The discussion below is directed at therapy for chronic hepatitis but much of what is presented can also be extrapolated to other types of liver disease in both the dog and cat. 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.

**Diet.** Adjusting diet therapy should be considered in all cases however only general guidelines should be given. First, palatability is important to assure adequate energy requirements are met. Next, there is a misconception about diet and liver disease 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 excess nitrogen byproducts associated with liver disease. As a general recommendation the dietary protein should represent 17 to 22% of digestible Kcal.

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.

There is also evidence that fiber may have several beneficial actions in patients having liver disease. First, dietary fiber effectively binds bile acids in the intestinal tract and promotes their removal. Secondly soluble fiber appears to have some benefit in managing hepatic encephalopathy by generation of fermentation products (short chain fatty acids). These act by impairing the intestinal uptake of the surrogate marker of HE, ammonia. Soluble dietary fiber has a similar effect as lactulose and would provide a logical long-term nutritional approach in the management of some animals with hepatic encephalopathy. Psyllium, as a source of soluble fiber given at a dose of 1-3 tsp/day can be used as a dietary supplement.

Diets low in copper are recommended for the dogs that have copper associated liver disease based on biopsy. The restriction of dietary copper may do little to lower hepatic copper concentrations in diseased dogs having large amounts of hepatic copper. Diet will lessen further absorption of the metal. It is difficult to limit dietary copper because most commercial dog foods contain supplemental copper that meet, or more frequently exceed the minimal dietary requirements. Most formulated “liver diets” have lower copper concentrations and are often supplemented with additional zinc. Homemade diets can also be prepared that do not to contain excess copper. These diets should exclude liver, shellfish, organ meats and cereals that are all high in copper content. Vitamins or mineral supplements should not contain copper or iron.

**Antinflammatory Therapy.** Decreasing inflammation as a specific therapy for chronic hepatitis in the dog or cholangitis in the cat is unproven although the author’s clinical impression suggests anti-inflammatory therapy 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 corticosteroids use in every case. Antiinflammatory therapy is indicated in suspected immune mediated chronic hepatitis.

In a study by Strombeck found that some dogs with chronic hepatitis tend to have a prolonged survival when treated with corticosteroids. This retrospective study is one with a wide diversity of diseases and concurrent therapies. But none-the-less, it appears that corticosteroids offer 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 eventually 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 re-biopsy 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. Alternatively one could stop steroids and recheck enzymes in 1 to 2 months. There is also evidence of improvement of immune hepatitis in humans when treated with budesonide. These patients had also less clinical signs because of the more "topical" effect on the liver subsequent hepatic clearance.

Because of the side effects of corticosteroids and the failure to successfully monitor liver enzymes while receiving steroids other immune suppressive therapy may be more rational approach. Azathioprine is an effective immunosuppressant drug that has shown to increase survival in man when treated for chronic hepatitis in conjunction with corticosteroids. This therapy may also be beneficial in dogs (don't use in cats) by increasing the immunosuppressive response and enabling a reduction of both steroid dose and their side effects. A dose of 2.2 mg/kg/day is the suggested starting dose and after several weeks given every two days. The level of glucocorticoids can frequently be reduced when using azathioprine. It is important to note that azathioprine has been infrequently been associated with a drug induced hepatic necrosis or acute pancreatitis. We have more recently been using cyclosporine A in some cases with a good clinical response. Our experience using 5 mg/kg bid or q 24 hrs (without steroids) has been very encouraging in dogs that are thought to have immune mediated chronic hepatitis. The veterinary formulation Atopica™ is a microemulsified preparation with the identical properties to Neoral™ that ensures more consistent bioavailability and better than the other human product Sandimmune™. Generally after 48 hours or longer I will get a blood level at the trough (right before the next pill). The ideal range of blood levels are within 400-600 ng/ml. Many dogs will develop gingival hyperplasia at the higher concentrations of cyclosporine. Azithromycin 10 mg/kg/day for 4-6 weeks will decrease the gingival hyperplasia. With evidence of clinical response at 5 mg/kg bid I will often decrease to once a day therapy. Using cyclosporine alone one can follow the liver enzymes making the need for a liver biopsy less frequently required.

Copper Reduction. If the liver biopsy of a dog with chronic hepatitis indicates significant abnormal hepatic copper accumulation, copper chelators or zinc therapy should be considered. Hepatic copper levels of greater than 1000 µg/g dry weight liver requires therapy to reduce copper concentrations (zinc or chelator). Animals having greater than 2,000 µg/g dry weight copper content should all have chelator therapy for at least some period of time.

Zinc therapy has a number of potential benefits in dogs with chronic hepatitis. Zinc has anti-fibrotic and hepatoprotective properties. Zinc given as the acetate, sulfate, gluconate or other salt has also been proven effective in preventing hepatic copper re-accumulation in Wilson's disease humans that have been decoppered with chelators. When patients were given oral zinc hepatic copper concentrations did not increase. 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 cell dies and is sloughed, the metallothionein bound copper becomes excreted through the stool. An initial induction dose of 15 mg/kg body weight (or 100 mg BID) of elemental zinc given twice a day is suggested. Following one to 3 months of induction the dose can be reduced in approximately half. The goal is to get serum zinc concentrations greater than 200µg/dl but less than 500. The zinc must be administered on an empty stomach and has the frequent side effect of vomiting. Replacement zinc therapy is administered at a dose of 2-3 mg/kg/day and is given for its antioxidant effects and replacement value in animals having zinc depletion in their liver.

Chelator treatment has a proven beneficial effect in dogs with abnormal hepatic copper concentrations. 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 bid given on an empty stomach. Side effects include anorexia and vomiting. Therapy using penicillamine is a slow and prolonged process taking months to years to cause a substantial reduction in hepatic copper concentrations however recent studies suggest penicillamine also has a protective effect in the liver beyond chelation therapy. It is believed penicillamine induces a hepatic copper binding protein, metallothionein, thus binding and sequestering copper in a nontoxic form in the liver. A second copper chelator is trientine (Syprine™) that
has been produced to use in patients intolerant to penicillamine. This drug is also given at a dose of 15 mg/kg bid and has less gastrointestinal adverse side effects. It is an “orphan drug” and must be special ordered by the pharmacist. In one study of Dobermans with hepatitis and copper penicillamine therapy for 3 months resulted in reduction of copper and the inflammatory damage.

**Antifibrotic Drugs.** Corticosteroids, zinc and penicillamine all have anti-fibrotic effects. Colchicine is a drug that has been used in treating persons with chronic hepatitis and other types of liver fibrosis. This drug interferes with the deposition of hepatic collagen and also stimulates collagenase activity to breakdown deposited fibrous tissue in the liver. It also is shown to have anti-inflammatory properties. There is still the lack of convincing data in humans and dogs with liver disease that colchicine is beneficial. A critical appraisal of colchicine in human liver disease having chronic hepatitis now questions its effectiveness. There are only 3 case reports of colchicine in dogs having questionable results. A dose of 0.03 mg/kg/day has been suggested. The drug given as a generic is inexpensive with only minimal gastrointestinal side effects sometimes noted at high doses.

**Choleretic Drugs.** Decreasing cholestasis has been shown to be of benefit in humans and animals having cholestatic hepatobiliary disease. As serum bile concentrations increase (these are predominately cytotoxic bile acids) they can cause cell membrane permeability changes and fibrogenesis. Ursodeoxycholic acid (Ursodiol -Actigall™- 300 mg caps) is a choleretic agent developed to dissolve gallstones but later found to have positive effects in patients with chronic hepatitis. 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, reduce hepatocellular inflammatory changes, fibrosis and possibly some immunomodulating effects. The hepatoprotective characteristics makes one believe ursodeoxycholic acts as an antioxidant. The dose for ursodeoxycholic acid is 15 mg/kg daily. No toxicity has been observed in dogs and cats at this dose. There has been a concern raised by some that it should not be used if there is any possibility of a bile duct obstruction for fear of biliary rupture. Although with obstruction surgery is indicated ursodeoxycholic acid is not a prokinetic and will not cause a rupture. In fact in experimental bile duct obstructions there was less secondary “toxic” changes in the liver in rats given ursodiol than placebo.

**Antibiotics.** Antibiotics are indicated for primary hepatic infections. There however may be evidence that bacterial colonization may take place in a diseased liver. Kupffer cell dysfunction could be a reason for secondary bacterial infections. It may be prudent for antibiotic therapy or trial for several weeks in patients having significant hepatic disease (i.e. chronic hepatitis). Amoxicillin, cephalosporin, or metronidazole are suggested. Metronidazole may have some immunosuppressive properties as well as antibacterial mechanisms. For liver disease I would use 7.5-10 mg/kg bid a much lower dose used for other bacterial infections because of hepatic metabolism of the drug.

**Antioxidants.** There has been recent interest in the management of certain types of liver disease using antioxidants. Antioxidants in general provide liver support to promote optimal hepatic function. Considerable evidence shows that free radicals are generated in chronic hepatitis and participate in the pathogenesis of oxidative liver injury in dogs and cats. Normally there is an extensive system of cytosolic and membrane bound enzymatic and non-enzymatic antioxidants which function to prevent oxidative damage by “scavenging” or “quenching” free radicals that are formed. It is reported that close to half the dogs and cats with liver disease have reduced glutathione concentrations in the blood and liver supporting that oxidative damage is present.

Vitamin E, d-alpha tocopherol, functions a major membrane bound intracellular antioxidant, protecting membrane phospoholipids from peroxidative damage when free radicals are formed. Vitamin E is shown to protect against the effects of copper, bile acids and other hepatotoxins. In a small study of dogs having chronic hepatitis we found all dogs had evidence of oxidative damage. In a three-month placebo controlled study treating only with vitamin E there was evidence improvement in the oxidant status of the treated dogs however we did not identify changes in clinical, laboratory or histology during this short treatment period.

A suggested vitamin E dose is 50 to 400 IU a day. The d-alpha tocopheryl formulation is much more potent than the most common commercial form (dL-alpha
tocolpheryl). Since bile acids are required for fat-soluble vitamin E absorption and may be reduced in cholestatic liver disease, a water-soluble formulation is suggested. For a water soluble form I use Twin labs Liqui-E. The vitamin E is derived from TPGS (d-alpha tocopheryl polyethylene glycol 1000 succinate) and has a rapid absorption. Because of the potential benefits of vitamin E, the lack of side effects and since the drug is inexpensive I place most all my liver patients on E therapy.

S-Adenosylmethionine (SAMe) [Denosyl™. Nutramax Laboratories] is a naturally occurring molecule found in all living organisms and is involved in a number of metabolic pathways that appear to be beneficial to the liver as well as other tissues. SAMe is involved in three major biochemical pathways. It is involved in cell replication and protein synthesis, has a modulating influence on inflammation and plays a role as a precursor of the antioxidant glutathione in the hepatocyte. Research has demonstrated that the exogenous administration of SAMe to have potential beneficial effects for a number of types of liver damage. In one study giving acetaminophen to cats at a sub-lethal dose we observed protective effects of SAMe when measuring markers of hepatic oxidative damage and RBC fragility.

Studies investigating naturally occurring liver disease in animals are required to determine the benefit of SAMe administration in liver disease. I will routinely prescribe SAMe (Denosyl™) in patients having acute liver toxicity and in many cases having chronic liver disease or other liver disorders. A recommended dose range is 20 mg/kg/day. It should be given on an empty stomach and the tablets not broken. There are numerous commercial sources of SAMe each having variable concentration or purity of the compound. Foil wrapped tablets produced by a company that provides reliable purity and potency is recommended.

Milk thistle has been used for centuries as a natural remedy for diseases of the liver and biliary tract. Silymarin the active extract consists of bioflavonoligans that have been reported to work as antioxidants, scavenging free radicals and inhibiting lipid peroxidation. Several recent human clinical trials have assessed the efficacy of silymarin in the treatment of liver disease. The data is somewhat difficult to interpret because of the limited number of patients, poor study design, variable etiologies, lack of standardization of silymarin preparations with different dosing protocols. There is however compelling evidence to suggest silymarin has a therapeutic effect in acute viral hepatitis, alcoholic liver disease, patients with cirrhosis, and in toxin or drug-induced hepatitis. Unfortunately, the purity of commercial products, and therapeutic dosage is unknown. Clinical trials are limited in small animals and reported success is only anecdotal. Dosage of milk thistle ranges from 50 to 250 mg bid. Milk thistle is reported to have an extremely low toxicity in humans and animals and has been used extensively in clinical patients with little concern for side effects.

To date there is only one published clinical study evaluating the efficacy of silymarin in the treatment of liver disease in dogs. In this placebo controlled experimental study dogs were poisoned with the Amanita phalloides mushroom. Researchers showed silymarin to have a significant effect on liver enzymes, the extent of histological liver damage and survival outcome. Based on this canine study and several clinical reports in humans poisoned with Amanita and treated with silymarin having a favorable outcome many physicians in Europe now accept silymarin as part of the standard protocol for mushroom poisoning.

Silibin appears to be a principle active isomer of the silymarin extract. Although silibin is a potent compound GI absorption is poor. Bioavailability is increased by complexing with phosphatidylcholine (Siliphos™). We have evaluated a commercially available complex (Siliphos™, Indea labs) in a preliminary pharmacokinetic study normal cats and found no clinical outward signs of toxicity giving a dose up to 5 mg/kg and have found improvement in oxidant status in the blood of normal cats and cats having liver disease. Marin™ (Nutramax labs) contains silybin-phosphatidylcholine complex and for cats it contains vitamin E and for dogs it has zinc and vitamin E. A new compound Denamarin™ is available containing SAMe and silybin and is available in a chewable formulation. It appears that the combination of both compounds have good a absorption. The Denamarin product appears to be very stable and not oxidized like the other SAMe products. I personally have no experience with other SAMe or milk thistle products.

**General Support Therapy.** The remainder of the therapy for chronic hepatitis involves treatment of secondary complications. These occur as the disease becomes
advanced. Hepatic encephalopathy, GI ulceration and ascites are common clinical occurrences in advanced hepatitis or cirrhosis.

The first step in the management of hepatic encephalopathy includes the use of enemas to clean the colon of both bacteria and protein substrates for ammonia production. Slightly acidic enemas will lower the pH of the colon thus ionizing ammonia and reducing its absorption. Povidone iodine (betadine) can safely be given by enema as a 10% solution (weak tea color) that will both acidify the colon and have an antiseptic action reducing bacterial numbers.

Nonabsorbable intestinal antibiotics are used to alter bowel flora and suppress urease-producing organisms important in formation of factors causing hepatic encephalopathy. Antibiotic suggestions include oral ampicillin, aminoglycosides (neomycin, kanamycin or gentamicin) or metronidazole. Metronidazole given at 7-10 mg/kg BID has been useful in controlling anaerobic urease producing bacteria. One should be careful as metronidazole is partially metabolized in the liver and a lower dose range is suggested.

A nondigestible disaccharide lactulose (Cephulac™ or Chronulac™) given orally acidifies the colon converting ammonia to ammonium that is poorly absorbable thus trapping ammonia in the colon. The fermentation products of lactulose will also act as an osmotic laxative reducing colonic bacteria and protein substrates. A dose of 1-10 ml orally TID is generally effective. Lactulose is not absorbed systemically and thus considered safe. The dose should be adjusted to cause 3 or 4 soft stools a day. If diarrhea develops the dose should be reduced. Lactulose can also be given by enema in treating the severe case of hepatic encephalopathy.

Gastrointestinal ulceration not only causes gastrointestinal signs such as vomiting and anorexia but blood loss into the intestinal tract promotes hepatic encephalopathy as blood is an excellent protein source for ammonia production. Gastric ulcers should be treated with the H2 blocker such as ranitidine (2-5 mg/kg BID/TID) and oral sucralfate (Carafate™ 1 mg tab/25 kg TID given 1 hour before ranitidine). Cimetidine is to be avoided in liver disease because it is metabolized by the liver and is an enzyme suppressor altering hepatic metabolism of other drugs.

Ascites occurs in chronic hepatitis when portal hypertension, hypoalbuminemia and renal sodium and water retention work in concert to cause fluid exudation. Diuretics are the major means of managing ascites in small animals. Too rapid removal of ascitic fluid can cause metabolic complications and can precipitate hepatic encephalopathy. The goal of diuretic therapy should be a gentle water diuresis. The loop diuretic furosemide (Lasix) is generally the treatment of choice. They can however cause marked dehydration and loss of potassium. In most cases furosemide provides a suitable diuresis. With hyperaldosteronism secondary to liver disease, sodium reabsorption at the distal tubule may be great and counter the effects of furosemide. If the patient does not respond to furosemide then spironolactone (Aldactone) should be tried in those cases. Often diuretics do not begin to work until improvement in hepatic function occurs. If an animal has tense ascites, paracentesis should be performed to decrease the intra-abdominal pressure, relieve compression of the venous circulation, and to increase patient comfort.