifactorial. It has been shown that (1) the peak PPSBA concentration for individual dogs is variable, (2) fasted dogs store about 40% of their newly produced bile in the gallbladder, and (3) a meal stimulates the release of only between 5% and 65% of the gallbladder bile. Undoubtedly these physiologic variables, in addition to physiological variation in intestinal transit time and concurrent underlying intestinal disease, contribute to the dichotomy.

Recently, urinary bile acids have become available as a diagnostic tool. Identifying increased urinary bile acids provides similar information to what is obtained from serum bile acids, and neither test appears to be better than the other. The advantage of urinary bile acid measurements would be for the screening of litters of young puppies for suspected inherited vascular anomalies where urine collection is simpler than paired serum samples.

In summary, there are a variety of markers with variable sensitivity and specificity that reflect hepatic tissue and portal vasculature pathophysiology. I support the conclusion of another study that found that the optimal test combination is the serum ALT activity and bile acid concentrations. This pairing provided the best sensitivity and specificity for liver disease in dogs. Clinical experience indicates that elevated serum AST concentration along with an elevated ALT helps to support a diagnosis of hepatocellular disease, and that the PPSBA concentration enhances the evaluation of hepatic function, with chronic hepatitis being a likely possibility.

**Normal Dog, Abnormal ALT and ALP**

The asymptomatic patient with an increased liver biochemical test should have the value confirmed at least once to exclude a spurious result from laboratory error and to avoid unnecessary and costly additional testing. A careful history is essential to exclude drug-associated enzyme elevations. The signalment of the patient may also provide insight into the possible etiology of the enzyme increase. For example, old dogs frequently have benign nodular hyperplasia, neoplasia, or systemic disease, while in younger and middle-aged dogs, chronic hepatitis is commonly encountered. There are also certain breeds that are predisposed to developing chronic hepatitis. A careful physical examination may provide clues to the diagnosis. The most common cause of abnormal liver enzymes is not primary liver disease, but rather, reactive hepatic changes occurring secondary to a primary nonhepatic disease. This would include such conditions as intra-abdominal disorders (inflammatory bowel disease, nutritional abnormalities), cardiovascular disease, or metabolic derangements, as just a few examples. Generally, these secondary changes in the liver are reversible once the primary disease is treated. Successful resolution of the nonhepatic disease and continued abnormal liver enzymes would then be an indication that further investigation of the liver is needed.

If no likely explanation for the laboratory abnormalities can be found, there are two courses of action that one can take: either begin a diagnostic evaluation of the patient, starting with bile acid determinations, or reevaluate the patient’s liver enzymes at a later date. A reasonable waiting period for reevaluation, in my opinion, is 4 to 6 weeks, given what is known about the half-life of liver enzymes and the time needed for liver recovery from an acute occult hepatic injury. It is best not to delay retesting beyond 6 weeks, however, in the event that an active disease process is present. During the waiting period, one may consider a trial therapy of antibiotics or liver support. Liver support therapy would include antioxidants such as S-Adenosyl methionine (SAMe) or milk thistle (silibin) therapy. Identification of persistent abnormal liver enzymes or abnormal liver enzymes and abnormal bile acid concentrations should dictate further hepatic investigation.

Generally, the next liver evaluation involves imaging using radiographs, or preferably, liver ultrasound. During ultrasound, I routinely perform fine needle aspiration of the liver and cytology. It is, however, important to note that hepatic cytology does not always correlate with histopathology interpretation (Simpson and Else 1987). In most instances, imaging and biochemical testing and liver cytology cannot replace liver biopsy. A liver biopsy is required for a definitive determination of the nature and extent of hepatic damage and to appropriately direct the course of treatment. The method for liver biopsy procurement may be surgery, laparoscopy, or needle biopsy. Each has certain advantages and disadvantages, and the decision of which procedure to use should be made in light of all the other diagnostic information, always considering what is in the best interest of the patient and client.

**Normal Dog, Abnormal ALP**
The identification of an older asymptomatic dog with significant elevations in ALP alone is quite common and can often be frustrating for the veterinarian attempting to determine the underlying etiology. Causes for ALP increases include bone (osteoblastic activity), hepatic cholestasis, and steroids (Twedt and Gary 2008). Bone source is usually easy to rule out, but differentiating cholestasis from steroids becomes a little more difficult. A study evaluating cases having histological evidence of a steroid hepatopathy found that patients either had steroid administration, Cushing’s disease, or some other, usually serious, illness. The authors concluded that chronic stress from disease could result in a vacuolar hepatopathy (Sepesy et al. 2006). Initial evaluation in these patients should proceed as described previously, by ruling out exposure to drugs or supplements and assessing for the possibility of nonhepatic disease, including endocrine, gastrointestinal, and neoplastic disorders. The history and physical examination should be repeated to ensure that clinical abnormalities are truly absent.

Options for further evaluation include monitoring ALP over time or pursuing additional diagnostics. For most cases it is appropriate to monitor ALP over 4 to 6 weeks. If progressive or persistent increases occur, further workup is indicated, as previously described. Abdominal ultrasound and bile acid measurements should then be performed to rule out obvious structural and functional abnormalities of the liver and biliary system. I have observed on ultrasound evidence of primary hepatic neoplasia in asymptomatic patients having an elevated ALP as the only clinical abnormality. The decision for additional monitoring or immediate evaluation may also be based somewhat on the degree of ALP elevation. Moderate to severe increases are more often associated with hepatobiliary disease or exposure to glucocorticoids and are unlikely to resolve over time.

Common hepatic causes of ALP elevation in asymptomatic patients include neoplasia, benign nodular hyperplasia, idiopathic vacuolar hepatopathy, and breed-related conditions. Idiopathic vacuolar hepatopathy is associated with vacuolated hepatocytes containing glycogen. The histological diagnosis of a vacuolar hepatopathy is quite common, and a study evaluating cases having this diagnosis found that most patients either had steroid administration, Cushing’s disease, or some other nonhepatic serious illness. The authors concluded that chronic stress from disease could result in a vacuolar hepatopathy (ibid.). In a small percent of the vacuolar hepatopathy cases, steroids and stress could not be implicated. We now believe that in most of these cases, having a “steroid liver” is the result of abnormal adrenal production of adrenal hormones, most commonly progesterone or 17-hydroxyprogesterone. An adrenal steroid panel should be obtained in conjunction with adrenocorticotropic hormone (ACTH) stimulation. Some also refer to this condition as atypical Cushing’s disease, because the liver biopsy changes are identical to those of a typical steroid hepatopathy. These patients often do not progress, and therapy is controversial; however, some report that melatonin or traditional hyperadrenocorticism therapy resolves hepatic changes and the elevations in corticosteroid induced ALP. We have also observed some of these dogs to have hypertension and proteinuria and occasionally to develop a biliary mucocele.

A common finding in Scottish terriers is ALP elevation, often without other concurrent laboratory abnormalities (Zimmerman et al. 2010). In one study, Scottish terriers were shown to have a high incidence of increased ALP (Nestor et al. 2006). An additional report describes seven Scottish terriers that were evaluated for increased ALP with no identifiable cause after thorough imaging, adrenocortical testing, and liver biopsy, suggesting that a benign familial hyperphosphatasemia may have been present (Gallagher et al. 2006). A study that we performed in non-Scottish terriers with abnormal ALP found the terriers to have elevated endogenous steroid hormone precursors (i.e., 17-hydroxyprogesterone). However, similar abnormalities in 17-hydroxyprogesterone and progesterone were also present in Scottish terriers with normal ALP. Currently, the underlying cause for elevations in ALP in Scottish terriers is unknown; however, the condition appears to be benign. I have, however, found a number of the vacuolar hepatopathies to have concurrent proteinuria and hypertension that should be addressed in the case management.

Hepatic nodular hyperplasia is a common and relatively benign intrahepatic event that is included in this section because it causes an increase in hepatic tests and histological changes that may include macroscopic or microscopic hepatic nodules containing vacuolated hepatocytes (Prause and Twedt 2000). Grossly, the nodules may be suggestive of chronic hepatitis or neoplasia. The etiology is unknown, but this appears to be a change related to aging in dogs. Most of those affected are more than 10 years old. Laboratory findings include an ALP increase, but some patients may have mild increases in ALT and AST concentrations. Liver function remains unchanged, though the incidence of nodules may progress with age. An ultrasound may be normal (many of the nodules are only microscopic in size and therefore may not be observed on ultrasound) or may demonstrate single or multiple hyper or hypoechoic nodules. A biopsy can confirm the diagnosis; however, a wedge section is preferred, as a needle biopsy may not demonstrate the nodules. There is no specific therapy.
Young Dog, Pre-Spay, Abnormal ALT
I find that an increased ALT in healthy young dogs under 1 year of age is not uncommon. The cause of this elevation in many cases is undetermined. It is important to exclude all types of nonhepatic disease that could potentially affect the liver, causing a secondary reactive hepatopathy. This is uncommon in young dogs, as they are usually very healthy, and it is also my experience that primary liver disease in young dogs under a year of age is uncommon. Chronic hepatitis or copper-associated hepatitis usually does not result in laboratory changes until dogs are several years of age or older. Some young dogs with ALT increases return to the normal range at maturity. The explanation for this observation is unknown, but one might speculate that hepatic visceral larval migrans could be a cause of ALT leakage, or possibly that the increase occurs during normal hepatic growth in some developing young dogs.

Another likely cause for ALT elevations in young dogs would be from hepatic vascular anomalies. Bile acids (FSBA and PPSBA) are very sensitive tests for hepatic vascular anomalies, and consequently, young dogs with unexplained elevations in ALT concentrations should have bile acids tested. If the bile acids are normal, I generally do no further workup and just recheck the ALT when the dog is a year of age or older. However, if the bile acids are abnormal, then I recommend investigation for a possible vascular anomaly. Two major types of vascular anomalies have been recognized: portal vein hypoplasia (PVH, also called microvascular dysplasia [MVD]) and macroscopic portosystemic shunts (PSS). Dogs having macroscopic PSS are often clinical for the disease and usually have bile acid concentrations of more than 100 µmol/L. One can document the anomaly using various types of imaging studies. It becomes more problematic to diagnose dogs with microscopic hepatic vascular anomalies. It is thought that these microscopic PSSs result from a primary portal vein hypoplasia (PVH) of the hepatic portal vein branches within the liver. The condition was initially referred to as “hepatic microvascular dysplasia.” “Hepatic portal vein hypoplasia” has now been suggested as a better term by the WSAVA Liver Standardization Group, in that it may better reflect the etiology of this condition (Cullen et al. 2006). 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 the embryologic development of the portal triad (artery, vein, and bile ducts). With a paucity in size or number of small portal veins, there is a resultant increase in arterial blood flow in the attempt to maintain hepatic sinusoidal perfusion. The hepatic arteries then become tortuous and abundant in the triad (portal arterialization). Sinusoidal hypertension occurs under this high-pressure arterial system. Lymphatic and venous dilation results, with opening up of embryologic sinusoidal vessels, and thus acquired microscopic shunts develop to transport some of this blood to the central vein, thus bypassing the sinusoidal hepatocytes. With portal shunting of blood, increased iron uptake occurs, which results in hepatic iron granuloma formation. Ascites or portal hypertension does not generally occur.

Because similar histological changes occur in dogs having congenital macroscopic portosystemic shunts, the diagnosis can be confusing. If a macroscopic intrahepatic or extrahepatic PSS is not observed through imaging studies, then portal vein hypoplasia becomes the probable diagnosis. Angiography or portal scintigraphy is normal with PVH. A needle biopsy is not always sufficient to provide enough portal areas to make the diagnosis, and consequently a larger wedge or laparoscopic biopsy is preferred. Also, because of the patchy nature of the hepatic lesions, multiple liver biopsies from different liver lobes should be obtained.

PVH was first described in Cairn terriers and now is felt to also occur in many other small-breed dogs. Yorkshire terriers and Maltese may be overrepresented (Christiansen et al. 2000). Dogs with PVH have abnormal serum bile acid concentrations (usually moderate elevations < 100 µmol/L) and variable liver enzymes (most often ALT). Most have no clinical signs and require no specific therapy. I suspect that because of histological changes observed in some PVH cases and elevations in ALT, there may be some degree of oxidative damage occurring, and antioxidant supplementation might be considered. The long-term prognosis is considered good for most dogs, but because of lack of reported long-term follow-up with this relatively new disease, we do not know for certain what the long-term prognosis will hold.

There is an uncommon fibrosis variant of the PVH that is associated with portal arterialization, portal bile duct proliferation, significant hepatic fibrosis, portal hypertension, and secondary acquired PSS (Van den Ingh et al. 1995). This condition has also been referred to as idiopathic noncirrhotic portal hypertension or congenital hepatic fibrosis because of the significant fibrosis in the portal areas and development of portal hypertension and ascites (Bunch et al. 2001). It is generally observed that dogs with congenital portosystemic vascular anomalies from a single intra- or extrahepatic shunting vessel have signs associated with hepatic encephalopathy but do not have portal hypertension or develop ascites. However, a subgroup of dogs with portal vein hypoplasia and fibrosis
develop ascites, portal hypertension, and secondary acquired portosystemic shunting. The hepatic histology demonstrates portal tracts associated with multiple arterioles, small or absent portal veins with variable portal fibrosis, lymphatic distension, and variable bile duct proliferation. The pathology is void of inflammatory infiltrates. There are also increased amounts of hepatic iron deposited in the liver. The fibrosis and bile duct replication may be a nonspecific reaction from increased growth factors that are promoting arterial proliferation.

This latter condition is generally observed in dogs under 3 years of age, and there is no breed prevalence; however, large breeds such as the golden retriever, the Doberman pinscher, the cocker spaniel, and the rottweiler may be overrepresented. The clinical presentation is similar to dogs having either congenital intra- or extrahepatic shunts except that most of these dogs have ascites. The liver enzymes are generally increased, with hypoalbuminemia and very high bile acid concentrations. Workup of these patients fails to identify a single shunting vessel, but these cases have marked portal hypertension associated with multiple acquired portosystemic shunts. Ultrasound is often helpful, showing microhepatia, hepatofugal portal blood flow, and multiple abnormal extrahepatic collateral shunts. Portal contrast studies demonstrate acquired portal shunts, and pressure measurements document portal hypertension. The prognosis for this condition is generally guarded, but some dogs are reported to have a prolonged survival from the use of antifibrotic agents and hepatic encephalopathy therapy.

**Sick Dog with Abnormal ALT and ALP**

*Reactive Hepatopathy*

When presented with a sick dog and abnormal liver enzymes, it is important in the initial workup to consider drugs as well as primary nonhepatic disorders that could secondarily affect the liver, causing abnormal liver enzymes. Liver changes occurring secondary to a primary nonhepatic disorder are referred to as “reactive hepatopathies.” Most of the reactive hepatopathies cause increases in laboratory tests that evaluate hepatocellular integrity (ALT, AST) and tests of hepatic cholestasis (ALP, GGT). In most cases, there are little, if any, abnormalities in tests that evaluate hepatic function (bilirubin, albumin, glucose, and BUN), and most of the animals with secondary liver disease also retain normal serum bile acid concentrations, which again supports a concept that there is generally minimal hepatocellular dysfunction in most of these disease conditions.

This group is characterized by nonspecific hepatocellular degeneration or necrotic changes without evidence of significant chronic progressive inflammation. The reason the liver often undergoes these changes is that the liver is involved in many metabolic and detoxification functions. Endogenous toxins, anoxia, metabolic changes, nutritional changes, and endogenous stress-related glucocorticoid release are examples of conditions responsible for the majority of these changes. Histological findings associated with secondary reactive changes include descriptors such as vacuolar degeneration, hydropic degeneration, swollen hepatocytes, lipidosis, intracellular or intrahepatic cholestasis, mild multifocal hepatitis, and periportal or variable hepatic necrosis. These changes are devoid of the typical progressive chronic inflammatory cell infiltrates characteristic of chronic hepatitis, which is discussed below.

An example of the concept of secondary reactive hepatopathy is inflammatory bowel disease. In this case, it is not unusual to observe mild inflammatory changes around portal triads that are presumed to be the result of abnormal portal uptake of gastrointestinal “toxins.” Throughout the liver and closely associated with portal areas are Kupffer cells (fixed macrophages) that function to filter the blood of injurious toxins, inflammatory mediators, and bacteria. When this macrophage system is abnormally insulted, the Kupffer cells release their own inflammatory mediators that in turn insult the hepatocytes. Another example would be the septic dog, in which reactive changes could be due to endogenous cortisol release from stress and secondary to endotoxin or cytokine alteration.

In a review of consecutive liver biopsies at Colorado State University, histology grouped as nonspecific reactive changes made up the largest category of abnormalities (approximately 25%). In this group we were able to identify an associated disease in many cases that could explain the likely cause for the hepatic enzyme increases and histological changes observed. Concurrent diseases identified in these patients included neoplasia, gastrointestinal, renal, autoimmune, dermatologic, dental, infectious, and cardiac disease, as a few examples. In some cases, an underlying disease may not be identified. The ALT values, on average, are 1 to 2 times the normal values, and the ALP values 1 to 3 times normal. It is interesting to note that when I reviewed 32 dogs having reactive hepatopathies, 8/8 cases in which serum bile acids were run, all were within the normal reference range, again suggesting that hepatic function remains intact.
This category appears to be the most common histological change to occur in dogs and is by far the most common cause of elevated liver enzymes. Based on this fact, dogs presented with elevations in ALT and ALP should always have primary nonhepatic disease ruled out first. These changes are usually very reversible, and no specific hepatic therapy is required short of treating the primary disease. The liver changes resolve once the primary etiology is successfully treated, and additional therapy providing good liver support, such as antioxidants, may be warranted.

When an underlying disease is not detected and liver enzymes persist in being abnormal, further investigation of the liver is indicated. Bile acids may help direct the urgency of investigation, as abnormal bile acid concentrations indicate decreased hepatic function, cholestasis, or PSS.

**Chronic Hepatitis**

In my review of 150 consecutive liver biopsies, the next most common condition identified was chronic hepatitis (23%), followed by hepatic neoplasia, vacuolar hepatopathy, and acute hepatitis. All of these groups generally require a hepatic biopsy for a definitive diagnosis and to plan a course of therapy. Of these categories, the most important one to diagnose is chronic hepatitis. With early identification of chronic hepatitis and appropriate therapy, I believe that many cases can have a prolonged survival and a favorable prognosis.

Chronic hepatitis is characterized by hepatocellular death from apoptosis or necrosis, a variable mononuclear or mixed inflammatory infiltrate, regeneration, and fibrosis. The proportion and distribution of these components vary widely. The presence of fibrosis in the hepatic biopsy denotes to me that it is chronic and often more serious consequences. Cirrhosis, a sequel of some chronic hepatitis cases, is often associated with portal hypertension, ascites, and multiple portosystemic collateral shunting. Some may have manifestations of liver failure, e.g., hyperbilirubinemia, coagulopathies, edema due to hypoalbuminemia, ascites, and hepatic encephalopathy.

The etiology of chronic hepatitis is generally not determined (Watson 2004). Copper-associated chronic hepatitis has been documented in a number of breeds as an inherited etiology. The hepatic copper accumulation increases to a level that becomes toxic to the hepatocyte, causing cellular death. Infectious causes of chronic hepatitis have been associated with leptospirosis and experimental infectious canine hepatitis virus. Chronic liver injury has also been reported in dogs with aflatoxicosis and drug-induced hepatitis. Some dogs treated with the anticonvulsant drugs primidone, phenytoin, and phenobarbital can develop chronic hepatitis. I have also observed some dogs given chronic nonsteroidal anti-inflammatory drugs (NSAIDs) to have hepatitis, and there could be a causal relationship in some cases, because we know NSAIDs can cause acute liver damage as an idiosyncratic reaction. Finally, immune-associated hepatitis may occur in the dog. Circulating autoantibodies are important diagnostic markers used to identify autoimmune liver disease in humans. Canine autoantibodies (ANA, antimitochondial antibodies [AMA], smooth muscle antibodies [SMA], liver membrane autoantibodies [LMA]) are often present in dogs having chronic hepatitis, but their importance in classifying canine chronic hepatitis is unknown, and they are thought by some to occur secondary to liver damage (Weiss et al. 1995). Nonetheless, immune-mediated mechanisms are believed to be associated with certain cases of chronic hepatitis, and this is supported by the fact that some dogs respond favorably to immunosuppressive therapy. There is, lastly, a lobular dissecting hepatitis characterized by a rapid diffuse spread of inflammation throughout the liver lobule. This condition is observed in younger dogs (often standard poodles) and is associated with rapid development of hepatic encephalopathy and ascites.

There are a number of breeds that have an increased incidence and suspected genetic basis. Some of these breeds have copper-associated chronic hepatitis. Other breeds not yet associated with copper include the standard poodle, cocker spaniel, springer spaniel, and Scottish terrier (Andersson and Sevelius 1991).

The diagnosis of abnormal copper accumulation requires a liver biopsy. The measurement of serum copper or serum ceruloplasmin levels is normal. Excess copper within the liver can be demonstrated using the histochemical stains rhodanine or rubine acid. Definitive determination of excess hepatic copper requires a quantitative analysis of tissue copper measured on the biopsy sample (Rolfe and Twedt 1995). Normal canine hepatic copper concentrations are less than 400 µg/g (ppm) dry weight liver. Hepatic copper concentrations in dogs with secondary copper accumulation are usually less than 1,000 µg/g dry weight, while breed-associated hepatotoxicities generally have higher concentrations (> 750 µg/g). The location of copper secondary to hepatic cholestasis is generally in the zone 1 (perportal) location. Liver disease with concurrent copper accumulation is reported in the Bedlington terrier, the Doberman pinscher, the West Highland white terrier, the Skye terrier, the Dalmatian, and, most recently, the Labrador retriever. Occasionally we see other pure-breed dogs as well as mixed-breed dogs with high copper concentrations and suspect some may have primary copper retention.
The average age at presentation generally ranges from 4 to 10 years. It is interesting to note that in both our series and in studies by others it is uncommon to observe chronic hepatitis/cirrhosis in dogs older than 10 years of age. I believe that as a general rule, old dogs (> 11 years of age) don’t generally present with chronic hepatitis/cirrhosis, or if they do, they are at or near end-stage disease. The clinical signs parallel the extent of hepatic damage. Early in the disease, there is usually no or minimal clinical signs. Only after the disease progresses do the clinical signs specific for liver disease become evident. Frequent early signs are gastrointestinal associated, with vomiting, diarrhea, and poor appetite or anorexia. Ascites, jaundice, and hepatic encephalopathy may then occur as the disease progresses. With development of these late signs, the long-term prognosis is generally poor.

The laboratory findings include consistently elevated ALT and ALP. The magnitude of the increase need not be marked, however. One report found that 75% of the cases at diagnosis had abnormal bilirubin elevation (mean elevation of 2.6 mg/dl) (Webster 2005). Serum proteins are variable. As the lesions become more severe, albumin levels decline. Serum bile acids are abnormal in most cases of significant chronic hepatitis. The measurement of bile acids appears to be a good screening test for the patient with unexplained elevations in ALT and ALP. In our study, all dogs evaluated with chronic hepatitis had abnormal bile acid concentrations and increases in both ALT and AST. ALT, AST, and bile acids appear to be the best indicators of chronic hepatitis.

There is little information on the prognosis of chronic hepatitis with and without therapy. The prognosis in dogs with advanced chronic hepatitis and cirrhosis is guarded. A study by Strombeck found mean survivals ranging from 6 to 16 months with therapy (Strombeck and Gribble 1978). This study also found that dogs with hypoalbuminemia, hypoglycemia, and coagulopathies had very guarded prognostic factors, and many died within 1 week of diagnosis. A second study of 79 dogs found that dogs with cirrhosis had a survival of less than 1 month, and dogs with chronic hepatitis had a mean survival in the range of about 20 to 30 months (Sevelius 1995). Most of these dogs were not advanced in their disease and had concurrent corticosteroid treatment. Low albumin, ascites, and hepatic encephalopathy are all poor prognostic indicators.

I have four general goals in therapy for chronic hepatitis: (1) remove the etiology, (2) provide an adequate diet, (3) provide specific therapy, and (4) provide general liver support. First, the therapy for chronic hepatitis involves removing the primary etiology if it can be identified. Short of treating the primary etiology, all other therapies suggested are unproven in the management of chronic hepatitis in dogs. Much of the therapy is directed at providing adequate liver support. This often involves the use of multiple therapies.

Diet therapy should be considered in all cases; however, only general guidelines can be given. First, palatability is important to ensure that adequate energy requirements are met. Next, there is a misconception that liver patients should be placed on a protein-restricted diet. Protein restriction should only be instituted in the patient that has clinical evidence of protein intolerance (i.e., hepatic encephalopathy). The goal of dietary therapy is to adjust the quantities and types of nutrients to provide nutrient requirements, but to avoid the production of the excess nitrogen byproducts associated with liver disease. As a general recommendation, one should feed a highly digestible protein source contributing 15% to 20% of dry matter basis (DM) (Bauer 1996). High carbohydrate and moderate fat content is important to supply caloric needs. Mineral supplementation containing high concentrations of both copper and iron should be avoided. A diet with the lowest possible copper content is advised (ideally < 5 mg/kg [ppm] copper DM).

The benefits of anti-inflammatory therapy for chronic hepatitis in the dog are unproven, although my clinical impression is that it is beneficial in some cases. The treatment of chronic hepatitis is quite controversial, and there are as yet no good controlled studies in animals to support corticosteroid use in every case. One study found that some dogs with chronic hepatitis tended to have a prolonged survival time when treated with corticosteroids (Strombeck and Gribble 1978). This retrospective study is one with a wide diversity of diseases and concurrent therapies. Nonetheless, it appears that corticosteroids offer a benefit in at least some cases (possibly around 25%). A suggested dose of 1 to 2 mg/kg/day using either prednisone or prednisolone should be instituted. When clinical improvement is suspected or after several weeks, the dose is then gradually tapered to a dose of 0.5 mg/kg/day or every other day. The only accurate way to evaluate a response to any therapy is to rebiopsy the patient in 6 months to 1 year, because the patient will develop a concurrent steroid hepatopathy, with increased liver enzymes, making laboratory determination of any improvement impossible. Because of the steroid hepatopathy, along with the negative side effects with steroids, I am now tending to use alternate immunosuppressive therapy. Azathioprine is an effective immunosuppressant drug that has been shown to increase survival in man when treated for chronic hepatitis in conjunction with corticosteroids. There are no studies in dogs with chronic hepatitis using azathioprine,
but we have recently also observed azathioprine-induced secondary hepatopathies. Consequently, I now tend to use cyclosporine in cases of chronic hepatitis because of its excellent immune suppression and the fact that a generic form is available and less expensive. I have observed resolution in a number of dogs treated with cyclosporine alone at a dose of 5 mg/kg b.i.d. I advise monitoring cyclosporine blood levels and adjusting the dose appropriately. When liver enzymes decline, I reduce the dose to daily administration. The advantage of this therapy, although it is expensive, is the lack of steroid side effects and secondary steroid hepatopathy, along with the ability to monitor progress through liver enzymes and the excellent clinical response we have observed in many cases.

Chronic hepatitis associated with abnormal hepatic copper accumulation requires copper chelator or zinc therapy. Hepatic copper levels of greater than 1,000 µg/g dry weight liver should have chelator therapy for at least some period of time. Chelators bind with copper either in the blood or the tissues and then promote copper removal through the kidneys. Penicillamine (Cuprimine, 250 mg capsules) is the most frequent copper chelator recommended for use in dogs. The dose is 15 mg/kg b.i.d. given on an empty stomach. A second copper chelator is trientine (Syrprine), which has been produced to use in patients intolerant to penicillamine. Zinc therapy can be used once the liver is decoppered with chelators. Oral zinc therapy works by causing an induction of the intestinal copper-binding protein metallothionein. Dietary copper binds to the metallothionein with a high affinity that prevents transfer from the intestine into the blood. When the intestinal cells die and are sloughed, the metallothionein-bound copper becomes excreted through the stool. An initial induction dose of 15 mg/kg body weight (or 50–100 mg b.i.d.) of elemental zinc is suggested (Brewer et al. 1992). Following 1 to 3 months of induction, the dose can be reduced by approximately half. The goal is to get serum zinc concentrations of more than 200 µg/dl but less than 500 µg/dl. The zinc must be administered on an empty stomach and has the frequent side effect of vomiting.

Other therapy for chronic hepatitis includes ursodeoxycholic acid (Ursodiol–Actigall). This drug is a synthetic hydrophilic bile acid that essentially changes the bile acid pool from the more toxic hydrophobic bile acids to less toxic hydrophilic bile acids. Ursodeoxycholic acid has been shown to increase bile-acid-dependent flow and reduce hepatocellular inflammatory changes, fibrosis, and possibly some immunomodulating effects (Leveille-Webster 2000). The hepatoprotective characteristics make one believe that ursodeoxycholic acid acts as an antioxidant. The dose for ursodeoxycholic acid is 15 mg/kg daily. Antioxidants can also be given to provide liver support to promote optimal hepatic function. Vitamin E, d-alpha tocopheryl, is a membrane-bound antioxidant. S-Adenosyl methionine (SAMe) (Denosyl) is a precursor of the antioxidant glutathione in the hepatocyte. Milk thistle has been used for centuries as a natural remedy for liver disease. Silymarin is the active extract and consists of bioflavonoligans that have been reported to work as antioxidants, scavenging free radicals and inhibiting lipid peroxidation. Marin (Nutramax Labs) contains a silybin-phosphatidylcholine complex, and it is the phosphatidylcholine that increases intestinal absorption.

The Icteric Dog

Clinical icterus is usually identified when serum bilirubin concentrations approach 2.5 mg/dl or higher in the dog. Icterus can be divided into prehepatic causes, hepatic causes, and posthepatic causes (Webster and Cooper 2008). A complete blood count, biochemical profile, and urinalysis will help classify the icterus. Prehepatic icterus is caused by hemolytic disease associated with a dropping hematocrit and regenerative anemia. Because the liver has such a reserve capacity to handle unconjugated bilirubin, the hematocrit must fall significantly (usually into the teens) before icterus is evident. Hepatic and posthepatic icterus is a little more difficult to differentiate. Posthepatic icterus generally is associated with ALP, GGT > ALT, AST concentrations. Abdominal ultrasound generally helps support either hepatic or posthepatic disorders such as bile-duct obstructions, gallbladder mucocele, cholecystitis, cholelithiasis, and pancreatitis. It is also difficult to differentiate pancreatic from biliary tract disease because the clinical and laboratory findings are frequently similar. With acute pancreatitis the liver can be involved in two ways. First, the release of inflammatory cytokines from the necrotic pancreas directly insults hepatocytes, and second, extensive pancreatic inflammation may extend to and impinge on the common bile duct, resulting in a mechanical extrahepatic obstruction. In some cases, acute hepatic inflammation or cholestatic disease will mimic changes seen with pancreatitis. The clinician must consequently use all information available, including the biochemistry and imaging information, to make a diagnosis. The Spec cPL test is the best laboratory test for the diagnosis of pancreatitis in the dog or cat. Amylase and lipase are of little value in diagnosing pancreatitis in the dog. Routine abdominal radiographs are useful in detecting effusions, changes in organ size, and masses. Ultrasound provides the best imaging technique for detecting parenchymal change, contour irregularities, cystic changes, or mass involvement. The pancreas can be seen in almost all cases; however, pancreatitis can be missed in up to one-third of the cases. Ultrasound is very helpful in detecting biliary tract changes. Cholelithiasis can be observed with
ultrasound, but not usually with radiographs, because canine choleliths are generally radiolucent. Intrahepatic bile ductular dilation is also suggestive of biliary obstructive disease.

**Mucocele**
To date, more 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 that can be detected with ultrasound (Crews et al. 2009). The changes described often 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. Most have serum elevations of total 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 a genetic defect in the MDR3 hepatobiliary transporter gene involved in phosphocholine transport into the bile (Ale et al. 2007). It is thought that the lack of phosphocholine in the bile may predispose to mucocele formation. Risk factors identified in mucocele cases include endocrine disease (hypothyroidism, Cushing’s disease), idiopathic vacuolar hepatopathy (progesterones), and 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 (with a wagon-wheel or kiwi-fruit appearance). This should be differentiated from biliary sludge by the absence of gravity-dependent bile movement; the mucocele is nonmovable. The gallbladder wall thickness and wall appearance are variable and nonspecific. The cystic, hepatic, or common bile duct may be normal in size or dilated, suggesting biliary obstruction. In one series, loss of gallbladder wall integrity and gallbladder rupture was present in 50% of the dogs, and a positive aerobic bacterial culture was obtained from bile in a majority of these dogs (Besso et al. 2000). Gallbladder wall discontinuity on ultrasound indicated rupture, whereas neither of the bile patterns predicted the likelihood of gallbladder rupture. Cholecystectomy is the treatment for mucoceles. There are reports of resolution of mucoceles using ursodeoxycholic acid (ursodiol), but even with a few cases reported to improve, the recommendation is still surgery in the sick dog (Walter and Dunn 2008). Ursodeoxycholic acid is thought to upregulate the MDR3 gene that may be the cause of mucocele production in some dogs.

Mucosal hyperplasia is present in all gallbladders examined histologically but infection is not present with all cases, suggesting biliary stasis and mucosal hyperplasia as the primary factors involved in mucocele formation. Based on information known to date, the recommended course of action with an immobile ultrasonographic stellate or finely striated bile gallbladder with clinical or biochemical signs of hepatobiliary disease is a cholecystectomy. A mucocele is reported to be the most common cause of a gallbladder perforation. Following cholecystectomy and recovery in the postoperative period, the prognosis is excellent, especially when the liver enzymes are normal. Mortality rates are reported to be in the 20% range, and some patients may persist in having liver disease with elevated liver enzymes.

**Cholecystitis/Cholelithiasis**
Bacterial cholangitis and cholecystitis are occasionally found in dogs but are quite common in cats. These animals often present with acute signs and laboratory findings of cholestatic liver disease. Fever, leukocytosis, and icterus are common. Biliary tract perforation results in bile peritonitis. Ultrasonography is a sensitive and specific indicator of extrahepatic biliary tract disease. Thickness of the gallbladder and duct wall is common with cholecystitis. In suspected cases possibly having a bacterial component, it is reasonable to perform an ultrasound-directed or laparoscopic-assisted gallbladder aspirate. Occasionally, gas within the lumen or wall is observed as an emphysematous cholecystitis. Emphysematous cholecystitis is usually secondary to a combination of gallbladder wall ischemia and proliferation of gas-forming bacteria, such as *Escherichia coli* or *Clostridium perfringens*, and has been reported as a complication with diabetes mellitus with an emphysematous cholecystitis. The most common isolates in bacterial cholecystitis are *E. coli*, followed by *Enterococcus*, *Enterobacter*, *Klebsiella*, *Streptococcus*, *Pseudomonas*, *Bacteroides*, and *Clostridium* spp. Treatment involves 3 to 4 weeks of appropriate antibiotic therapy based on culture. With fear or evidence of gallbladder perforation, a cholecystectomy is indicated.

Cholelithiasis and choledocholitiasis account for less than 1% of patients with liver disease. Cholesterol gallstones are common in humans but very rare in dogs and cats. Most often canine and feline choleliths are bilirubin pigment gallstones with variable amounts of calcium salts. I believe that most of these develop secondary to a biliary
infection resulting in deconjugation of soluble bilirubin, with precipitation of bile being the nitus of the stone formation. Cholelithiasis is a reported to be of higher incidence in miniature schnauzers and toy poodles. Most choleliths are clinically silent; however, clinical signs associated with cholelithiasis are usually related to cholecystitis associated with vomiting, anorexia, icterus, fever, and abdominal pain. We have seen some dogs with vague abdominal pain to have choleliths. In some cases, a bile-duct obstruction or biliary tract rupture and peritonitis may occur. In clinical cases, surgical removal is indicated and appropriate antibiotic therapy initiated.

References


