The most important and most common primary liver disease in the dog is chronic hepatitis. Chronic hepatitis is not a single disease but rather the inflammatory changes can be due to many of etiologies. The therapy should be directed first at the cause of the inflammation. In most all cases a liver biopsy is required to confirm the diagnosis before effective therapy can be begun.

Chronic hepatitis is an etiologic diverse and morphologically variable condition associated by mixed inflammatory cell infiltrates. It is characterized by hepatocellular apoptosis or necrosis, a variable mononuclear or mixed inflammatory infiltrate, regeneration and fibrosis. The proportion and distribution of these components vary widely. Plasma cells, lymphocytes and macrophages predominate with a lesser number of neutrophils. Because we see non-specific mild portal inflammation as a common non-specific reactive change frequently secondary to intra-abdominal disorders like IBD I need the pathologist to tell me the severity of inflammation and chronicity of the disease. The presence of fibrosis in the hepatic biopsy usually denotes to me more serious consequences. As damage progresses cirrhosis can result with diffuse fibrosis, alteration in hepatic lobular architecture with the formation of regenerative nodules and abnormal vascular anastomoses. Cirrhosis, a sequel of some chronic hepatitis cases, is often associated with portal hypertension, ascites and multiple portosystemic collateral veins. Some may show manifestations of liver failure, e.g., hyperbilirubinemia, coagulopathies, edema due to hypoalbuminemia, ascites and hepatoencephalopathy. This type of chronic inflammation is uncommon in the cat as their inflammatory disease is directed at bile ducts causing cholangitis.

**ETIOLOGY**

The etiology of this chronic inflammatory condition is generally never determined. To date the best-described etiology of chronic hepatitis is the copper associated hepatitis of the Bedlington terrier (see below copper associated hepatitis). This breed and others are thought to have an inherited copper associated chronic hepatitis. Copper accumulates in hepatocyte from abnormal metabolism to a level that then becomes toxic causing hepatocyte death. There are also likely breeds that have difficulty in handling copper if taken in orally in excess amounts.

Infectious chronic hepatitis in man is most often associated with viral etiologies. The search for a viral etiology of hepatitis in the dog however has been unrewarding. The canine adenovirus type 1 given experimentally to partially immune dogs did caused hepatitis and fibrosis. Others identified a suspected acidophil cell hepatitis virus in dogs that were vaccinated with liver homogenates from dogs dying from chronic hepatitis. The vaccinated dogs developed fibrosis and inflammation in their livers. Subsequent further research or publications into viral etiologies are lacking. Chronic hepatitis has also been associated with leptospirosis with the authors describing "atypical leptopsires" in a colony of dogs having hepatitis. However we have examined over 50 dogs livers havng hepatitis using PCR for Leptospirosis and did not identify a single positive case. Other infectious agents suggested as a possible etiology include *Helicobacter sp*, Bartonella, and Leishmaniasis.
Chronic liver injury has also been reported in dogs with aflatoxicosis as well as various drug-induced hepatitis. Some dogs treated with anticonvulsant drugs primidone, phenytoin and phenobarbital will develop chronic hepatitis. We have also observed some dogs treated with NSAIDs to also have hepatitis which asks the question of NSAIDs being related to hepatitis. In man alpha-1-antitrypsin (AAT - also referred to as alpha one protease inhibitor) deficiency is known to cause chronic hepatitis and cirrhosis. Investigation by researchers in Sweden using immunostaining for AAT in hepatocytes found some dogs with chronic hepatitis to be positive for AAT in the hepatocytes but the dogs differ from man in that serum AAT remained in the normal range while humans have low concentrations. It is not known if the AAT accumulation is the cause or the result hepatocyte damage. The breed most often associated with AAT accumulation is thought to be the cocker spaniel.

Finally immune associated hepatitis may also occur in the dog. Autoimmune liver disease in humans is an important cause of chronic hepatitis and is associated with diagnostic circulating autoantibodies. It appears that autoantibodies (ANA, antimitochondrial antibodies [AMA], smooth muscle antibodies [SMA], liver membrane autoantibodies [LMA]) are markers of autoimmune hepatitis in humans. A number of studies have been performed in dogs looking for liver associated antibodies and cell-mediated responses to support autoimmune disease as an etiology. Findings so far suggest autoimmune liver disease exists but studies fail to conclusively prove its existence. The pathogenesis proposed is that an insulting agent damages the hepatocytes thus releasing liver antigens that initiate a secondary immune response perpetuating chronic hepatitis. Nonetheless, immune-mediated mechanisms are thought to occur in some cases of chronic hepatitis and this is further supported by the fact that some dogs respond favorably to immunosuppressive therapy.

There are also a number of breeds that have an increased incidence of chronic hepatitis and are thought to be inherited. Some of these breeds have copper associated chronic hepatitis and are discussed below. Other breeds not yet associated with copper include the standard poodle, Cocker spaniel, Springer spaniel and Scottish terrier. The pathogenesis of the hepatitis is yet unknown. Cocker spaniels both English and American tend to be more commonly males and ATT accumulation may play a role in their disease. More recently in Europe English Springer Spaniels have been reported to have a breed associated hepatitis. Standard poodles are more commonly females and tend to have prolonged survival with immunosuppressive therapy. We are currently studying the standard poodle at Colorado State University.

**COPPER ASSOCIATED HEPATITIS**

Copper is an essential trace element required as a redox co-factor for many different enzymes. Copper enters the body through the diet and approximately 30% is absorbed by the upper small intestine with unabsorbed copper passing through the feces. Although the exact details of intestinal Cu absorption is not completely delineated it is clear that copper is taken up in the intestine through an active transport mechanism shared with zinc. Intestinal copper is quickly bound to the cytosolic protein metallothionein. Intestinal Cu is subsequently transported to the liver bound to albumin and transcuprein. The liver is responsible for the uptake and storage of copper, as well as the regulation of excretion of this metal into the bile. Hepatic copper is either complexed to ceruloplasmin, an acute phase reactant protein, and transported to peripheral tissues for utilization, or Cu is redistributed among the various metallothioneins in the liver. Metallothioneins are cysteine-rich, cytosolic proteins capable of binding several metal ions, including copper.
Metallothioneins function are to protect the hepatocyte against the toxicity from free Cu catalyzing oxygen free radicals and also to mediate Cu transport into the bile for removal from the body. The normal hepatic copper concentrations in dogs are maintained at approximately 200-400 µg/g dry weight liver.

Recently there has been characterization of the genetic regulation of copper excretion by the liver. A specific gene in humans ATP7b is a copper-transporting ATPase expressed within the secretory pathway of hepatocytes and plays a critical role in copper excretion and ceruloplasmin production. A second gene encoding COMMD1 (MURR1) is expressed in the liver suggesting that this protein also plays a role in hepatic copper transport and biliary copper excretion. Wilson disease in humans is an inherited mutation in the gene encoding human ATP7b and results in hepatic copper overload and decreased Cu-ceruloplasmin production. Bedlington Terriers also have an inherited disorder of copper homeostasis. These animals have impaired copper excretion into bile but no abnormality in copper incorporation into ceruloplasmin suggesting that the defect occurs distal to the function of ATP7b in intracellular copper transport. This disorder in the Bedlington terrier has recently been shown to result from deletion of a gene on chromosome 10 encoding a small cytosolic protein termed COMMD1 (MURR1). Clinically affected dogs have a progressive hepatic Cu accumulation occurring with age ranging from 1,000 to 12,000 µg/g dry weight of liver. The extent of hepatic damage tends to parallel the increasing hepatic Cu concentrations. The morphological changes extend from focal necrosis to chronic hepatitis that may ultimately lead to cirrhosis. In some cases, acute hepatic necrosis and Cu associated hemolytic anemia and acute liver failure may occur.

The pathogenesis of hepatic damage is thought to occur when the metallothionein sequestration ability for Cu becomes exceeded and free copper is released. The mitochondria appear to be the first organelle to become damaged resulting in mitochondrial electron leak initiating lipid membrane peroxidation and eventual cellular death.

The excess hepatic copper is sequestered in lysosomes bound to metallothionein proteins. Routine stained histological sections may show abundant golden-brown refractile hepatocellular lysosomal granules that contain the sequestered Cu. These granules are nonspecific for copper, but may indicate abnormal copper accumulation. A more reliable semi-quantitative estimation involves histochemical staining for hepatic Cu. Reliable tissue bound copper stains include rhodanine and rubeanic acid. The copper tends to accumulate in a centrilobular location. A grading system of 1-5 estimating the quantity of Cu granules correlates roughly with quantitative determination of hepatic Cu when the values approach >750 µg/g dry liver weight.

Definitive determination of the amount of hepatic Cu requires a quantitative analysis of tissue Cu. Hepatic copper content is measured using atomic absorption spectroscopy and can be determined on needle biopsy samples, although larger samples provide better accuracy. Samples for analysis should be placed in a Cu free container (such as a serum blood tube) for analysis. Normal canine hepatic Cu concentrations are less than 400 µg/g dry weight liver. The concentration at which abnormal hepatic Cu contributes to hepatic damage is unknown. It is possible to take adequate size biopsy sample embedded in paraffin for histology and de-paraffinize the sample to obtain a quantitation of copper.

**Other Breeds.** Since the discovery of the Bedlington terrier copper hepatopathy other breeds have been found to have abnormal concentrations of hepatic copper and hepatitis. The mechanism of copper sequestration in other breeds is unknown but thought
to be different than the Bedlington terrier. Doberman hepatitis is a form of chronic hepatitis. The incidence is unknown but may occur in as high as 4 to 6% of dogs. The high percent suggests a genetic predisposition. Females seem to be over-represented. The disease begins in young dogs (1-3 years) with increased ALT concentrations and having sub-clinical hepatitis. Clinical evidence of liver disease usually begins around 4-7 years of age with chronic hepatitis and cirrhosis. Copper appears to be associated with the disease and recent studies suggest that copper is often increased prior to development of clinical hepatitis. Cu$^{64}$ isotope studies demonstrate affected dogs have an impaired biliary excretion of copper. Copper chelator therapy in sub-clinical dogs normalized copper concentrations with improvement in the grade of histological damage. In affected dogs the copper concentrations generally range from 1000-2000 µg/g DW liver. At this point no specific gene has been identified for this disease to determine the mode of genetic transmission. The above evidence suggests a primary defect in copper metabolism in the breed but awaits further conformation. An autoimmune mechanism is also suggested but this too requires further investigation.

A retrospective study summarizes 10 Dalmatians suspected of having hepatic copper toxicosis. Two of the dogs were related and all presented for gastrointestinal clinical signs, had elevated liver enzymes and necroinflammatory hepatic changes associated with copper-laden hepatocytes most prominent in a centrilobular location. The mean hepatic copper concentration was 3,197µg/d dry weight liver. In 5 of these 9 dogs, hepatic copper concentrations exceeded 2,000 µg/d DW liver with several dogs having copper levels as high as those observed in Bedlington Terriers. These findings support the hypothesis that a primary metabolic defect in hepatic copper metabolism occurs in the Dalmatian breed. The mechanism and genetic basis of this condition is under further study.

The West Highland White terrier has been associated with liver disease and hepatic copper accumulation. The clinical findings appear to be different than other breeds associated with copper accumulation. Dogs reported showed evidence of hepatitis or cirrhosis and had increased hepatic copper ranging from 1000-3000 µg/g dry weight liver. Twenty-four dogs described ranged from 3-7 years of age. Some dogs in this report had high copper concentrations but no evidence of liver disease while others did. While the Bedlington Terrier tends to accumulate Cu with age it was not apparent in this group of dogs. Affected dogs that were bred produced offspring with elevated copper concentrations supporting a genetic defect. Several dogs were treated with zinc therapy and showed reduction in hepatic copper concentrations.

Chronic hepatitis is reported to be common in this breed and there is evidence that copper accumulation is associated with some, but not all the cases. We find females are more commonly affected and the diagnosis is generally made between 2 to 7 years of age. Hepatic copper concentrations generally range between 750 to 2000 µg/g dry weight liver. The histological location of the Cu being centrilobular suggests that Cu elevation is probably not secondary to cholestasis. It appears that copper chelation is beneficial in some dogs with hepatitis and copper accumulation.

The Skye Terrier, Anatolian Shepherd, and possibly the Keeshond as well as other breeds have also been reported with liver disease and increased copper accumulation. The exact mechanism or extensive description in specific breeds is lacking.

**Secondary Copper Accumulation**

Copper may also concentrate in the liver secondary to cholestatic liver disease or from increased oral copper intake. Recently the Labrador retriever is reported to have
copper associated hepatitis and when chelated and then placed on a low copper diet the liver copper concentrations remain low. The author believes most all commercial dog foods meeting AFFCO feeding standards contain too much copper and some dogs or possibly breeds can not handle those copper concentrations and subsequently develop hepatitis. This newer and emerging problem appears to have become accentuated when the dog food companies changed the type of copper they supplement in the diet to a form that is much more biologically available. The prescription liver diets contain low copper concentrations.

**CLINICAL FINDINGS**

The incidence of chronic hepatitis makes up approximately one fourth of the cases having liver biopsies at Colorado State University (based on a review of 150 consecutive liver biopsies). Chronic hepatitis is more common in female dogs. The average of presentation 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. 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 are usually no or minimal clinical signs. Only after the disease progresses do the clinical signs specific for liver disease becomes 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 rise need not be marked however. One report found 75% of the cases with abnormal bilirubin elevation (mean elevation of 2.6 mg/dl). Serum proteins are variable. As the lesions become more severe albumin levels decline. Serum bile acids are abnormal in most cases having significant chronic hepatitis and measurement of bile acids appear 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. In a second study only 8/26 dogs with chronic hepatitis had normal fasting bile acids. However, postprandial samples were not determined in these cases. Determining postprandial bile acids has been shown to increase the sensitivity of this test.

A presumptive diagnosis is made based on the clinical features and persistent increases of ALP and ALT values. A definitive diagnosis requires a hepatic biopsy showing characteristic morphological patterns. Needle aspirates are not helpful in making the diagnosis of chronic hepatitis because it is important to see the architecture of the liver and location and extent of the inflammation. One must work with the pathologist when making the diagnosis of chronic hepatitis and to be certain that characteristic abnormalities found in chronic hepatitis are present.

**PROGNOSIS**

There is little information of the prognosis with and without therapy. The prognosis in dogs with advanced chronic hepatitis and cirrhosis is guarded. In a study by Strombeck found mean survivals ranging from 6 to 16 months with therapy. This study also identified that dogs with hypoalbuminemia, hypoglycemia and coagulopathies have 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 one month and dogs with chronic hepatitis had a mean survival in the range of about 20 to 30 months. Most of these dogs were not advanced in their disease and had concurrent corticosteroid treatment.
TREATMENT

I have four general goals in therapy: 1) remove the etiology, 2) provide an adequate diet, 3) give specific therapy and 4) providing general liver support. First step in the therapy for chronic hepatitis and other liver diseases 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 liver disease in dogs. Much of the therapy is directed at providing adequate liver support. This often involves the use of multiple therapies. Without an etiology and significant inflammation and necrosis I use anti-inflammatory therapy. The traditional therapy is to use corticosteroids. The problems with steroids are the side effects, the steroid hepatopathy and the inability to know if the dog is responding short of a liver biopsy. We have more recently been using cyclosporine with good success and can easily document improvement of liver enzymes. Initial dose has been 5 mg/kg bid. Other therapy may include ursodeoxycholic acid and liver support medications. Please refer to lectures on liver therapy for further information and detail.