Persistent increases in ALT is usually a reasonable indication for hepatic biopsy. Even if the dog or cat is clinically normal, persistent elevations of ALT should be investigated, which usually means biopsying the liver. Increased SAP can be indicative of severe disease, but it is much less likely to be indicative of important hepatic disease than is an increased ALT. You should explain to the client that you hope you will find nothing of significance. However, it is better to diagnose severe hepatic disease before it causes severe clinical signs (which is when you can usually do more to treat and control it) than after the patient is so ill that it can no longer compensate for the hepatic disease (which is when you usually cannot do as much with your therapy as you wish you could). Also, do not be fooled into thinking that you can predict whether or not the hepatic disease will be significant based upon the hepatic enzymes. Most of us have seen a lot of dogs that have increased SAPs that were found on routine blood screening when the ALT, GGT, and bilirubin concentrations were normal (along with the rest of the panel except perhaps for an increased cholesterol). These are typically older dogs which are otherwise normal. Remember that hyperadrenocorticism is not worth looking for unless there is something in the history or physical examination that is suggestive of hyperadrenocorticism: there is no such thing as “asymptomatic” Cushing’s. After abdominal ultrasound to masses and obvious anatomic abnormalities of the liver, we tend to want to ignore the increased SAP because dogs without historic or physical examination findings suggestive of hyperadrenocorticism almost invariably have some sort of vacuolar hepatopathy which is clinically insignificant. However, the important word is “almost”. Dogs like this can also have clinically important disease that needs to be diagnosed. It happens very rarely (probably well less than 5% of the time), but it does happen.

Icteric animals have either hemolytic disease or hepatobiliary tract disease. First measure the hematocrit. If the hematocrit is greater than 20-25% (assuming that the patient is not markedly dehydrated), then it is extremely doubtful that hemolysis is responsible for icterus, especially if the serum bilirubin is persistently > 3 mg/dl. If there is an extremely strong regenerative response, then you will have to consider hemolysis as being responsible for icterus when the hematocrit is above 20%, but this is very rare. Check reticulocyte numbers and RBC morphology, especially looking for Heinz bodies and mycoplasma (i.e., Haemobartonella) in cats, and for spherocytes and autoagglutination in dogs. Occasionally one will find schistocytes which are suggestive of microvascular angiopathy (i.e., disseminated intravascular coagulation). If there is no evidence of a markedly regenerative anemia, Heinz bodies, or Haemobartonella, then hemolysis probably does not need to be further considered. However, if the hematocrit is < 20%, one should probably recheck the CBC in 2-5 days to see if a regenerative response has developed. It might be that the patient has had a sudden episode of hemolysis but had not yet
developed the regenerative response when you first examined it. Conjugated (direct) and unconjugated (indirect) bilirubin measurements are useless.

If hemolysis is eliminated as the cause for icterus, then it must be due to hepatobiliary disease. The next question is whether the animal has hepatic parenchymal disease or extrahepatic biliary tract obstruction. Abdominal ultrasonography is the best noninvasive tool to distinguish the two; it is very rare that ultrasound does not detect biliary tract obstruction that has been present for more than 4-5 days. It is important to remember that any anorexic animal will have a large gall bladder since there has been no stimulus for it to contract and empty. Biliary tract obstruction is diagnosed by finding dilated tortuous bile ducts in addition to a large gall bladder. However, you can see dilated bile ducts in some animals with bacterial cholangitis/cholangiohepatitis or cholecystitis. Such dilatation tends to be less than is seen with severe extrahepatic biliary tract obstruction; and, finding dilated bile ducts in a patient with a normal to small gall bladder will be very suggestive of biliary tract inflammation as opposed to biliary tract obstruction. Distinguishing between hepatocellular and biliary tract disease will help you determine whether your next step will be to biopsy the liver by some percutaneous technique -- preferable laparoscopy (i.e., for hepatocellular disease), or perform an abdominal exploratory surgery if you suspect the patient has biliary tract disease that is not due to pancreatitis.

Ascites is a common sign in dogs with hepatic as well as non-hepatic disease. The most common causes of high-protein transudates (also called modified transudates) are right-sided heart failure, hepatic disease (e.g., especially cirrhosis) and neoplasia. Heartworm disease, cardiomyopathy, and pericardial effusion are more common causes. The latter may not be real obvious if it is early and the pericardial sac has not yet stretched out and assumed the expected "basketball" shape. Thoracic radiographs, auscultation and sometimes ECG are usually enough to diagnose right-heart failure. A jugular pulse is probably the best screening test on physical examination for right-sided heart failure. If a true jugular pulse is present, right heart failure is almost always present. If a jugular pulse is absent, right-sided heart failure is possible, but it is much less likely (e.g., a thrombus in the posterior vena cava, a mass blocking the posterior vena cava from entering the right atrium). If one is still in doubt, measuring the right atrial pressure (via central venous pressure) will usually allow one to definitively rule-in or rule-out right-sided heart failure unless the failure is due to an obstruction where the posterior vena cavae enters the right atrium.

Hepatic disease can cause modified transudates by portal hypertension and/or retention of salt via the renin-angiotensin system. Abdominal ultrasonography is useful in evaluating ascitic patients and should be employed whenever possible. If right-sided heart failure is eliminated and there is evidence of significant hepatic disease, the assumption is made that hepatic disease is causing the ascites. This is usually correct but a hepatic biopsy is necessary to a) confirm the diagnosis and b) determine if the underlying disease can be treated or if symptomatic therapy will be the only option. If you find yourself doing a laparoscopy or abdominal surgery looking for neoplasia (see next paragraph) but find nothing obviously malignant, strongly consider doing a hepatic biopsy as long as you are in abdomen. Despite earlier enthusiasm, use of serum-effusion albumin gradients has not been helpful in distinguishing effusion due to hepatic disease from effusion due to other causes.

If right-sided heart failure and hepatic disease have seemingly been eliminated, then occult neoplasia is the next major concern. Most abdominal effusions due to neoplasia do not
have neoplastic cells evident in the fluid. Reactive mesothelial cells so perfectly resemble malignant cells that everyone with any experience is extremely reluctant to diagnose neoplasia by means of abdominal fluid cytology. If all else fails, then abdominal exploratory surgery or laparoscopy may be necessary. If no cause is obvious, one should be prepared to biopsy the liver, measure portal venous pressures and/or perform a mesenteric venoportogram to look for portal or vena cava obstruction.

Adverse drug reactions may cause mild to fatal hepatic disease. They can be due to almost any drug (e.g., cimetidine, amoxicillin, clindamycin, etc, etc, etc); however, some drugs are clearly more likely to cause hepatic disease than others. Whenever there is any doubt as to whether a particular drug might be responsible for hepatic disease in a patient, stop administering it and observe the results. Again, as for cats, the healthier the patient is, the more inclined we are to wait and see what happens after stopping the drugs. The sicker the patient is, the quicker we are to biopsy, just in case there is something more significant that we need to eliminate now.

**Doxycycline** occasionally causes increased ALT and even icterus. Although this is not a commonly recognized problem, we use so much doxycycline for suspected rickettsial diseases that it is very important to recognize the possibility. I have seen a few dogs that appeared to have substantial hepatic side effects (including icterus) from doxycycline administration.

**Sulfa drugs** are famous for causing severe hepatic disease (as well as bone marrow, cutaneous, joint, ocular and renal problems). Furthermore, the hepatic disease caused by sulfa drugs may not occur for 1-2 weeks after starting the drug, even if the patient has not received the drug for over a week. The hepatic lesions caused by sulfa drugs can look a lot like idiopathic chronic hepatitis. Doberman pincers and Rottweilers appear to be especially sensitive to sulfa drugs.

**Carprofen** (i.e., Rimadyl) causes hepatotoxicity in dogs, especially Labrador retrievers. The histologic changes seen in carprofen hepatotoxicity can resemble chronic hepatitis, so be sure that you have an adequate history. Also, be aware that hepatotoxicity may not be seen until 1-2 weeks after starting a drug; in fact, the patient may have stopped taking the medication several days before clinical signs of toxicity occur.

**Amiodarone** is an anti-arrhythmic drug that can cause substantial hepatotoxicity, and patients receiving this drug should be monitored closely. Some breeds appear to be excessively prone to adverse effects from specific drugs.

**Itraconazole** can cause icterus, but the signs usually regress quickly after withdrawing the drug.

**Anticonvulsants** (i.e., phenobarbital and Primidone) are famous for causing severe hepatic disease, eventually resulting in cirrhosis. This is why it is so important to perform therapeutic blood monitoring and measure the serum phenobarbital levels in patients receiving these drugs.

**Azathioprine** can cause severe, acute hepatocellular necrosis in some patients. This may be due to different rates of metabolism of the drug in different patients. I have not seen this problem when the patient was receiving azathioprine on an every-other-day basis as opposed to receiving it daily.

**Acetaminophen** is toxic and fatal when overdosed. Dogs tolerate it better than cats, but you need to be very careful if you decide to use this drug in a dog.

Chronic hepatitis is probably one of the main reasons it is a good idea to biopsy dogs’
livers. It is a reasonably common disease, and a lot can often be done for the dog if you diagnose it before the hepatitis causes cirrhosis. Chronic hepatitis can be found in almost any breed of dog, although Doberman pinchers (especially young to middle-aged females) seem to have a very high incidence of the disease. There are several clinical presentations of this disease. First, one may see a chronically ill dog with high ALT and SAP. Second, one may be presented with a dog that was normal until it was stressed (e.g., underwent surgery or anesthesia). Third, one may see a dog that was normal until a few days ago but that now suddenly presents with signs of hepatic failure and is found to have an absolutely end stage cirrhotic liver (see discussion under cirrhosis) even though the clinical signs have only been present for 1-3 days. Finally, one may see a clinically normal dog that has an increased ALT that was fortuitously found during routine health screening or during a preanesthetic work up for a dental. The ALT typically remains increased despite the dog acting and appearing fine. Chronic hepatitis is more common than many people realize and is one reason why it is better to biopsy clinically normal dogs with persistent increases in ALT rather than wait until clinical signs occur.

Treatment of chronic hepatitis usually centers around a) removing the cause, if possible, b) administration of anti-inflammatory therapy (i.e., steroids, azathioprine), and c) administration of supportive therapy (i.e., ursodeoxycholic acid and anti-oxidants).

Two causes of chronic hepatitis that you might be able to remove are drugs and copper. Copper is a bit confusing in that it can be the cause of chronic hepatitis, it can be secondary to chronic hepatitis but not causing a clinical problem, and we think that it can sometimes be secondary to chronic hepatitis and yet be severe enough to cause disease in and of itself. There has been one report that seemed to show that removing copper from the liver of dogs with chronic hepatitis in which the copper accumulation clearly appeared to be secondary to the hepatic disease was clinically beneficial to the dogs. You can measure copper levels in biopsies, or you can do special stains on hepatic biopsies. If you are in doubt as to how significant the hepatocellular copper is, it is probably best to just remove it. If the decision is made to remove copper, then one may elect oral zinc therapy before meals or copper chelation with D-Penicillamine. Feeding a copper restricted diet is reasonable; but, feeding a copper restricted diet by itself often will not lower hepatic copper concentrations sufficiently. One exception to this may be the Labrador retriever. Chelator therapy or zinc therapy must also be used. D-Penicillamine (10-15 mg/kg bid) is the drug typically used to lower hepatic copper concentrations. This drug occasions causes vomiting, and administering it with food seems to lessen that problem. If the dog is clearly being intoxicated by very large concentrations of hepatic copper, chelators should be used.

Zinc can be used to prevent copper accumulation, but it can also act as an antifibrotic agent. Various forms can be given, but the idea is to administer approximately 100 mg of elemental zinc daily for 3-6 months and then decrease it to about 50 mg daily. Zinc should be administered on an empty stomach, and generally should not be given with copper chelators. Be aware that zinc administration can rarely cause hemolytic anemia, and periodic blood zinc measurements are not a bad idea in patients receiving zinc therapy.

Dogs with chronic hepatitis not due to copper accumulation or drugs often need anti-inflammatory agents. This usually includes glucocorticoids. However, it seems important to use the lowest effective dose of the corticosteroid. If you give too much corticosteroid to a dog with steroid-resistant hepatic disease, you may create a vacuolar hepatopathy in addition to the preexisting hepatic disease. When corticosteroids are used for this disorder, they should
typically be used at an anti-inflammatory dose (1 mg prednisolone/kg/day) and then tapered quickly. The steroid treatment should be for relatively short periods of time (i.e., until a week or two after clinical signs substantially diminish or disappear). Severely affected patients and patients that require excessive amounts of corticosteroids may benefit from **azathioprine** or **cyclosporine** therapy. Azathioprine may cause severe hepatic disease, but this appears to be an idiosyncratic reaction, possibly due to differences in the rate of metabolism of the drug in different dogs. I do not hesitate to use azathioprine when it seems like it may be helpful. Indications seem to be when steroids are insufficient to control signs, when excessive doses of steroids are required to control signs but cause substantial side effects, and when very severe hepatic disease is found on the initial biopsy. While 1 mg/lb daily is a commonly quoted dose, I typically give azathioprine at the same dose but only every other day, which seems to be much safer.

Supplementation with **B-complex vitamins** is probably useful. Occasionally a bleeding diathesis is present and you can try supplementing **vitamin K₁** (1 mg/kg/day, given SQ). Theoretically, antibiotics may be used to try to decrease the number of bacteria coming out of the intestines and into the portal circulation. Amoxicillin is often used for this purpose.

Patients with hepatic disease may also benefit from supportive therapy, especially those drugs and nutraceuticals that are antioxidants. Antioxidants (i.e., vitamin E, s-adenosyl-L-methionine, silymarin, phosphatidylcholine, vitamin C, N-acetylcystine) and ursodeoxycholic acid are what should be called “hepatosupportive” therapy. These drugs will generally not cure severe disease all by themselves, but they can substantially help the patient if appropriate therapy is being directed at the primary cause. In general, antioxidants are poorly effective if used as single drugs. Rather, antioxidant therapy is best accomplished if multiple drugs are used simultaneously.

**Vitamin E** (400-500 units per day) seems to have substantial anti-oxidant capabilities and is widely used. The d-alpha form is the effective form; the l-isomer is inactive. We prefer to use the water soluble form, hoping that it has better bioavailability. Vitamin E is very safe as long as it is not grossly overdosed. **Vitamin C** might be helpful, but there is evidence that it might make some forms of hepatic disease worse, especially those with disease due to copper or iron accumulation in the hepatocytes. Therefore, it is very useful to have a hepatic biopsy since some dogs with chronic hepatitis accumulate copper while others do not. **S-adenosyl-L-methionine** (20 mg/kg sid) is a nutraceutical that appears to have benefit in some patients with hepatic disease. It increases hepatic glutathione concentrations as well as enabling a variety of important, intermediary metabolism reactions. The drug appears to have no adverse effects, and there is good evidence that it helps protect against alcoholic hepatitis in people. It should be given on an empty stomach, and the patient should not be feed for 30 minutes. It comes in foil-wrapped, enteric coated tablets. **Phosphatidylcholine** seems to have some potential for preventing fibrosis and protecting hepatocellular membranes. It also appears to increase the bioavailability of other drugs (e.g., silybin). The dose in dogs and cats is unknown, but people generally take 3-9 grams daily, in divided doses. **Milk thistle** (silymarin) (4-8 mg/kg/day OR 50-250 mg/day) is a herbal treatment that has proven efficacy in some diseases (e.g. Amanita mushroom poisoning). There are different active fractions, and silybin seems to be the most active. There is one preparation in which silymarin is complexed with phosphatidylcholine complex (i.e., Marin by Nutramax) which seems to have increased uptake and bioavailability. **N-acetylcysteine** can be obtained from the health food store. It is an anti-oxidant, and has been
given to dogs and cats at a dose of 70 mg/kg tid. It seems to be safe, but should be given on an
empty stomach. It seems that s-adenosyl-L-methionine is probably effective in promoting
intracellular glutathione concentrations. It is important to note that administering glutathione
orally is ineffective; the orally administered drug will not increase intracellular glutathione
concentrations. **Superoxide dismutase** has been tried recently, but its effectiveness is very
uncertain at this time.

**Ursodeoxycholic acid** (15 mg/kg/day) is beneficial because of its ability to displace more
toxic hydrophobic bile acids from the hepatocyte membrane. Like the antioxidants, it generally
should not be used as sole supportive therapy. It seems to work best if combined with anti-
oxidants.

Copper storage is reported in Bedlington terriers, where it commonly causes chronic
hepatitis that progresses to cirrhosis. West Highland White terriers often have excessive hepatic
copper accumulation, but it is different than what is found in Bedlington terriers and seldom
causes clinically significant hepatic disease. Dalmatians, Labrador retrievers and Skye terriers
have recently been reported to have a copper-associated hepatic disease in which accumulation
of copper by the liver may be the cause of the clinical disease. Recently, there is increased
concern that many dog foods have increased amounts copper that is more bioavailable than
before, making it easier for some breeds (e.g., Labrador retrievers) to accumulate toxic amounts
and develop chronic hepatitis. Biopsy with special stains or preferably quantitated copper
analysis performed on frozen hepatic tissue is required for diagnosis.

Cirrhosis is an end-stage hepatic disease that may be caused by various problems,
especially chronic hepatitis. In particular, Cocker spaniels seem to have a distinct genetic
predisposition to having cirrhosis at inordinately young ages (i.e., < 5 years of age). This may be
due to an inherited problem in which they accumulate alpha-1 protease inhibitor in their
hepatocytes, which eventually results in cellular death. In general, these dogs are clinically
normal until they have completely exhausted all of their hepatic compensatory mechanisms.
This means that there is usually little or nothing that can be done when they start showing
clinical signs. Unfortunately, many of these dogs have normal serum ALT and SAP activities
when they are approaching end stage. Serum albumin and BUN are often decreased, and serum
bile acids, if measured, are typically markedly increased (e.g., > 90 umol/L). However serum
bile acids are not as sensitive or specific as desired. If blood ammonia is increased, that is very
specific for hepatic insufficiency, but we are not sure how sensitive it is. Chronic hepatitis may
cause the identical scenario in other breeds (especially but in no way limited to the Doberman
pincher). There may be ascites due to portal hypertension and salt accumulation in cirrhotic
animals. In such animals there is usually acquired hepatic portal shunting with many tortuous
shunts seen in the abdomen, especially around the kidneys. Hypoalbuminemia can make the
ascites more likely and more severe if it occurs.

Although controversial, I believe it is usually appropriate to biopsy dogs that you strongly
suspect of having cirrhosis, unless the anesthesia risks are too great. I say this because I hope to
find other disease in the liver (e.g., inflammation that caused the cirrhosis in the first place) that
can be treated. By treating the apparent primary hepatic disease, you may a) prevent further
cirrhosis, and b) allow the remaining hepatocytes to heal and recompensate the patient.
However, remember that a dog with cirrhosis may have exhausted all of its compensatory
mechanisms, and even minimal anesthesia may result in acute decompensation and death. This
is not common or likely, but it is devastating when it happens.
Most patients with hepatic cirrhosis die shortly after diagnosis. However, some can live for months or even over a year with aggressive supportive therapy. It is hard to know which dogs will respond in which way. All you can do is treat and hope.

The antioxidants and other supportive therapy mentioned under chronic hepatitis are potentially useful in these dogs. **Steroids** should not be given to dogs with cirrhosis unless you have good evidence of inflammation in the liver. Such inflammation will only be diagnosed by hepatic biopsy, not with a CBC. If you give too much corticosteroid to a dog with steroid-resistant hepatic disease, you may create a vacuolar hepatopathy (i.e., hydropic change) in addition to the preexisting hepatic disease which might actually make things worse. While vacuolar hepatopathy is usually clinically insignificant, dogs that are surviving on the smallest of safety margins may or may not be able to tolerate this additional insult, even though other dogs might not even notice if they had it.

**Colchicine** (0.03 mg/kg SID) can be used to try to prevent and reverse fibrosis and cirrhosis. Unfortunately, many patients with chronic hepatitis causing cirrhosis have such advanced disease that they die before treatment with colchicine has a chance to help; but, colchicine is worth trying if clients understand the experimental nature of the therapy and the potential risks. There is less enthusiasm for colchicine than there was 15 years ago. Zinc and d-Penicillamine are believed to also have anti-fibrotic effects.

Patients with severe cirrhosis should have their diet modified if hepatic **encephalopathy** is a problem or seems imminent. It is important to note that this does not mean feeding a NO protein diet; rather, you should feed as much protein as the patient can tolerate. The liver needs protein to try to regenerate hepatocytes, and giving substantially too little protein may be as bad as giving too much. Milk and vegetable proteins seem to be best tolerated. Lactulose and antibacterials may also be helpful. Sometimes encephalopathy is due to GI bleeding from gastric ulcers/erosions secondary to the hepatic disease. Bleeding into the GI tract is about the same as a high protein meal. Therefore, it is seldom wrong to also give H-2 receptor antagonists (e.g., famotidine) and/or carafate to such patients. Cimetidine seems to have more effects upon the liver than famotidine (i.e., inhibits P450 enzymes); therefore, cimetidine should probably be avoided. Remember that most dogs with gastric bleeding due to ulcers and erosions neither vomit nor pass melena.

For patients that do respond to supportive therapy, it may also be useful to control ascites. Symptomatic therapy for abdominal effusion is usually only necessary if the ascites is so severe that it is making it difficult to breath. It is rare that ascites causes severe abdominal pain. Very rarely, ascites can be associated with hyponatremia and hyperkalemic hypoadrenocorticism. The hyperkalemic can be severe enough to threaten the patient's life. While this is particularly uncommon, it must be considered in any patient with a 3rd space disorder that seems inappropriately ill. If dyspnea or hyperkalemia is occurring, one should promptly drain the fluid from the abdomen by a trocar. A multi-fenestrated catheter is most useful for this purpose. It is best to try to avoid physically drawing the fluid off the abdomen as repeated drainage procedures will lower the serum albumin concentration which will make it even easier to form more ascites. If one decides to symptomatically treat a patient that is not critically ill, a low-salt diet should be a major part of the therapy as it may allow one to avoid diuretics altogether or at least use a much smaller dose (and thereby avoid hypokalemia, which can be very severe if the patient stops eating while it is receiving furosemide).