CONGENITAL PORTOSYSTEMIC SHUNTS IN DOGS

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Congenital portosystemic shunts (pss) are much more common and certainly much more confusing than we ever imagined. At Texas A&M, we infrequently see the “classic” congenital PSS with the relatively straight forward presentation (i.e., young Yorkie with post prandial hepatic encephalopathy), probably because those cases are efficiently filtered out and never referred to us. Some breeds are more commonly affected (i.e., Yorkshire terriers, Pugs, Maltese, Schnauzers, Poodles, Shih Tzus, Havanese, Irish Wolfhound, Golden Retrievers, and Labrador Retrievers), but any dog may have a congenital PSS. We infrequently see classic post-prandial hepatic encephalopathy; rather, we more commonly see a young dog (e.g., one of the above breeds that is less than a year old) that is a “poor doer” who is not as big or as strong as the litter mates with very intermittent vomiting (i.e., “he or she has always had a sensitive stomach”) and subtle signs of encephalopathy. Therefore, it is important to eliminate intestinal parasites and hypoglycemia in animals with suspected congenital PSS since the signs may be very similar. Polyuria-polydipsia can be a major clinical sign. In fact, in our practice, most young animals referred for possible central diabetes insipidus turn out to have hepatic disease, especially congenital PSS.

Classic hepatic encephalopathy consists of post-prandial seizures, coma, somnolence, blindness, head pressing and/or aggression. However, we are seeing more and more animals in which hepatic encephalopathy is manifested simply by their laying around a lot, acting tired or lethargic, or just not being interested in anything. In many cases, there is no obvious relationship between eating the signs. In some cases, about all you can say is that he patient has always been a “calm” dog and never really caused a lot of trouble by getting into things. In older dogs, the only comment by the owner may be that they dog is “getting older and slowing down a bit”. To make matters more confusing, we are finding dogs that have hepatic encephalopathy that do not respond to medical management with lactulose or metronidazole. Some of these patients only quit having signs of hepatic encephalopathy when the shunt is surgically corrected. Therefore, you cannot allow lack of response to medical therapy help you decide whether or not a dog has hepatic encephalopathy due to a congenital PSS. Cats with hepatic encephalopathy due to congenital portosystemic shunting often have drooling as a major presenting complaint.

We sometimes see hematuria due to ammonium urate urolithiasis, but this usually often
happens in older dogs (especially Schnauzers) that have had chronic hyperammonemia. Many times, this is the only clinical sign in the affected patient. Contrary to what is often described in textbooks, you can sometimes see major increases in ALT and SAP. We occasionally see patients with major increases in ALT (i.e., > 1,000 U/L) that appear to have acquired hepatic disease, probably toxic in nature. The ALT waxes and wanes with clinical signs. Our guess is that these dogs only have signs when they develop liver disease secondary to exposure to “toxins” that the atrophied liver cannot process because it is insufficient.

To further complicate the situation, we are seeing more and more dogs with congenital PSS that are being diagnosed for the first time when they are 7 or even > 10 years old. This appears to be especially common in Schnauzers, although other breeds may also be affected. Many times these patients have relatively minor signs that have been considered as normal for the particular patient (i.e., has always been a quiet dog, has always been a smallish dog, etc).

Ascites is exceedingly rare in animals with congenital portosystemic shunts. This is in distinction to dog with congenital hepatic AV fistula, which is another congenital vascular abnormality but which is entirely different from the standpoint of signs, diagnosis, and treatment. Ascites is relatively common in dogs with acquired portosystemic shunting. Therefore, if ascites is seen, one should first look for other hepatic diseases. In like manner, icterus is very seldom caused by congenital portosystemic shunts, and finding hyperbilirubinemia is an indication to first look for other diseases. In summary, congenital PSS present in a variety of ways, many of which are not the “classic” presentation that is described in textbooks.

The major criteria for presumptive diagnosis of congenital portosystemic shunts has classically consisted of an appropriate history and physical examination as well as obvious microhepatia and very increased serum bile acid concentrations. It was generally anticipated that dogs with congenital PSS would have serum bile acid concentrations > 90 mmol/L. Hypoalbuminemia, hypocholesterolemia, and/or decreased BUN are common findings on clinical pathology, but they are not invariable; some patients with congenital PSS do not have any abnormalities on the serum biochemistry panel. Ammonium biurate crystals in the urine are useful if they are present; but, most of the cases of dogs with congenital portosystemic shunts that we see do not have ammonium biurate crystals in the urine.

It now appears that serum bile acid concentrations are not as easy to interpret or as definitive as many people think. First, you must always measure both resting and post-prandial concentrations because about 20% of dogs have a resting serum bile acid concentration that is higher than the post-prandial serum bile acid concentrations. Second, there can be marked variation in serum bile acid concentrations from day to day. It is easy to see a two-fold
difference in values taken a few days apart, and we have seen a three-fold increase in samples that were taken 72 hours apart. Third, some dogs with congenital portosystemic shunts have surprisingly low serum bile acid concentrations. We have found dogs with congenital PSS that have what we would consider relatively modest increases in serum bile acids (e.g., 55-65 mmol/L, which is a value found in many animals with clinically insignificant hepatic disease), and rare cases have completely normal serum bile acid concentrations. In distinction, some dogs without any demonstrable hepatic pathology other than vacuolar hepatopathy have values in excess of 200 mmol/L. This major overlap in the values of serum bile acid concentrations in dogs with and without clinically significant hepatic disease leads to diagnostic confusion in some cases.

Hyperammonemia is very specific for hepatic insufficiency, especially congenital PSS. However, it is easy to have laboratory artifacts that falsely increase these values. This test can only be run in house, and the instructions must be followed to the letter to avoid artifactual results. Measuring only fasting blood ammonia concentrations is approximately 80% sensitive for congenital PSS (and lower for diseases causing acquired hepatic insufficiency). The ammonia tolerance test is an excellent test with very high sensitivity and specificity, but it is a royal pain to do (e.g., would you like to drink ammonia chloride or have it infused into your rectum?) and consequently is seldom performed. Measuring blood ammonia concentrations 4-8 hours post-prandially seems to enhance the sensitivity for congenital PSS up to about 90%.

Imaging can be helpful, but one must recognize the limitations of these techniques. We expect to see microhepatia in dogs with PSS, although sometimes the change is very modest. Sometimes there is a marked difference in the apparent size of the liver on the left lateral versus the right lateral projection. Radiographs are a much more sensitive way to find microhepatia than ultrasound. If there is any doubt about the size of the liver, one can administer a few mls of barium sulfate to help outline the stomach, allowing one to easily ascertain the cranial border of the stomach. The area between the cranial border of the stomach and the diaphragm is usually the liver. However, occasional animals will appear to have a small liver when in fact they have a normal sized liver. Fortunately, this situation appears to be unusual and should be picked up if lateral and DV views are obtained.

Ultrasound is commonly employed when looking for congenital portosystemic shunts. A good ultrasonographer can find a congenital PSS about 50-75% of the time, if they are accomplished and can take their time and look. Truly exceptional ultrasonographers seem to find congenital PSS about 90% of the time. Therefore, you must remember that failing to find a congenital PSS on ultrasound does not eliminate it. Furthermore, one cannot look at the liver to
see if there are apparently normal portal areas as a means of deciding if a congenital shunt is more or less likely. We have seen animals with congenital PSS that appeared to have normal portal vasculature on ultrasound, to the point that the conclusion was that a congenital shunt was very unlikely. Ultrasonography is a very good way to check for an intrahepatic shunt, which is much harder to correct than an extrahepatic shunt.

Other imaging techniques may include operative or percutaneous portograms, nuclear scintigraphy, and MR or helical CT. These latter techniques should primarily be done for one of two reasons. First, the case is “atypical” and it is important to absolutely confirm the presence of a congenital PSS before going to surgery. The second reason is that the surgeon is unable to find the shunt during an exploratory laparotomy. In general, it is not always necessary to definitively “see” the shunt via some imaging modality before going to surgery. If the case is classic in that it is a young animal with appropriate signs and an obviously small liver and obviously high serum bile acids or ammonia, then one is justified in going to surgery even if the shunt has not been visualized. If the shunt cannot be found during surgery, then an intraoperative portogram can be performed. However, if any of those three criteria are not met (i.e., “classic” history, obviously small liver, obviously increased serum bile acids or ammonia), then confirmation by portography, scintigraphy, CT or MR is appropriate.

Retrograde portography is often preferred when an intrahepatic shunt is believed likely because we prefer to fix these with catheters (i.e., putting in a stent and then coils). Nuclear scintigraphy is also very nice, but requires special facilities. One advantage of portography is that one may place the catheter in the shunt and leave it there in order to help the surgeon find the shunt if they are having a very difficult time finding it.

Lastly, it is important to do a full work up (i.e., CBC, serum chemistry panel, abdominal radiographs, abdominal ultrasound, serum bile acids or blood ammonia) on all dogs with suspected congenital PSS. These dogs may have other, concurrent diseases. In fact, dogs with previously well compensated congenital portosystemic shunts may not become symptomatic until another disease process causes the patient to start showing signs due to the shunt. Furthermore, a reasonable number of affected dogs have cystic calculi that can be removed during the surgery to correct the congenital shunt.

Surgical correction is usually preferred for younger animals and for those that have signs of encephalopathy that are not controlled with medical therapy. But, surgery is not without risks. The Ameroid constrictor makes the surgery much easier and quicker than before. However, about 15-20% of dogs that have surgery to correct a PSS will have some post-operative complications (usually something minor like ascites). This is usually not a major problem, but
the owner needs to be warned ahead of time. Some dogs develop enough portal hypertension to cause acquired PSS, and a few (i.e., 5-7%) have major, life-threatening problems (e.g., post-ligation seizures, portal hypertension) and die. Not every dog with a congenital PSS is benefitted by Ameroid constrictors.

A major concern centers around dogs (especially those 5 years old and older) with congenital PSS that are clinically normal and that have minimal changes on serum biochemistry panel and a liver that is not too small on radiographs. We are finding these dogs because awareness of congenital PSS has substantially grown, and more and more people are looking for them and diagnosing them in animals with minimal or even no clinical signs. If the liver is not too small on radiographs, the serum albumin is > 2.0 gm/dl, and there are minimal to no clinical signs, then we might decide to watch them to see if they will ever need surgery. Dogs with congenital PSS causing hepatic encephalopathy may benefit from corrective surgery, but some do not. There is concern that dogs > 5 years of age are more likely to have severe complications from corrective surgery. While this might be the case, many dogs have benefitted from surgery despite being > 5 years of age. This entire area is currently very controversial. We see some dogs with congenital PSS that seemingly live a normal life and never need corrective surgery. Therefore, if you are considering surgery in an older dog (e.g., > 6 years old) without any major clinical signs, you should probably have a long talk with the owners about how the dog could be worse after the surgery than it was before.

If post-ligations seizures occur, you must first be sure that the dog is not hypoglycemic. The cause of this problem is uncertain, but some suggest it might be due to cerebral edema. We have not treated for cerebral edema in these patients; rather, we typically anesthetize them with a constant rate infusion of propofol until the seizures have stopped. Do not use diazepam or phenobarbital. Some people recommend treating dogs with potassium bromide or Keppra and cats with phenobarbital before surgery for congenital portosystemic shunts, in an effort to avoid this problem. This approach is contentious, and time will tell if it is correct or not. In general, cats with congenital portosystemic shunts do seem to have more post-operative problems than dogs.

Dogs with intrahepatic shunts have a worse prognosis because the surgery is technically much more difficult to perform. If you can refer the dog to a center which can place coils in the shunt via intravenous catheters used with fluoroscopy, that might be a much safer way to try to correct the problem.

The medical treatment for hepatic encephalopathy is relatively straightforward; lactulose, metronidazole, and a low protein diet. However, the concept of low protein must be revisited.
Giving too little protein is extremely detrimental to the liver. The goal is to give as much protein as the liver can tolerate. In particular, it is best to give milk and vegetable proteins instead of meat proteins.
CHOLECYSTITIS

Cholecystitis is much more common than many people realize. Dogs that have evidence of antibiotic responsive hepatobiliary tract disease may have a bacterial cholecystitis. Typically, both the ALT and SAP are increased, and icterus is common. Most dogs with cholecystitis do not have discernable gall stones. Many (maybe most) gall stones found in dogs and cats are clinically insignificant and only serve to confuse veterinarians. Ultrasound findings in dogs with bacterial cholecystitis are non-specific: finding "sludge" in the gall bladder can also occur in clinically normal dogs.

At this time, aspirating bile via ultrasound-guided, percutaneous puncture with a 22-25 gauge needle may be the best diagnostic test we have. You are much more likely to find bacteria in the bile than you are to find them in hepatic parenchyma (this applies for cytology/histopathology as well as culture). Rarely, such percutaneous aspiration techniques will cause a vagal response that will cause extreme bradycardia (this is rare, but it is more likely in cats than in dogs); however, if this happens all that is usually needed is an injection of a parasympatholytic such as glycopyrrolate. If you use ultrasound guidance to insert the needle through the quadrate lobe of the liver (which is adherent to the gall bladder), then there is no risk or concern with leakage of bile into the abdomen. In this case, if bile leaks from the gall bladder, it will simply leak into the liver lobe which is harmless.

Finding WBCs and/or bacteria in the bile seems to be very specific, but we are not really sure how sensitive this test is for cholecystitis. It is important to note that normal dogs and cats can have a very few bacteria in the bile. This is because there is a normal entero-hepatic-biliary circulation of bacteria in bacteria go from the intestines to the liver (probably due to translocation across the intestinal mucosa) where they are excreted into the bile and then ejected with the bile back into the intestinal lumen. Therefore, you need to find more than just one or two bacteria in the bile before you make this diagnosis.

Therapy of infectious cholecystitis usually involves chronic (i.e., > 6-8 weeks) antibiotic therapy. If I can see lots of bacteria but cannot culture the bacteria and obtain a sensitivity assay (which happens surprisingly often), I prefer to use a combination of amoxicillin and enrofloxacin. If that approach is unsuccessful, then cholecystectomy is usually the next step. Do not do a cholecystotomy or an incisional biopsy of gall bladder wall; dehiscence appears to
be a major cause of morbidity and mortality after such surgery. Rather, remove the entire gall bladder and submit it for histopathology and microbiology. Be sure that you do not ligate or transect the common bile duct, or you may kill the dogs. Remember that cholecystectomy may be required to cure a patient with cholecystitis.

Emphysematous cholecystitis is classically associated with diabetes mellitus or hyperadrenocorticism, but it probably occurs just as often in non-diabetic animals. This malady is diagnosed radiographically: gas in the wall of the gall bladder or gas within the gall bladder lumen. Both lesions are typically very obvious on abdominal radiographs, but care must be taken to not off-handly attribute any gas seen in the cranial abdomen to gastric or intestinal gas. Treatment with antibiotics that are effective against gas-producing anaerobic bacteria (e.g., penicillin, metronidazole, chloramphenicol, or clindamycin) is indicated. If that approach is unsuccessful, then cholecystectomy will be required.

Necrotizing cholecystitis is typically the result of long standing bacterial cholecystitis or mucocoele (see below). The three most important things to remember about this problem are that a) necrotizing cholecystitis can be clinically obvious or clinically occult, b) abdominal ultrasound can be relatively specific for cholecystitis, but it is insensitive, and c) if the gall bladder ruptures, the prognosis is grave.

Sometimes during surgery or laparoscopy, the gall bladder obviously looks like it may be necrotic. However, some dogs with severe necrotizing cholecystitis have a gall bladder that visually appears normal. It is critical to realize that a gall bladder can look and feel normal and yet have transmural necrosis and be about to spontaneously rupture. This lack of obvious gross changes in affected animals is one of the major reasons why cholecystotomy is such a bad idea. If you try to suture diseased (often necrotic) tissue together, perforation is almost expected.

Ultrasound might reveal changes that are very suggestive of necrotizing cholecystitis (e.g., discontinuous wall, markedly thickened wall, trilaminate wall), mildly suggestive of necrotizing cholecystitis (e.g., pericholecystic edema or hyperechoic fat), or nothing at all. Aspirate cytology is still the most reliable diagnostic test.

If rupture of the gall bladder is suspected, immediate surgery is indicated. Rupture of a gall bladder with necrotizing cholecystitis releases bacteria as well as bile into the abdomen. Such patients can almost literally melt in front of your eyes in a matter of hours. This is a genuine surgical emergency.

MUCOCOELES
Sometimes excessive mucus is secreted into the gall bladder and becomes so thick and inspissated that it essentially becomes a solid mass. This is referred to as a biliary mucocoele. Endocrinopathies (e.g., hyperadrenocorticism, diabetes mellitus, excessive androgens as are suspected to occur in Scottish Terriers) and animals with problem of lipid metabolism (e.g., Schnauzers) seem to be at increased risk, but the cause is probably multifactorial. Poor emptying of the gall bladder seems to be important, but its cause is uncertain. Biliary mucocoeles are essentially unknown in cats. For reasons that are not clear, the incidence of this disease appears to have substantially increased compared to 15 years ago.

As mucus fails to be evacuated from the gall bladder, it accumulates and becomes thicker, similar to the consistency of extra-thick jell-O. Initially, the gall bladder expands as it becomes more and more filled. Eventually, as the gall bladder becomes more filled, the mucus will be pushed into the cystic duct, causing occlusion and extra-hepatic biliary tract obstruction (EHBO). Diagnosis is typically accomplished by abdominal ultrasound. You are not looking for gravity-dependent sludge; rather, you are looking for a “stellate” appearance to the gall bladder (the so-called “kiwi fruit” appearance). Cholecystectomy appears to be the only appropriate therapy. Many of these patients have necrosis of the wall of the gall bladder due to the pressure exerted by the lumen of mucus. Because the gall bladder is typically a very thin-walled structure, this intraluminal pressure can result in avascular necrosis with eventual rupture causing peritonitis. Prognosis is good, as long as you do surgery before the gall bladder ruptures and there are no post-surgical complications such as pancreatitis.

A couple of very controversial points are what constitutes the ultrasonographic diagnosis of an immature biliary mucocoele, and whether gall bladders with non-gravity dependent “sludge” need to be removed or not. Some animals with “immature” mucocoeles seemingly resolve if treated with choleretics such as ursodeoxycholic acid.

**GALLSTONES**

Gall stones, as mentioned are usually there simply to distract the veterinarian. I am not saying that they never cause disease. I am saying that they are usually innocent of causing disease. If you find gall stones, you should first look elsewhere for the cause of the patient’s illness. If you can find nothing else that seems likely to be responsible for causing hepatobiliary tract disease in the patient, only then should you allow yourself to focus on the gall stones. Of course, if there are bacteria in the bile, then the gall stones are likely to be very important and should be removed so as to prevent recrudescence of the infection.
EXTRHEPATIC BILIARY TRACT OBSTRUCTION FROM OTHER CAUSES

Pancreatitis is the most important cause of extrahepatic biliary tract obstruction (EHBO) in the dog. If EHBO is present in a sick dog and appears to be idiopathic, it should generally be assumed to probably be due to pancreatitis until there is evidence to the contrary. History and physical examination are helpful in diagnosing pancreatitis, but not as useful as we’d like. Schnauzers and Yorkies are famous for pancreatitis, but these breeds get a lot of other diseases that cause vomiting, and pancreatitis can be found in any breed of dog. Canine pancreatitis is classically considered to present with acute vomiting and anorexia. Abdominal pain is frequently present, but it is easy to miss during physical examination, and fever is occasionally seen. However, we are recognizing more and more atypical cases to the point that we are no longer sure what a typical case of canine pancreatitis is. We are now recognizing more and more cases of severe disease which present in shock due to systemic inflammatory response syndrome (what used to be called septic shock, until we found out that you can have the same thing occur with any cause of massive inflammation); such patients may die very suddenly. We are also recognizing more and more dogs with acute pancreatitis that present as though they had an acute, septic abdomen. Some have substantial amounts of abdominal fluid. If acute pancreatitis is associated with or due to pancreatic carcinoma (rare), you may also see a dog that has widespread subcutaneous fat necrosis causing sterile abscesses that are typically painful and cause cutaneous discoloration. Most cases of canine pancreatitis are related to either ingestion of fat or lipemia associated with diabetic ketoacidosis. Trauma and drugs can also cause canine pancreatitis. Drugs that are suspected of causing pancreatitis in people and animals include azathioprine, sulfonamides, tetracycline, and potassium bromide.
CHRONIC HEPATIC DISEASE IN DOGS
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CHRONIC INFLAMMATORY/NECROTIC DISEASES

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.

Lomustine is a chemotherapeutic used as rescue therapy when treating lymphoma. It will reliably cause severe hepatic disease if used inappropriately.

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. You need to be very careful if you decide to use this drug in a dog.

Vacuolar hepatopathy (hydropic change) is probably the most common histologic change seen in hepatic biopsy of canine livers. In general, this lesion seldom causes any clinical signs. I did not say it never caused clinical disease; rather, it very seldom causes clinical disease itself. There are some suggestions that severe change is sometimes responsible for hepatic failure. Vacuolar hepatopathy is best known for being associated with steroids. Both exogenous or endogenous steroids can be involved. Furthermore, it appears that vacuolar hepatopathy can be due to hyperadrenocorticism or to dogs with excessive steroid release associated with significant illnesses (e.g., tumors, infections). Classically, these dogs have a high SAP with a relatively minor (or no) increase in ALT. The GGT may be increased.

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. D-Penicillamine (10-15 mg/kg bid) is the drug typically used to lower hepatic copper concentrations. This drug occasionally causes vomiting, and administering it with food seems to lessen that problem. Trientine is another copper chelator (Cuprimine) that is also effective (10-15 mg/kg bid) and seems to have fewer side effects than d-penicillamine. 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-inflammatories, and 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.

Patients with hepatic disease may also benefit from supportive therapy, especially those drugs and nutraceuticals that are antioxidants. Antioxidants (i.e., s-adenosyl-L-methionine, silymarin, phosphatidylcholine, N-acetylcysteine) 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.

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. 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 antioxidant, 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. **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.

You must be very careful about diagnosing cirrhosis based upon clinical appearance. There are several diseases that look like cirrhosis but that are not cirrhosis.

**Hepatic lobular collapse** looks much like cirrhosis when viewed grossly, laparoscopically, or by ultrasound. However, there is no fibrosis, just loss of hepatocytes. Therefore, there is no need to use potentially dangerous drugs (e.g., azathioprine, colchicine) or even prednisolone. This disease can be associated with dermatohepatopathy, which sometimes responds to amino acid infusions. However, we have also seen improvement with more conservative management aimed as protecting the hepatocytes.

**Noncirrhotic portal hypertension** closely mimics cirrhosis in its clinical appearance, but is easily distinguished from cirrhosis by biopsy. This disease in particular is an important reason why you need to biopsy the liver of dogs with “obvious” cirrhosis; they might have a very different disease. Noncirrhotic portal hypertension generally has a much better prognosis than cirrhosis. It is now believed that this disease might be a manifestation of portal vein hypoplasia (discussed under congenital portosystemic shunts and microvascular dysplasia). The dog can have a small liver, polyuria-polydipsia, acquired portosystemic shunting, massive ascites, and still have a much better prognosis than seen in animals with cirrhosis. Animals with noncirrhotic portal hypertension often respond well to conservative, symptomatic and supportive therapy to alleviate ascites. They may be successfully controlled for months or years. It is sometimes important to combine diuretic therapy with low salt diets so as to enhance the effectiveness of the diuretic therapy. If the patient stops eating, it becomes very important to monitor serum potassium and magnesium concentrations.

**Lobular dissecting hepatitis** is another disease that mimics cirrhosis. It is a “chronic hepatitis/cirrhosis”-like disease in which there is fibrous connective tissue infiltrating between hepatocytes. It typically occurs in younger dogs, causing ascites and signs of hepatic failure. Diagnosis requires biopsy, and the prognosis is much worse than that of chronic
hepatitis or non-cirrhotic portal hypertension or lobular collapse.
The most commonly diagnosed chronic large bowel diseases causing diarrhea in dogs in our practice are so-called irritable bowel syndrome (IBS) (which is not the same as irritable bowel disease in people), fiber-responsive colonic dysfunction (which is probably a subset of irritable bowel syndrome), dietary intolerance (by which I am referring to allergic as well as non-allergic dietary problems), clostridial colitis (which might be better called “tylosin-responsive colitis”), parasites and fungal infections (i.e., histoplasmosis and pythiosis). The most commonly diagnosed large bowel diseases in cats in our practice are fiber-responsive disease, dietary intolerance, antibiotic-responsive colitis and inflammatory bowel disease (IBD), especially lymphocytic-plasmacytic infiltrates. Fortunately, colonic histoplasmosis is much less common in cats than it is in dogs.

The first concern is parasites. Whipworms can be very difficult to demonstrate on fecal flotation. Direct fecal examination will be more useful than fecal flotation if the flotation solution is not dense enough to ensure that the whipworm ova will float. Whipworms can be very easily missed by fecal flotation; therefore, it is appropriate to treat any dog with chronic large bowel disease with fenbendazole.

If the diarrhea persists after eliminating parasites from consideration, the next question is whether to try a therapeutic trial or perform tests. If the patient is hypoalbuminemic or has lost substantial weight, then extensive diagnostics aimed at infiltrative diseases, especially histoplasmosis, pythiosis, and cancer are indicated. Otherwise, a therapeutic trial (e.g., dietary therapy or empirical antibiotic therapy) plus modest diagnostics (e.g., fecal examination) may be particularly helpful. It is worth noting that many of the more common diseases affecting the colon are better diagnosed with a therapeutic trial than with an extensive diagnostic work up that includes blood tests and endoscopy/biopsy. The main therapeutic trials are usually a fiber-supplemented diet, an elimination diet, anthelmintics, and/or antibiotics (e.g., tylosin or amoxicillin). Good therapeutic trials are better at diagnosing some of the more common large bowel disorders of dogs than are endoscopic examinations and biopsies.

Clostridial colitis might better be called “antibiotic-responsive colitis”. It is a very important disease in the dog, but we are not sure how important or common it is in the cat. We think that it is caused by toxigenic strains of Clostridium perfringens. However, even when a toxigenic strain of Clostridium perfringens is established in the colon, it does not generally
produce disease unless there is sufficient toxin being produced due to upregulation of toxin production in the bacteria. Toxigenic strains upregulate the amount of enterotoxin produced when they sporulate, and it is this toxin which damages the colonic epithelium and produces diarrhea.

Diagnosing clostridial colitis is not as “easy” as it was a few years ago. One cannot reliably diagnose clostridial colitis by finding spores in the feces on fecal cytology, performing quantitative cultures for *Clostridium perfringens*, or assaying for clostridial enterotoxin in the feces. Looking for fecal spores is an especially easy screening procedure, and the spores can be detected with a variety of stains. However, just as the disease can wax and wane unexpectedly, the presence and number of spores may likewise vary. Biopsy is not that helpful; there may or may not be histologic changes in the colonic mucosa in animals with clostridial colitis. Besides, the histologic lesions seen with clostridial colitis are nonspecific, and cannot be reliably differentiated from IBD or dietary allergy/intolerance. We used to think that the most definitive method of diagnosing clostridial colitis was to assay the feces for the presence of toxin; however, this is relatively expensive and is no more sensitive or specific than other tests. Many of us currently just treat for the disease and observe the clinical response. While this approach can cause a problem when there are two things happening concurrently (e.g., clostridial colitis PLUS dietary intolerance), it seems to currently be one of the better ways to diagnose clostridial colitis. Response to amoxicillin or tylosin may be one of the best ways to presumptively diagnose clostridial colitis. Many patients with clostridial colitis do not respond to metronidazole.

**Tylosin** is an antibiotic that seems to be consistently effective against *Clostridium perfringens*. This is a wettable powder that is used to treat poultry. Animals that respond to tylosin usually do so within 3-7 days. The dose is 10-40 mg/kg bid. Some patients will need treatment for the rest of their lives while others can be slowly weaned off the drug. Tylosin tends to have an unpleasant taste and needs to be mixed into the food, and sometimes it is better to put it into capsules and give it that way instead of putting it on the food. Amoxicillin is also effective in almost all animals with clostridial colitis. Many animals with chronic clostridial colitis that require antimicrobial therapy can be well controlled with one treatment of amoxicillin or tylosin every 2-3 days.

**Metronidazole** is very effective against anaerobic bacteria in general, but metronidazole is inconsistently effective in animals with clostridial colitis, possibly because metronidazole does not reliably achieve therapeutic levels throughout the feces. Some dogs with clostridial colitis respond to **fiber supplementation**, which makes sense because fiber will usually remain
relatively intact until it reaches the colon where it may have profound effects on the microenvironment of the colonic bacterial flora. The goal is not necessarily to eradicate _Clostridium perfringens_ from the animal (you probably can’t do that even if you wanted to); rather, it is to prevent the bacteria from elaborating and releasing its toxins. The preferred long term therapy of clostridial colitis is to maintain the animal on a high fiber diet which controls signs and not have to give antibiotics; however, not all animals can achieve this level of control.

We will use the term “dietary-responsive” to include both dietary allergy (an immune process) and dietary intolerance (a non-immune process). Dietary-responsive disease is more common than many suspect, especially in cats with chronic large bowel disease. You cannot count on finding eosinophils in the colonic mucosa of animals with dietary allergies; most patients with dietary intolerance have minimal histologic changes or have nonspecific lymphocytic and/or plasmacytic and/or eosinophilic infiltrates. Because the histologic findings are nonspecific, it is often preferable to try elimination diets prior to performing colonoscopy. The biggest problem in these patients is finding an effective diet. We often see cases in which the right thing was done (i.e., an elimination diet was used), but was so poorly planned or implemented that the effort was wasted. Most of the time, all that is needed is to carefully investigate the history and see what the patient has eaten in the past. However, sometimes it is difficult to find a diet that is "right" for a particular patient. This might be because you do not know if the problem is an allergy or an non-allergic intolerance. In some cases, all of our well-planned hypoallergenic diets failed but a chance try at some commercial brand works. It is easy to do a poor job of feeding a “hypoallergenic” diet and thereby make the client so discouraged with dietary therapy that they end up requesting costly work ups when a good dietary trial done at the beginning would have worked. Also, if you do a thorough work up and do not find a reasonable cause of the diarrhea, it is probably a dietary intolerance or allergy, and you will have to simply try diet after diet until you finally find the right one.

Histiocytic ulcerative colitis, also known as “Boxer colitis” is being seen more commonly now than it was 5-10 years ago. First described about 30 years ago, it was a horrible, progressive disease of young Boxers (and sometimes related breeds, such as the French Bulldog) that invariably had a terrible prognosis. The signs are those of severe large bowel disease (lots of hematochezia and fecal mucus) plus weight loss. Diagnosis is made histologically by finding PAS-filled macrophages in the mucosa. Recently, it has been discovered that this is an antibiotic-responsive disease caused by enteroadherent strains of _E. coli_. Initially, enrofloxacin seemed to be particularly effective but any number of antibiotics would work. Unfortunately, there has been an upsurge in antibiotic resistance of the _E. coli_
responsible for this disease. Many strains are no longer sensitive to enrofloxacin. Therefore, it is recommended that mucosal samples (not fecal samples) be taken for bacterial culture and sensitivity analysis. The biggest problems are that a) many people (clients and veterinarians) are reluctant to biopsy the dogs because they assume that any disease so severe must have a bad prognosis, and b) many pathologists have never seen it and miss it, even when it is fairly obvious to the experienced eye. It is best to biopsy the dog instead of giving empirical enrofloxacin therapy since other treatable diseases may be present (e.g., histoplasmosis) that also can be successfully treated if therapy is begun in a timely fashion. If antibiotics are given, it is important to treat for several weeks (at least 6) to ensure eradication of the bacteria lest resistant strains be selected for and allowed to cause a relapse that is more difficult to control than the initial presentation. Unlike some diseases, failure to eradicate the infection with the first choice of antibiotics is almost uniformly associated with subsequent resistance to the antibiotic(s) used initially.

Recently, we have seen miniature Dachshunds with what is initially diagnosed as multifocal inflammatory polyps. However, FISH analysis shows that these are bacterial in origin (something now shown by special histologic stains). At least some of them respond exceedingly well to aggressive antibiotic therapy. However, relatively few have been seen so far, so broad-sweeping statements are not appropriate.
PROTEIN-LOSING ENTEROPATHIES IN DOGS
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When concerned with protein loss of any cause, one should measure serum albumin concentrations as opposed to the serum total protein concentration. Do not use human clinical pathology laboratories because their technology sometimes does not detect canine albumin; this means that they routinely report serum albumin concentrations of < 1.5 gm/dl in clinically normal dogs. If the patient has substantial hypoalbuminemia, the first step is to examine the skin for obvious lesions which can cause protein loss. Cutaneous lesions sufficient cause such hypoalbuminemia are obvious; you should be able to just look at the patient and know if this is the problem or not. Next, hepatic function testing (e.g., resting and post-prandial serum bile acid concentrations) and a urinalysis are requested. If there is any doubt on the urinalysis, then a urine protein:creatinine ratio will quantify the magnitude of urinary protein loss. Severe hypoalbuminemia (i.e., < 2 gm/dl) in an animal with diarrhea suggests a protein-losing enteropathy (PLE); however, diarrhea (even when severe) in no way is sufficient to eliminate hepatic disease as the cause of the hypoalbuminemia. To further complicate matters, a very substantial number of dogs and cats with PLE do not have vomiting or diarrhea. Some are asymptomatic while others only have ascites. This may be especially true of dogs with primary intestinal lymphangiectasia.

In general, once severe, exudative cutaneous disease, protein-losing nephropathy, and hepatic insufficiency are eliminated, then PLE is becomes a diagnosis of exclusion in patients with a serum albumin < 2.0 gm/dl. Fecal concentrations of alpha-1 protease inhibitor can be used as a means of confirming PLE if there is confusion because of concurrent hepatic or renal disease. The major use for this test in clinical medicine seems to be the hypoalbuminemic patient in which you strongly suspect PLE (e.g., based upon it having severe diarrhea or having hypocholesterolemia), but which also has PLN and/or hepatic disease. However, there are several nuances about this test, especially collecting samples, that make it potentially difficult to interpret. We seldom need this test in clinical practice. Finally, contrary to what the textbooks say, PLE may be associated with a low, normal or increased serum globulin concentration – personally, finding “panhypoproteinemia” is not very helpful in my patients.

Hypoalbuminemia has been reported to be a poor prognostic sign in patients with chronic GI disease; however, there may be one or more subset(s) of patients that respond well to appropriate therapy if diagnosed in a timely fashion. Therefore, diagnosing PLE is not
necessarily cause for despair. Aggressive diagnostics are typically an appropriate recommendation if PLE patients. Although therapeutic trials can be chosen in place of classic diagnostic tests in many of the more common alimentary tract diseases (e.g., dietary allergy, dietary intolerance, antibiotic-responsive enteropathy, parasites), such an approach is generally ill-advised if the serum albumin concentration is less than 2.0 g/dl. This is true because it may be necessary to perform an antibiotic and/or dietary therapeutic trial for 3-6 weeks in order to ascertain if it is being effective, and a patient with severe PLE can become markedly worse in that time if the serum albumin concentration is falling rapidly.

Any GI disease can cause PLE if it is severe enough. Many acute GI disease cause PLE (e.g., parvoviral enteritis); however, these diseases typically are comparatively easier to treat than the chronic GI disease causing PLE. Therefore, the focus in this lecture is PLE in animals with chronic GI disease. The major causes of PLE in adult dogs tend to be intestinal lymphangiectasia, alimentary tract lymphoma (LSA), intestinal fungal infections (i.e., histoplasmosis and pythiosis), and inflammatory bowel disease (IBD). Other causes include alimentary tract ulceration/erosion, severe disease of intestinal crypts, antibiotic-responsive enteropathy, and parasites. The major causes of PLE in juvenile dogs tend to be parasites and chronic intussusception. Cats with PLE usually have IBD or alimentary tract lymphoma.

Many dogs with PLE have hypocholesterolemia. Pets with protein-losing nephropathies usually have hypercholesterolemia, while those with hepatic insufficiency often have hypocholesterolemia. Fecal examinations for parasites are appropriate. Although parasites are an uncommon cause of PLE in adult animals, pets in select environments (e.g., confined areas where patients can reinfect themselves) may incur substantial parasitic loads.

Once PLE has been diagnosed, intestinal biopsy is usually the ultimate means of establishing a diagnosis. Biopsy can be done via laparotomy, laparoscopy, or endoscopy. Feeding a small, fatty meal (use canned food, not dry, and add in cream or corn oil) the night before the procedure might (?) make it easier to diagnose lymphangiectasia. Flexible endoscopy, when done by someone who is trained in how to take diagnostic tissue samples and submit them, is usually more than adequate to obtain diagnostic samples. However, if endoscopy will be used to biopsy the small intestines, it is preferable to first ultrasound the abdomen to make sure that there are no focal infiltrates that are out of reach of the endoscope, or which might be more easily diagnosed by ultrasound-guided fine needle aspiration. Furthermore, there are ultrasonographic changes (streaks in the submucosa) that can be diagnostic. Radiographs and barium series are seldom as sensitive as ultrasound. If flexible endoscopy will be done, one should biopsy both the duodenum and ileum. There have been
numerous cases in which lymphangiectasia, IBD or LSA were obvious in the ileum but not in the duodenum. It is not necessary to enter the ileum with the endoscope to obtain a good tissue sample of the ileal mucosa.

Laparotomy and laparoscopy are good means of obtaining diagnostic samples, but it is surprisingly easy to procure non-diagnostic samples with these techniques (i.e., “full-thickness sample” is not synonymous with “diagnostic sample”). Endoscopy does have the advantage of allowing one to visualize mucosal lesions that are “invisible” when looking at the serosa. In some cases, the diagnosis can only be obtained by biopsying these focal lesions. If full-thickness biopsies are obtained in severely hypoalbuminemic animals, then serosal patch grafting will minimize the risk of suture line leakage. A nonabsorbable or a poorly absorbable suture (PDS) should also be used.

Intestinal lymphangiectasia seems particularly common in Yorkshire terriers and Soft-Coated Wheaten terriers, but may occur in any breed. Sometimes these dogs have distinct ultrasonographic findings: “streaks” in the mucosa that represent dilated lymphatics. While histopathology is obviously the desired means of diagnosis, one can sometimes make a definitive diagnosis based upon grossly visible endoscopic findings (i.e., numerous, erratic, grossly engorged lacteals seen as large white blebs on the mucosa). These lesions are “fragile” and apparently may be destroyed by biopsying them (both endoscopically and surgically) if the endoscopist or surgeon is not careful. It is important to note that lymphangiectasia can be a relatively localized disease in the intestines, being present in only the ileum or only the jejunum or only the duodenum; therefore, it is important to biopsy as much of the intestinal tract as possible. Furthermore, if one biopsies the intestines and cannot find a cause of PLE, sometimes lymphangiectasia can be tentatively diagnosed by elimination (i.e., by eliminating IBD, lymphoma, parasites, intussusception, fungal infections, etc).

Diagnosis by means of endoscopic biopsy is certainly possible if the endoscopist is trained in taking high quality tissue samples. However, recent work has demonstrated that poor quality mucosal biopsies (e.g., primarily villus tips or substantial “squash” artifact) makes is much more difficult or even impossible to find the lesions. If one is taking high quality tissue samples (i.e., total length of the villi plus subvillus mucosa down to the border of the mucosa and muscularis mucosa), it typically takes about 6-7 tissue samples to have 90-99% confidence in finding lymphangiectasia. However, it can take 5-7 times as many tissue samples to have the same assurance if you are obtaining poor quality tissue samples that primarily consist of villus tips.
When doing endoscopy, it is important that ileal biopsies be taken in addition to the typical duodenal biopsies. We are finding that ileal biopsies often reveal lesions not found on duodenal biopsies. This is true for lymphangiectasia as well as lymphoma and other lesions. With basic training, an endoscopist should be able to obtain ileal biopsies endoscopically at least 85%+ of the time. Typically, ileal biopsies are often of higher quality than duodenal biopsies.

Therapy for intestinal lymphangiectasia revolves around an ultra-low fat diet, preferably with anti-inflammatory therapy designed to alleviate the lipogranuloma formation that commonly occurs within the intestinal wall and/or mesentery. Supplementation with medium chain triglyceride oil (MCT) used to be recommended because MCT oil supposedly bypasses intestinal lymphatics thus preventing further rupturing of the lacteals. Pancreatic enzymes were often added to the diet to ensure digestion of the medium chain triglyceride oil. MCT oil is seldom used anymore, probably because appropriate dietary therapy is usually more than sufficient. Feeding homemade diets that are highly digestible and ultra-low in fat (e.g., white turkey meat plus potato or rice) or feeding commercial diets is often very helpful in these patients. Commercial low fat diets can be used very successfully, but they need to have the lowest possible fat content. Such a diet can be so successful that it might occasionally be appropriate to use it as a therapeutic trial. Dogs with lymphangiectasia often show a marked increase in serum albumin concentration within 7-14 days of starting such a diet.

The important of lipogranulomas in the intestinal wall and mesentery is uncertain. However, we hypothesize that some patients fail to respond to appropriate dietary therapy because of formation of very large or excessive numbers of lipogranulomas that so completely obstruct the intestinal lymphatics that even an ultra-low fat diet cannot prevent lacteal rupture. Therefore, once a diagnosis of lymphangiectasia is made (either by histology, grossly at endoscopy, or tentatively by response to an ultra-low fat diet), it seems to be appropriate to use anti-inflammatory therapy designed to prevent granuloma formation/enlargement. Prednisolone, azathioprine, and/or cyclosporin are commonly used for this purpose. I do not like prednisolone, simply because of all the side effects it has in these patients. I like cyclosporine, but be aware that it is critical that you measure blood levels of the drug if you use cyclosporine. Not only is there a major difference between patients in how much they absorb, but the bioavailability of the same product may change as the intestine heals.

If the serum albumin is very low (e.g., < 1.3 gm/dl), one is often tempted to administer a plasma transfusion while waiting to see what effect the diet will have. However, it is exceedingly difficult to increase the serum albumin concentration by transfusing PLE patients with plasma.
because so much of the albumin is quickly lost out the gut. You would probably have to give at least two and possibly three units of plasma to a 15 lb dog in order to raise the serum albumin from 1.0 gm/dl to 1.6 gm/dl, and sometimes you would have to give more. However, any benefit will probably be so short lived that it is not cost-effective. If it is critical to raise the plasma oncotic pressure, then administering hetastarch may be preferred because it costs less than plasma, and it stays in the intravascular compartment longer than albumin.

These patients may be a increased risk for hypomagnesemia which may potentiate the problem of hypocalcemia. At this time, we do not know how important it is to supplement magnesium to patients, but severe hypomagnesemia can be resolved by a constant rate infusion of magnesium sulfate.

Lesions of the intestinal crypts have been recognized as being associated with PLE in dogs. We have identified two different lesions of the small intestinal crypts that can cause PLE. One type is characterized by crypts (usually duodenal) that are filled and somewhat distended with proteinaceous fluid and necrotic inflammatory cells. While such dilated crypts can be found in many animals, including clinically normal dogs, finding large numbers of them in multiple tissue samples seems to be consistently associated with PLE. We do not know if this is a cause-and-effect relationship, or if the dilated crypts are simply a marker for some other process but are not causing the protein loss themselves. Several of these patients have responded to therapy with elemental diets, total parenteral nutrition, prednisolone, azathioprine, and/or metronidazole. We have seen this lesion associated with IBD as well as lymphangiectasia (especially in Yorkshire terriers).

A second type of crypt lesion that appears to be less common than the first, if characterized by focal accumulations of mucus causing massive distention of the intestinal crypts. This has been reported once before, and we have seen a few such cases. The most important aspect of diagnosis seems to be the fact that the lesion may be very focal, almost appearing as ulcers when looking at the intestinal mucosa through an endoscope. Therapy similar to that used on animals with the other form of crypt lesion may be helpful. We have used cyclosporin, but do not know if it is helpful, or if the clinical response is due to the other drugs that the patient is receiving.

These lesions have not been commonly reported. Recent work has shown that these lesions are extremely easy to miss if poor quality endoscopic biopsies are performed. While 7-12 high quality tissue samples (i.e., full length of villi plus subvillus mucosa down to the level of the muscularis mucosa) will find these lesions 90-99% of the time, about 7 times as many tissue samples will be needed if poor quality samples primarily consisting of villus tips are submitted.
Chronic intussusception is a relatively important, and often missed cause of PLE in juvenile animals. The classic history is one of acute enteritis (e.g., parvoviral enteritis) which does not resolve as expected. The patient feels somewhat better, but continues to have diarrhea, and the serum albumin concentration gradually diminishes. It can be very hard to palpate an ileo-colic intussusception; abdominal ultrasound is clearly the preferred way to diagnose intussusception. Therapy is surgical.

Although uncommon, nematodes may cause PLE in adult animals if there are large numbers of them. Whipworms and hookworms in particular may occasionally be responsible for PLE in older dogs. However, giardiasis has been reported to cause PLE in people.

We believe that we are starting to recognize ARE as a cause of PLE in dogs. We now have several patients that appeared to have marked increases in their serum albumin concentration associated with antibiotic therapy. However, because dietary change is often performed simultaneously with antibiotic therapy in these patients, cause-and-effect is not clearly established. However, since we believe that bacteria (i.e., ARE or dysbiosis) is probably the ultimate cause of IBD, it makes sense that treating ARE may resolve some cases of PLE.
INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD), depending upon how you define it, is not the most common cause of chronic small or large bowel diarrhea in dogs and may not be as common in cats as was once believed. In this discussion, we will define IBD as “idiopathic inflammation of the intestines”. This means that you cannot diagnose IBD just by histopathology. You diagnose IBD by finding intestinal inflammation and showing that it is idiopathic by eliminating diet, parasites, bacteria and fungal agents as the cause. You cannot eliminate dietary causes and bacterial causes by histopathology or blood tests; therapeutic trials are necessary. This is very important because diagnosing IBD generally results in anti-inflammatory or immunosuppressive drugs being used. However, if the patient has dietary-responsive or antibiotic-responsive disease, then these drugs are generally unnecessary. I stress this point because many patients have been erroneously diagnosed, improperly treated, and significantly harmed because IBD is a “fashionable” or “trendy” diagnosis. IBD is a real syndrome and is important for the veterinary practitioner to understand. However, it often degenerates into an excuse of convenience rather than a real diagnosis. More and more evidence is accumulating that shows that bacteria are probably a major source of the inflammation in dogs and cats with this disease. See below, under Antibiotic-responsive enteropathy.

DOGS WITH CHRONIC SMALL BOWEL DIARRHEA (NOT PLE)

Once parasites, protein-losing enteropathy, and maldigestion are eliminated (i.e., you have determined that the patient has a non-PLE malabsorptive disease), the question is whether to recommend therapeutic trials or a major diagnostic work up. If the patient can tolerate a possible delay of 4-8 weeks without undue risk, then therapeutic trials are reasonable. If therapeutic trials are performed, they must be designed such that even if they fail, useful information is obtained and the clinician is further ahead than previously. Always ask yourself: "If this therapy fails, will I really know more about what the patient probably has, or will I be as confused as I was before treating it?".

An elimination diet for dietary responsive disease is often useful for non-protein-losing malabsorptive disease. There is no such thing as a commercial diet which is an appropriate elimination diet (i.e., is hypoallergenic and appropriate to look for non-allergic intolerance) for all
dogs. We often see cases in which the right thing was done (i.e., an elimination diet was used); but, it was done in such a poorly planned or implemented fashion that the effort was wasted. One must carefully investigate the history and see what the patient has eaten in the past. However, even when you have determined what dietary ingredients the patient has previously been exposed to, it is sometimes difficult to find a diet that works for that particular patient. In some cases, all of our well-planned hypoallergenic diets fail but a chance try at some commercial brand works.

When starting the patient on an elimination diet, one may use a homemade diet or a commercial diet. There are many excellent commercial diets, and they usually work. Homemade elimination diets sometimes work when commercial diets do not; however, this is very uncommon. Therefore, you will have to decide which is most appropriate in the patient that you are treating. The hydrolyzed diets are usually good but are not always the best choice for every patient. Some animals respond better to a novel protein diet than a hydrolyzed diet, and vice versa. Which ever elimination diet is used, one must be prepared to feed it and it alone for an absolute minimum of 3-4 weeks before its efficacy can be accurately determined. Rare cases need to be fed a diet for 6-8 weeks before they respond, but this is probably well less than 5% of cases. If a diet seems to be effective (i.e., weight gain plus resolution of diarrhea) then continue it for at least another 3-4 weeks to be sure that it was the diet that made a difference as opposed to the patient having some transient improvement due to any number of causes.

Antibiotic-responsive enteropathy (ARE) seems to be a relatively common problem in dogs. It can best be described as a syndrome in which there are substantial numbers of bacteria in the upper small intestines AND the host responds to them in such a manner as to cause intestinal dysfunction. These bacteria are not usually obligate pathogens. Rather, they can be of any species, and *E. coli*, *Staph, Strep*, and *Corynebacterium* are particularly common aerobic/facultative anaerobic bacteria found in the upper small intestines, while *Clostridium* and *Bacterioides* are especially common anaerobic bacteria. These bacteria are probably commensals or they may represent contamination from ingested material which is not eliminated by normal host defense mechanisms. The signs they produce, if any, seemingly depend upon at least two factors: a) which bacteria are present and b) how the host responds to them. The relationship of ARE to IBD is unclear, but it seems very possible that bacteria could be responsible for either initiating and/or perpetuating the intestinal inflammation we call IBD. The term “dysbiosis” has been suggested as the bridge between ARE and IBD – that is to say that having bacteria that are somewhat prone to cause problems (i.e., usually enterics such as *E. coli*) as opposed to having overt pathogens.
Antibiotic-responsive enteropathy is hard to definitively diagnose with laboratory tests. Histopathology and cytology of the intestinal mucosa are extremely insensitive at detecting ARE. Serum cobalamin and folate concentrations have been used for diagnosis, and finding both a low serum cobalamin and an increased serum folate concentration has been considered to be relatively specific for ARE. Measuring serum cobalamin and folate concentrations is relatively insensitive and non-specific for detecting ARE. There are many dogs with chronic GI disease that respond to antibiotic administration but which have normal cobalamin and/or normal folate concentrations. It would seem that treatment for ARE is justified regardless of whether the serum cobalamin and folate concentrations are normal or abnormal, leading one to ask whether there is any benefit to measuring them to diagnose this disorder. Finding hypocobalaminemia or low serum folate levels is beneficial when looking for otherwise occult gastrointestinal disease. Supplementing cobalamin can clearly make cats feel better and diarrhea diminish. In fact, it is almost getting to the point where it is never wrong to give any sick cat cobalamin injections, regardless of blood values of the vitamin. Severe hypocobalaminemia has been suggested to be a poor prognostic signs. While the value of supplementing cobalamin to cats is clear (in fact, it is almost never wrong to give any sick cat supplemental cobalamin), the clinical value of administering cobalamin to dogs with low serum cobalamin concentrations is very uncertain.

Culture of the small bowel was once considered the “gold standard”, but this test is fraught with problems. First, it is technically hard to do it correctly. Samples must be obtained without contaminating them with oral secretions. Then they must be processed correctly in an expedient manner so as not to lose any anaerobic bacteria while not allowing the numbers of aerobes to increase. Many investigators have snap frozen fluid samples to culture them later, but such freezing appears to kill large numbers of bacteria, especially anaerobic bacteria. We now know that culture only detects about 30% of the bacteria in the gut; the other 70% cannot be cultured. This makes one seriously question the value of culture unless one is searching for a specific pathogen, and even then there are culture-less methods (e.g., PCR) that may be better. Finally, as has already been said, just culturing bacteria from the small bowel does not allow one to make a diagnosis of a bacterial disease of the small intestines. Large numbers of bacteria (i.e., > 10^7 CFU/ml) can be present in dogs without any evidence of any clinical disease. For these reasons, we very rarely culture the small intestine of dogs with chronic GI disease. However, there are rare patients that appear to have ARE and yet are resistant to treatment with commonly used antibiotics. Seemingly, these dogs may have one or two very resistant bacteria in their GI tracts, and culture may be required to determine what antibiotic will
be effective. However, we have only seen this scenario twice, and we believe it to be very rare.

Because of the apparent difficulty in diagnosing ARE with lab tests, empirical antibiotic therapy is often chosen as a means to diagnosis instead of laboratory tests. The obvious drawbacks to this approach are a) clinical “response” of the patient to the administered antibiotics may be due to the antibiotics or may be due to something else, b) if the patient did not respond to the antibiotic, it may be that you used the wrong antibiotics, and c) even if the patient does have ARE, there may be yet another disease present (e.g., a tumor causing a partial intestinal obstruction) which predisposed the patient to the ARE.

Because any bacteria can be present in the upper small intestine, the species of bacteria in the upper small intestine may change from week to week, and we seldom know which bacteria we are treating, broad spectrum antibiotics designed to lessen bacterial numbers seem to be indicated. You can never sterilize the GI tract. However, because clinical signs are due to a combination of large numbers plus an altered host response, simply lessening the numbers of bacteria often seems beneficial. Oral aminoglycosides were generally considered a poor choice to treat ARE because anaerobic bacteria (which have been suggested to be more of a problem) are resistant to aminoglycosides. However, this opinion is not clearly correct as there are occasional patients that clearly improve when given amikacin orally. Tetracycline is often effective; but, giving tetracycline is inconvenient. Tetracycline must be administered alone (i.e., without any food) and yet be washed down with water to ensure that the capsule to tablet does not stick in the esophagus and cause esophagitis. Tylosin powder has also been useful and is revered by many clinicians. Some clinicians like metronidazole; however, I have not been impressed with the efficacy of metronidazole for ARE. Metronidazole seems to have real benefit in many GI disorders, probably because it is so effective in eliminating many anaerobic bacteria. For patients that are EXTREMELY ill in which we need to know RIGHT NOW whether or not it will respond to antibiotics (i.e., that patient is so ill that you cannot take a chance of being 2-3 weeks from now and not having a response to therapy), I use a combination of enrofloxacin and metronidazole. I did not say that I used this combination for long periods of time. I use this combination when I absolutely MUST know whether or not I will have a clinical response within the next 2-3 weeks or take a chance on losing the patient.

Regardless of which drug is used, such a therapeutic trial should be performed for at least 3 weeks before a decision is made as to its efficacy. Remember, you must not only suppress the numbers of bacteria, but you must also allow the intestinal mucosa time to heal. Finally, it appears that concurrently feeding a high quality elimination diet can substantially enhance the efficacy of the antibiotic therapy. Therefore, we now routinely use both in our
If the patient appears to respond to this therapeutic trial of elimination diet and antibiotics, then it appears best to continue everything unchanged for an additional 2-4 weeks to be sure that the patient responded to this therapy (as opposed to the patient having some fortuitous, transient response to who-knows-what). If the patient is still doing well at that time, then you either a) stop the antibiotics and see if they diet alone is sufficient to control signs or b) slowly wean the antibiotics to their lowest effective dose (e.g., once a day or even once every other day). It all depends upon how frequently the clinical signs occur. If the signs occur once every 2+ months, then it obviously makes sense to only treat when the patient is symptomatic. If the signs consistently recur within a few days of stopping the antibiotics, then you are probably stuck with treating almost constantly. In some cases, the patient will breakthrough and re-develop clinical signs after several weeks or months, and a different antibiotic must be used. If the decision is made to stop administering the antibiotics, then the owners should be warned that it is possible that the signs are likely to recur at some point. For ARE to occur, there is probably some defect in host defense mechanisms that allowed the commensal bacteria to cause the clinical signs, and this defect is unlikely to disappear. The question is how severe is the defect (i.e., is the dog likely to have problems continually or only once in a while)? You should warn the clients that they are likely to have to deal with this problem repeatedly and you need to explain the difference between “cure” and “control”.

It may be a good idea to routinely treat all dogs with chronic small intestinal disease for ARE, even if you have histologic evidence of IBD or other disease. I will treat for ARE almost every time I diagnose a dog with a malabsorptive disease since there is no test for ARE that is reliable in ruling this disorder out, including cobalamin and folate determinations.

Other options that are becoming increasing more interesting are prebiotic and probiotic therapy. In particular, these therapies are being looked at as possible alternatives to protracted antibiotic therapy.

If the patient is so sick that you cannot chance a 3 week therapeutic trial that may fail; or if the owners insist upon obtaining a diagnosis, then tests are the next step. If, based upon history, physical examination, laboratory data, fecal examination and/or abdominal ultrasonography you are sure that the small intestine is involved, then the best next step is usually intestinal biopsy.

Intestinal biopsy may be accomplished two ways: endoscopy and surgery. CBC, serum chemistry profile, and urinalysis are useful and may point out systemic manifestations of the disease which will aid in correctly diagnosing and prognosing the problem (e.g.,
hypoalbuminemia due to histoplasmosis), but are also useful as a preanesthetic work up before endoscopy. **Ultrasound** is useful to look for enlarged mesenteric lymph nodes, focal intestinal/gastric lesions, and loss of mucosal layering. Focal enlargements may suggest a tumor (e.g., alimentary lymphoma or carcinoma), as may lymphadenopathy. However, animals with severe IBD may also have mesenteric lymphadenopathy (as may dogs with histoplasmosis or pythiosis). If the lymph nodes are enlarged, it is reasonable to aspirate them percutaneously with ultrasound guidance. Mesenteric lymph nodes are typically reactive, making it more difficult to interpret cytology from them. However, finding obvious sheets of lymphoblasts or fungal organisms (e.g., histoplasmosis) allows diagnosis. Sonographic examination of the intestines is important (i.e., you may make a diagnosis), but it does not detect intestinal mucosal disease in many patients that are afflicted with such disease. If loss of mucosal layering is seen, then severe infiltration is likely (either inflammatory or neoplastic), but normal-appearing mucosa may have marked disease present. Most of the time, ultrasound’s major use is to help you decide whether to perform intestinal biopsy using endoscopy or laparotomy. If there is an obvious lesion where an endoscope cannot reach, it is best to perform laparotomy instead of endoscopy. Abdominal radiographs (plain or contrast) are rarely helpful or cost-effective in these patients.
CANINE PANCREATITIS
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DIAGNOSIS

History and physical examination are, as always, critically important; but, they are not that helpful for ruling pancreatitis in. Rather, they are more useful for finding other problems that may be mimicking pancreatitis. Regarding signalment, Schnauzers and Yorkies are famous for acute pancreatitis, but these breeds get a lot of other diseases that cause vomiting. Furthermore, acute pancreatitis can be found in any breed of dog. Canine pancreatitis is classically considered to present with acute vomiting and anorexia. Abdominal pain is frequently present, but it is easy to miss during physical examination, and fever is occasionally seen. However, we are recognizing more and more and more cases in which a) vomiting is not as severe as we have come to expect, and b) in which we are initially strongly drawn to other diagnoses to the point that many of us are no longer sure what a “typical” case of canine pancreatitis is. Some dogs (especially those with pancreatic abscesses) may have relatively mild, intermittent, unimpressive vomiting and continue to eat a reasonable amount of food. Many of the severely ill patients may present in classic systemic inflammatory response syndrome (SIRS) which is what used to be called septic shock, until we found out that you can have the same thing occur with any cause of massive inflammation. Many dogs with very severe acute pancreatitis present as though they had an acute, septic abdomen. Some have substantial amounts of abdominal fluid. If acute pancreatitis is associated with or due to pancreatic carcinoma (rare), you may rarely see a dog that has widespread subcutaneous fat necrosis causing sterile abscesses that are typically painful and cause cutaneous discoloration. Most cases of canine pancreatitis seem to be temporally related to either ingestion of fat or lipemia associated with diabetic ketoacidosis. Trauma and drugs can also cause canine pancreatitis. Drugs that are suspected of causing pancreatitis in people and animals include azathioprine, sulfonamides, tetracycline, and potassium bromide.

CBC’s often show an inflammatory leukogram, but 1) this is a relatively nonspecific finding and may be due to any number of problems and 2) not all animals with acute pancreatitis have a notable leukocytosis. Degenerative left shifts and substantial toxicity of circulating WBCs can be seen if the patient is in SIRS. Likewise, thrombocytopenia due to DIC is not infrequent in severely affected patients. However, some animals with clinically severe pancreatitis have absolutely normal leukograms. There are no findings on CBC that definitively
diagnose or definitively eliminate pancreatitis. Serum biochemical panels are not as helpful as we would like. Serum lipase and amylase activities are insensitive (each is about 50%) and nonspecific (again, about 50%) for pancreatitis and should probably never be requested. Dogs with acute pancreatitis and even pancreatic abscesses have had normal serum lipase activities. We have also identified dogs with drastically increased serum lipase activities that have intestinal foreign objects or gastritis, but no gross evidence of acute pancreatitis. Lipase is produced by the canine gastric mucosa which explains why inflammation or damage to the stomach can result in excessive serum lipase activity. Canine TLI is a little more specific than amylase and lipase, but it is still not a sensitive test (approximately 35%). Therefore, it too has very poor negative predictive value. We have seen plenty of dogs with pancreatitis that had normal serum TLI's.

The immunoreactive canine pancreatic lipase assay (i.e., cPLI or Spec cPL) appears to be the most sensitive (approximately 80-85%) test for pancreatitis available. There are a few false negative results with this test, but it is clearly much more sensitive than any other blood test available. The real question is how specific it is for clinically important disease (i.e., lesions of the pancreas that are causing clinical disease as opposed to microscopic lesions that are clinically silent). The biggest advantage is that if the cPLI test is negative, it is much less likely that pancreatitis is the real problem and you need to look very hard for extra-pancreatic disease in the dog.

Blockage of the main pancreatic duct due to swelling due to generalized pancreatitis, an intrapancreatic granuloma, or an abscess that subsequently blocks the pancreatic duct may cause extrahepatic biliary tract obstruction (EHBO) with a notable increase in serum alkaline phosphatase and serum bilirubin. Pancreatitis is probably the most common cause of EHBO in the dog. Thus, while EHBO is very suggestive of acute pancreatitis (assuming that the patient does not have a mucocoele, which is usually easy to detect with ultrasound), relatively few dogs with acute pancreatitis develop EHBO. Furthermore, there are reasons for this triad of signs besides acute pancreatitis and extrahepatic biliary tract obstruction (e.g., cholangitis-cholangiohepatitis). Ultrasonographic evaluation of the abdomen (discussed below) is particularly helpful in these patients.

Plain abdominal radiographs help eliminate other diseases which may mimic acute pancreatitis. Not finding evidence of other abdominal disease (e.g., foreign object) is helpful in eliminating obstruction and narrowing the list of differential diagnoses. Occasionally, one finds radiographic signs which specifically suggest acute pancreatitis. A sentinel loop (i.e., a dilated, air-filled segment) in the descending duodenum, and/or lack of serosal detail in the upper right
abdominal quadrant, and/or lateral displacement of the descending duodenum on the ventro-
dorsal projection, and/or a mass medial to the descending duodenum (on the ventro-dorsal
projection) and/or a mass just behind the liver and just below the pylorus (on the lateral
projection) are somewhat suggestive of acute pancreatitis. These findings are only meaningful
if present; many dogs and cats with acute pancreatitis do not have any of these radiographic
findings. Probably the most greatest value of abdominal radiographs is that they help eliminate
other diseases that could be causing signs similar to those caused by pancreatitis.

Abdominal ultrasonography often finds abnormalities that suggest or are consistent with
pancreatitis as well as eliminate other potential causes of vomiting and abdominal pain.
Ultrasonography has been suggested to be about 40-70% sensitive in finding canine
pancreatitis. One may sometimes detect hypoechogenicity surrounded by hyperechoic fat in
the region of the pancreas that is due to pancreatitis. At other times, a markedly thickened
pancreas may be found. Both findings are very specific evidence of pancreatitis. Evidence of
EHBO (i.e., dilated bile ducts, not just a big gall bladder) is very suggestive of pancreatitis.
Rarely, you will find dilated bile ducts due to inflammatory biliary tract disease, but this is not
nearly as common a cause as is biliary tract obstruction. Any dog with extra-hepatic biliary tract
obstruction (that does not have a mucocoele) and that is vomiting/anorexic should be assumed
to have pancreatitis until proven otherwise. It is very important to note that the ultrasonographic
appearance of the pancreas can change dramatically within a few hours, so repeating
abdominal ultrasound on the same day is not necessarily a bad idea if you strongly suspect
pancreatitis but are finding nothing.

Diagnosing pancreatitis during laparotomy is the least desirable method of diagnosis.
Some patients present exactly like acute septic peritonitis but are ultimately diagnosed as
having non-septic pancreatitis. There is nothing wrong with doing an exploratory laparotomy in
a patient in which septic abdomen is a major consideration, only to find out that the patient has
non-septic pancreatitis. We very rarely have reason to biopsy a normal appearing canine
pancreas, and what grossly appears to obviously be pancreatitis in the dog seldom requires a
biopsy unless carcinoma is a concern. However, you should never simply look at what appears
to be an obviously neoplastic mass in the pancreas and make a diagnosis of carcinoma without
biopsying it, no matter how extremely terrible it appears. Pancreatitis is much more common
than pancreatic carcinoma, no matter how bad the pancreas looks or how many adhesions are
present. If you biopsy the pancreas, it is important to obtain a biopsy that goes deeper than the
superficial necrotic surface or adhesions. Cytology can be useful for making a presumptive
diagnosis; however, I have seen at least one case in which cytology of a pancreatic mass was
read out as carcinoma by two accomplished cytologists and yet multiple biopsies all came back as necrotic pancreatitis. Anecdotally, there appears to be more risk of causing iatrogenic pancreatitis with surgery in the dog than in the cat. Maintaining excellent mesenteric perfusion during anesthesia and performing the surgical biopsy with reasonable care and good technique minimizes the risks. Laparoscopic biopsy of the pancreas might be safer than surgical biopsy, but that is just anecdotal at this time.

Chronic pancreatitis (i.e., chronic pancreatitis with intermittent, relatively mild recurrences) can be challenging to diagnose. Dogs with episodic vomiting due to recurrent bouts of pancreatitis may not have any other signs of disease, and they invariably are admitted to your clinic for a work up after the last bout has run its course or is on the mend. Episodes of vomiting and anorexia due to recurrent pancreatitis can be random and unpredictable. In such patients, the previously mentioned diagnostics may be attempted, especially when acute exacerbations occur. Very rarely, upper gastrointestinal barium contrast radiographs may rarely reveal duodenal abnormalities (e.g., dilatation, stricture) which suggest that recurrent bouts of acute pancreatitis have caused scarring of the pancreas which in turn have compromised the maximum size of the duodenal lumen. Ultrasonographic changes are nice if they are present, but they can be minor making it difficult to accurately interpret them. Feeding an ultra-low fat diet for 3-4 times longer than what was previously the longest interval between episodes may sometimes be helpful in making a presumptive diagnosis. If episodic vomiting/anorexia does not recur while feeding such an ultra-low fat diet for an interval so long that you would have been sure to experience another episode, then we can often assume (rightly or wrongly) that the signs were due to pancreatitis (or perhaps some other dietary-responsive disease). Anytime you find exocrine pancreatic insufficiency (diagnosed with TLI) in a breed that is not commonly affected with pancreatic acinar atrophy (e.g., German shepherd, rough-coated Collie), then chronic pancreatitis becomes a major concern.

Pancreatic abscesses in dogs (as opposed to cats) are invariably sterile. Affected dogs typically can have a much more chronic, smoldering course (e.g., vomiting for a month or more, mild loss of appetite) than most dogs with more typical acute pancreatitis. We have even found a few dogs which had pancreatic abscesses that were completely asymptomatic. Abdominal pain may be present or absent. CBC and serum biochemistry findings are unpredictable. Diagnosis requires ultrasound. Treatment may be surgical marsupalization, percutaneous ultrasonographic drainage or just observation.
As of this writing, there is not a single, well-designed, robust, prospective, stratified study on the treatment of canine acute pancreatitis. Therefore, all any of us has is opinions, period.

Nothing per os (NPO) has been the classic therapy for pancreatitis for many years. While it is true that they feed people with pancreatitis earlier than we feed dogs, you must remember that human pancreatitis is unassociated with dietary fat. People get pancreatitis from alcohol, trauma, gall stones and MOF (multiple organ failure). Canine pancreatitis is associated with dietary fat (as well as surgical trauma when poor technique is used around the pancreas). Some preliminary work from in Australia suggests that it is safe and perhaps beneficial to feed dogs with acute pancreatitis per os or with an esophagoscopy tube as soon as they can tolerate it (i.e., they do not get worse, even if they are still vomiting). I recommend that a) you feed as low a fat content as possible, and b) if the feeding is associated with worsening of the vomiting, that you stop it and either try again in a day or two, or go to jejunostomy feeding. Do not try to get full caloric intake into the patient; rather, start with small amounts to see if the patient will hold down the food. Obviously, if feeding is associated with worsening of the vomiting or general condition, stop the feeding. I generally start feeding potato or rice (i.e., no fat) and gradually work my way up to commercial diets with low fat content.

Fluid therapy is critical, and subcutaneous administration of fluids is clearly inferior to IV fluids for all but mildly affected animals. IV fluid administration is often sufficient, even in dogs in which a pancreatic granuloma has temporarily blocked the main bile duct. Adequate pancreatic circulation is probably crucial for healing damaged pancreatic tissue; therefore, it is probably better to provide a little too much fluid rather than a little too little fluid unless the patient has congestive heart failure or oliguric renal failure. The abdominal viscera is not "first in line" to receive circulation when the patient is dehydrated (which most dogs with pancreatitis are when they come to your office). Obese and fat dogs (which describes a lot of dogs with pancreatitis) do not necessarily have skin tenting when they are dehydrated. Likewise, although you might expect dry, tacky oral mucus membranes, a nauseated animal may be salivating enough to make the mucus membranes moist even though it is dehydrated. If a vomiting dog is not eating or drinking, then it is dehydrated regardless of how well hydrated it appears on physical examination. However, if you give substantially too much crystalloid and dilute the serum protein concentrations, this could be detrimental.

One should monitor the serum albumin concentration during fluid therapy in these patients. If the serum albumin concentration decreases significantly (i.e., to < 2.0 gm/dl), then the plasma oncotic pressure likewise decreases which diminishes the effective perfusion at the capillary level. Since perfusion is so critical to treating dogs with pancreatitis, one should
probably become concerned whenever the serum albumin concentration falls below 2.0 gm/dl. It is very hard to administer enough plasma to significantly raise the plasma albumin concentration. Half of the albumin in the plasma that you administer will end up in the extravascular compartment instead of the intravascular compartment. Hetastarch is a better choice because it will stay in the circulation and raise the plasma oncotic pressure for much longer than plasma. Human albumin can be used effectively, but it occasionally causes anaphylactoid reactions that can kill the patient; therefore, it is not recommended. Canine albumin is safer, but it does not last as long as hetastarch. There is some thought that plasma might be more effective than administering hetastarch because plasma might also restore circulating protease inhibitors and replenish AT III (which is a treatment for DIC). This is a very contentious point. One retrospective study has shown that plasma did not help treat dogs with pancreatitis; however, this study suffers from the problems inherent in all retrospective studies.

If the patient cannot tolerate early refeeding (i.e., the vomiting becomes worse), then jejunostomy feeding is another option. It is safer, less expensive, and less dangerous than parenteral nutrition, and has been associated with a better prognosis. In particular, it should be considered if an exploratory laparotomy was performed when the pancreatitis was diagnosed because a J-tube can be placed at that time. Alternatively, one can place a jejunostomy tube via laparoscopy, through a G-tube, and via the nose (naso-jejunostomy).

Total parenteral nutrition (TPN) is expensive, labor-intensive, and can only be done in facilities where there is 24 hour coverage by trained individuals. For whatever reasons, it has been associated with a worse prognosis than enteral feeding. Partial parenteral nutrition (PPN) is something that almost anyone can use in practice. The goal is to provide approximately ½ of the caloric requirement by using a combination of D5W, 8.5% amino acids plus electrolytes, and 20% lipid emulsion. One typically provides approximately 1/3 of the desired calories with each of the three ingredients, and then administers the solution through a peripheral catheter. Much less monitoring is required with PPN than with TPN. In general, PPN is used for 5-7 days to help the patient “get over the hump”; it is not usually intended to be used for more than a week. The best source of information on partial parenteral nutrition is: Compendium of Continuing Education 21: 512, 1999. However, enteral feeding is clearly preferred.

Antiemetics are useful in patients that are vomiting repeatedly or that feel so nauseated that they feel terrible. I prefer to only use antiemetics for short periods of time because I want to see if the patient is improving enough so that it no longer needs the antiemetic to stop vomiting. However, if the patient is vomiting multiple times per day or obvious feels terrible due to the nausea, then maropitant (1 mg/kg SQ) appears to be very useful. Maropitant might also have
the advantage of providing some analgesia because it blocks Substance P binding. Dolasetron (0.3-1.0 mg/kg qd) and ondansetron (0.25 mg/kg qd) can also be effective.

H-2 receptor antagonists have been used to prevent gastric ulceration and erosion. It is doubtful that ulceration/erosion is a common problem in all but the sickest patients. Furthermore, if it is desired to provide some level of protection to the gastric mucosa, the proton pump inhibitors are far superior to the H-2 receptor antagonists. Pantoprazole (1 mg/kg IV qd) or omeprazole (1.5-2 mg/kg PO bid) are the most commonly used drugs. I suspect that they provide more benefit by being antidysepsic in nature (thereby making the patient feel better) than they do by preventing ulcers, but that is a guess.

**Antibiotics** have been used to “prevent” secondary bacterial infection of the inflamed pancreas, which is supposed to be "fertile ground" for infection. However, there is minimal evidence that bacterial infection is of any significance in routine canine pancreatitis. Antibiotics do not hurt these patients, but it is very questionable how helpful they are. However, dogs in SIRS due to pancreatitis may be a different story. Any dog in SIRS from any reason is potentially at increased risk of infection due to severely compromised mesenteric circulation.

Drugs designed to decrease pancreatic secretion have been disappointing, which is not surprising when one considers that acute pancreatitis may be associated with pancreatic hyosecretion instead of hypersecretion.

**Corticosteroids** are very controversial in the treatment of pancreatitis. While they increase serum amylase and lipase activities, they do not cause pancreatitis. It is possible (this is controversial) that they may be useful in treating patients that are in Systemic Inflammatory Response Syndrome (i.e., SIRS, which used to be called “septic shock”) due to the pancreatitis. At this time, there are good data showing that it is probably reasonable to give physiologic doses because dogs in SIRS typically can have what has been termed “Critical illness related corticosteroid insufficiency” (CIRCI), that is to say that they are relatively hypoadrenal. This is a controversial statement. If steroid therapy for pancreatitis is contemplated, it should probably be reserved for the severely ill dog which is not responding to fluid resuscitation. If steroid therapy will be administered, you need to warn the owners of the unknown nature of this therapy. A larger question is whether steroids may be useful in treating the inflammation found in severe pancreatitis. We have some minimal evidence at this time that anti-inflammatory doses of steroids might (?) be helpful in some patients. At least, the steroids did not overtly hurt the patient, and it got better (either because of or inspite of the steroids).

Although **heparin** therapy used to be the treatment for DIC (which can probably make acute pancreatitis worse), it has not been shown to be useful. If DIC appears to be a major
problem, aggressive administration of fresh frozen plasma to replace clotting factors and anti-thrombin III concentrations is probably more effective.

**Analgesics** can be very useful. One must remember that dogs are clearly much “tougher” than people, and they often hide their pain well. Unless there is some good reason to the contrary, it is best to routinely assume that dogs with acute pancreatitis are in pain and will benefit from analgesic. In mild cases, butorphanol is sufficient. In moderate cases, methadone is reasonable. As the pain becomes more severe, we progress to constant rate infusions of fentanyl. In the most severe cases, we administer a constant rate infusion of fentanyl, lidocaine and ketamine.
Hematemesis necessitates a slightly different approach than we take with other vomiting cases because some rule-outs become more likely while others become much less likely. We will be including upper gastrointestinal bleeding of any cause in this discussion. For starters, we will not be discussing vomiting that produces “flecks” of blood because this can be seen in any dog (and perhaps cat) with vigorous vomiting in which the gastric mucosa is traumatized by the physical act of vomiting. It is easy to identify fresh blood in the vomited material as long as the patient is not eating something that is red or that produces a pink color to the vomited material simple secondary to pigment leaching out of the food material. Most of the time, hematemesis is denoted by a “coffee-grounds”-like material that most clients (and some veterinarians) do not recognize as blood. A common mistake is being concerned over “dark stools”. Noting that a patient has dark stools is generally useless. Lots of dogs have dark stools and no problems or GI blood loss at all. The color of the stool is not an issue until the stool is pitch-tar-coal-asphalt black. Then it may be melena (if it is not due to Bismuth or a lot of green bile giving it a near-black appearance). If in doubt, just place some fresh feces on absorbent white paper and see if a reddish color diffuses out from the feces, confirming that there is blood present. Melena is only seen if there is acute loss of a lot of blood into the upper GI tract. Most dogs losing blood in the upper GI tract do not have any important changes in the color of the feces. Rather, you might see anemia and hypoalbuminemia. Also remember, you may or may not see hypoglobulinemia; it all depends upon what the serum globulin concentration was before you started losing blood. Sometimes the BUN is higher than expected based upon the serum creatinine, but again this is only expected if there is a lot of blood being lost in a short period of time. Fecal occult blood tests are seldom that helpful or necessary, but can occasionally be informative in confusing cases. However, you need to use a test for which the laboratory has substantial experience in dogs so that the results can be meaningfully interpreted. Some fecal blood tests will routinely give a positive reaction when used on canine feces.

When there is a substantial amount of blood being ejected from the mouth, there tend to be 3 major reasons: coagulopathy, swallowing blood from elsewhere and gastrointestinal ulceration/erosion (GUE).

**ULCERS AND EROSIONS:**

*Drugs* are still a very important cause of GUE in the dog, despite all the newer, “safe”
NSAIDs. High doses of dexamethasone also have substantial potential for significant GUE. Prednisolone by itself is generally not ulcerogenic unless it is used in very high doses (e.g., > 2-3 mg/lb/day) or is administered to a patient with other “ulcerogenic” risk factors (e.g., hypoxia, poor perfusion), and even then it is not particularly bad. Combining steroids and non-steroidal drugs can be devastating. You can use ultra-low dose aspirin (0.5 mg/kg once daily) when treating IMHA dogs with steroids.

There continues to be a substantial problem with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in dogs. All NSAIDs have the potential to cause devastating GUE, and some of these non-steroidal drugs are renowned for their toxic effects (i.e., indomethacin, naproxen, flunixin). Ibuprofen is also particularly ulcerogenic in the dog because it undergoes an enterohepatic circulation. Flunixin is a particularly dangerous drug from the standpoint of causing GUE. It is extremely potent and can be devastating if combined with steroids like dexamethasone. While able to cause significant ulceration and bleeding all by themselves, the ulcerogenic potential of NSAIDs is particularly augmented by other factors, especially concurrent administration of another NSAID or a corticosteroid, and hypoperfusion of the alimentary tract. Even though many dogs seemingly tolerate such combination therapy, you need to realize that you are “walking on thin ice” (see comments above on use of ultra-low dose aspirin). Many to most of the dogs treated with NSAIDs have endoscopically visible erosions, hemorrhages and/or ulcers, depending upon the drug used and the dose administered. It is important to note that most dogs with GUE due to NSAIDs may be completely asymptomatic. Finally, there is tremendous between-dog variation regarding the alimentary tract response to NSAID’s; some dogs may almost bleed to death because of a small dose of aspirin while most dogs would tolerate a much larger dose with relative impunity.

While the newer Cox-2 NSAIDs (e.g., carprofen, etogesic, deracoxib, meloxicam, etc) have much less potential for causing GUE than the older NSAIDs, you can still see GUE (and even perforation) due to these drugs. Part of the problem is that these “safe” drugs are being used so extensively and casually. The problem often revolves around using inappropriately high doses (after all, the drug is so safe that ...), using the drug at the wrong time (e.g., when the patient is experiencing shock or has poor perfusion to the alimentary tract), and possible using the drug too soon after stopping some other NSAID. The concept of a “washout” period when changing from one NSAID to another is extremely controversial. There is published literature to the contrary, but the fact is that nobody really knows at this time.

**CLINICAL APPROACH TO THE PATIENT WITH HEMATEMESIS OR GI BLEEDING:**

There is often something in the history that is suggestive of the cause of the bleeding
(e.g., use of NSAIDs, shock, etc). If that is the case, then it is often reasonable to begin appropriate therapy after requesting basic laboratory testing (e.g., CBC, serum chemistry panel) to determine the severity of the bleeding and if there are other diseases (e.g., hepatic disease, renal disease) present. Imaging (especially ultrasound) is typically appropriate but not necessarily imperative at this time. If the cause of the GI bleeding or hematemesis is not obvious, if the patient has not responded to 5-7 days of appropriate therapy, or if the bleeding is severe, then additional diagnostics are important and should be performed promptly.

Medical management: If the patient is not exsanguinating, the cause is known or strongly suspected, and the patient has not had 5-7 days of appropriate medical therapy, then medical therapy is often reasonable as opposed to doing a major diagnostic work up. In distinction, if the patient is exsanguinating or if the patient has not shown any appreciable response to 5-7 days of appropriate medical therapy for the ulceration, then it is usually reasonable to surgically resect the ulcerated area. Note – when I say “response”, I am not referring to the patient being cured; I am referring to clear evidence of improvement. If surgery will be considered, it is usually very wise to perform gastroduodenoscopy before the surgery to be sure that you find all of the sites of ulceration. It is very easy to fail to detect an ulcer at surgery, and endoscopy usually allows one to easily find all areas of ulceration. Sometimes intraoperative endoscopy is necessary to help the surgeon find the ulcer(s).

If medical management is elected, first be sure to remove the cause of the GUE. If the cause is not removed, medical management tends to be far less successful. Next, be sure that the patient is well hydrated; healing of the gut requires or is at least benefitted by adequate perfusion. If there is significant gastroduodenal reflux of bile, metoclopramide or cisapride may be helpful in preventing bile from entering and/or staying in the stomach and augmenting the ulcerogenic process.

H-2 receptor antagonists are commonly used. Cimetidine, ranitidine, and famotidine are good medications for decreasing the gastric hydrogen ion concentration. Cimetidine (5-10 mg/kg) needs to be given 3-4 times per day if you are really serious about decreasing gastric acid secretion. However, famotidine (0.5 mg/kg) only needs to be given once or twice daily. In most patients, cimetidine is more than adequate to allow healing of gastric ulcers. However, the over the counter (OTC) preparations are all oral and some patients are vomiting so vigorously that they must receive parenteral medication. Ranitidine (2.2 mg/kg) is usually effective if given twice daily, but may cause vomiting if given as an IV bolus. There is some evidence that ranitidine is not particularly effective in decreasing gastric acid secretion, but that is not certain at this time. Side-effects of the H-2 receptor antagonists are rare but may include diarrhea, drug
eruption, hyperpyrexia, thrombocytopenia, granulocytopenia, and CNS problems including seizures. I think (?) I have seen a couple of dogs in which ranitidine was responsible for large bowel diarrhea or seizures. The primary value of the H-2 receptor antagonists is in treating existing ulcers and erosions. They can be helpful in preventing some types of ulcers, but this is not true with all types of ulcers (e.g., they are not effective in preventing ulcers due to NSAIDs or due to steroids).

Proton pump inhibitors are the most effective antacid drugs we have. Omeprazole, lansoprazole and pantoprazole are the most effective inhibitors of gastric acid secretion we currently have available. Omeprazole is available OTC as Prilosec®. The H-2 receptor antagonists seem quite adequate for GUE except in some animals with gastrinomas and those with esophagitis due to gastroesophageal reflux: these seem to be the main reason for using the PPI’s. The dose of omeprazole is 0.7-1.5 mg/kg qd, although I have often used it at up to 2 mg/kg bid in patients with severe reflux esophagitis or gastrinomas. The dose of lansoprazole (Previcid), pantoprazole (Protonix), and esomeprazole (Nexium) is 1 mg/kg IV (not approved for use in dogs). It generally takes 2-5 days for a PPI to have maximal efficacy; but, the immediate effects on gastric acid secretion is often still better than that obtained by high dose H-2 receptor blockade. Very rarely, an H-2 receptor antagonist will work better than omeprazole; be prepared to experiment in your difficult cases

Misoprostol (Cytotec®) is a prostaglandin E analog which was primarily designed to be a prophylactic drug used to prevent GUE due to NSAIDs. It is also useful in treating existing ulcers, but its higher cost and more plentiful side effects usually make it undesirable as a first line therapy for GUE. It is typically used at a dose of 2-5 ug/kg, 3-4 times daily. It can cause abdominal cramping and diarrhea, but the drug seems relatively safe in dogs. The main disadvantage is that it must be given orally, which is not possible in some vomiting animals. Because it is a prostaglandin analog, it should not be used in pregnant females for fear of causing abortion or miscarriage. It is the best drug available that can be used to prevent NSAID-induced ulceration, but it is not uniformly effective in dogs. The main indications to use it appear to be a) the patient that must have NSAID’s to function, but which evidences side-effects from them (e.g., anorexia, vomiting) and b) the patient that seemingly needs to receive NSAID’s that have substantial potential for such side-effects (e.g., piroxicam).

Sucralfate seems to be extremely effective in protecting those areas which are already ulcerated and helping them heal. The only common side-effect is constipation. There is minimal absorption from the intestines, but it does have the capacity for adsorbing other drugs (e.g., enrofloxacin). While carafate is effective in treating ulcers, it is not always effective in
preventing ulceration. In patients with severe hematemesis and anemia, we sometimes use a large "loading" dose (e.g., 3-6 grams) initially and then decreasing the dose to 1 gram tid to qid. Nobody knows if the loading dose is beneficial or not. My major problem with this drug is that it must be given orally, which does not always work in vomiting dogs. Sometimes you may dissolve the tablet in water or buy the suspension and have less problem with that being vomited.
Acquired esophageal weakness is usually (but not always) easy to distinguish from obstruction radiographically, especially when a barium contrast radiograph is performed. However, the severity of the radiographic lesion (i.e., the degree of dilatation) does not always correlate well with the clinical severity. Acquired esophageal weakness is typically difficult to resolve because it is hard to find the underlying cause. Myopathy, neuropathy, myasthenia gravis, dermatomyositis, dysautonomia, esophagitis, Addison's disease, *Spirocerca lupi*, tick paralysis, central nervous system disease, or infiltrative non-obstructive esophageal tumors are possible causes. Generalized myopathies and neuropathies often affect the esophagus because it is composed of striated muscle in the dog. Signs of lower motor neuron disease in these patients are sometimes seen and can include loss of muscle mass, weakness, an inability to bark, or a change in the quality of the bark. Some clients report that their animal has laryngitis, which may seem likely because these pets typically have repeated respiratory infections due to aspiration pneumonia. Treatment of the myopathy or neuropathy should resolve the problem, but symptomatic therapy for the esophageal dilatation is indicated.

Generalized myasthenia gravis usually presents as weakness during exertion which resolves after resting; however, generalized myasthenia can present in a variety of ways, including apparent lameness or permanent weakness. Electromyography and assay for circulating antibodies to acetylcholine receptors are the most definitive tests. Localized myasthenia in the dog is a syndrome in which the esophagus is the only muscle which is obviously weak. Up to 25-30% of dogs with acquired esophageal weakness have this syndrome. Third degree heart block may also be seen in some patients with megaesophagus due to myasthenia. This is diagnosed in dogs with esophageal weakness by detecting serum antibodies to acetylcholine receptors. The antibodies are relatively stable and require little special handling other than refrigeration. If myasthenia is strongly suspected but the titer is negative, it can be valuable to repeat the titer as they sometimes seroconvert later. You cannot perform an edrophonium response test to diagnose localized myasthenia. Myasthenia gravis will sometimes spontaneously resolve. Treatment for myasthenia gravis that does not spontaneously resolve may include anti-acetylcholinesterase drugs, corticosteroids and/or cytotoxic agents. Azathioprine and mycophenolate seem to be effective drugs for this purpose. In general, we try to avoid steroids as they seem to be associated with more problems. In really
severe cases, we can place a percutaneous gastrostomy tube to support the patient and lessen aspiration while waiting for the drugs to have an effect. However, a gastrostomy tube will not prevent all aspiration as the dog is still swallowing saliva which can be regurgitated and aspirated.

Hypoadrenocorticism may be responsible for causing esophageal weakness, even when the serum electrolytes are normal. This is especially true in standard sized, black poodles, but it can occur in any breed. Treatment for hypoadrenocorticism is steroids, which can make the esophagus start functioning again. However, if your diagnosis is wrong and you give steroids because you suspect the dog may have hypoadrenocorticism, all you are doing is making aspiration pneumonia and subsequent death that much more likely.

**Idiopathic megaesophagus** (i.e., either congenital megaesophagus or acquired megaesophagus for which a cause cannot be found) can only be treated with symptomatic therapy, which usually consists of feeding the animal 3-4 meals of gruel from an elevated platform and making the pet remain in the near vertical position from 5-10 minutes after eating. Near-vertical means just that. It is useless for the dog to just lift its head up while eating; it should be standing on its back legs. The Bailey chair is a very useful device. You can find out more about it on the web ([http://www.caninemegaesophagus.org/support.htm](http://www.caninemegaesophagus.org/support.htm)). If necessary, use a portable ladder or put the dog in a large trash can to help it remain vertical during this time. This approach is a time-honored treatment, but it does not always work. Some animals with idiopathic esophageal weakness are controlled as well (or better) if they are fed free-choice dry food from an elevated platform. Some can even be fed from the floor. Free-choice feeding encourages the pet to eat small amounts of food throughout the day, thus avoiding intermittent large meals which are more likely to be retained and further dilate the esophagus. If there is any esophageal motility remaining, the dry food may be easier for the esophagus to propel than gruel. It is difficult to predict which feeding regime will work best for a particular patient, and both of these feeding regimes may need to be tried. While most dogs with idiopathic megaesophagus die from aspiration, there are enough of them that respond well that it is very much worth trying. A reasonable percentage of dogs with idiopathic, congenital megaesophagus will spontaneously improve and have normal or near normal function. You cannot predict response to therapy or spontaneous remission; all you can do is support the patient and see what happens.

Some individuals have tried using cisapride in selected patients with idiopathic esophageal weakness that do not respond well to nutritional modification. Theoretically, cisapride would not be expected to work in these animals because cisapride primarily works on
smooth muscle and canine esophagus is striated muscle. Furthermore, cisapride is expected to tighten up the lower esophageal sphincter, thus making it harder for food to pass out of the esophagus and into the stomach. Perhaps cisapride helps patients when gastroesophageal reflux is part of the problem.

Some owners elect to have a permanent gastrostomy tube placed in the patient. This will not eliminate all regurgitation or aspiration, because the patient is still swallowing saliva which will remain in the esophagus until it is regurgitated. However, gastrostomy tubes will help eliminate most of the regurgitation and can markedly prolong such a patient's quality, comfortable life.

Aspiration pneumonia is a major problem and cause of death in dogs and cats with esophageal weakness causing regurgitation. If the respiratory disease cannot be stopped by alleviating the regurgitation by dietary therapy, then it must be controlled by antibiotics. A transtracheal wash with cytology and culture will help identify optimal antibiotics. Until culture results are known, use of broad-spectrum, bactericidal drugs (i.e., amikacin plus either cephalothin or amoxicillin; enrofloxacin plus amoxicillin or clindamycin) are used. In severe cases of aspiration pneumonia, one may have to bypass the esophagus with a gastrostomy tube to prevent further aspiration. These tubes can be place with the aid of a flexible endoscope and be used for days to months.

**Esophagitis** is much more common than many clinicians are aware. The difficult partly arises from the fact that esophagitis can present with clinical signs that lead one to believe the dog is vomiting instead of regurgitating. Furthermore, mild esophagitis may only cause minor signs (mild regurgitation of mucus and phlegm) while severe esophagitis can cause so much pain that patients refuse to swallow water or even saliva. Because there can be so wide a range of clinical signs, it is easy to forget that esophagitis is a differential for a patient. It is critical to identify that esophagitis is present as delayed diagnosis can have serious clinical repercussions. Substantial inflammation of the esophageal mucosa causes muscular weakness by interrupting the reflex arcs within the esophagus and/or between the esophagus and the brain. However, this weakness is not always reflected by finding megaesophagus. Most patients have very minor esophageal distention and yet can have major signs. Likewise, barium esophagrams can have relatively minor changes and not reflect the severity of the esophagitis. Esophagoscopy typically shows an edematous, reddened, bleeding esophageal mucosa, + structure formation, making it the diagnostic method of choice to find esophagitis. However, in rare cases, there may be more subtle changes with thickening and discoloration (especially at the lower esophageal sphincter of cats).
Adding to this problem is the fact that there is such a wide range of causes of esophagitis. Severe esophagitis may be caused by anesthetic procedures in which animals are placed in dorsal recumbency and then have gastric acid pool in their esophagus for relatively long periods of time. However, gastroesophageal reflux from any cause can be responsible. Hiatal hernias occasionally are responsible for such reflux. Rare animals ingest caustic substances (e.g., lye), and some cats will like caustic disinfectants off their fur. However, a surprisingly large number of animals are administered caustic substances by veterinarians. In particular, tetracyclines, NSAIDs, ciprofloxacin and clindamycin are recognized as having substantial potential to cause esophagitis. Pills and capsules are notorious for lodging in the esophagus of cats, and it is therefore not surprising that doxycycline is a recognized cause of esophageal stricture in cats. Esophagitis may also be secondary to any cause of protracted vomiting. In particular, parvovirus enteritis may cause such intense vomiting that esophagitis results. If a vomiting animal has the character of its vomitus change, which seems to suggest regurgitation, consider the possibility that esophagitis has occurred secondary to the persistent vomiting. Gastrinoma (a tumor which secretes gastrin and results in massive gastric acid secretion) also causes esophagitis because of the vast and unending amounts of acid the esophagus is exposed to as the dog continually vomits. Gastroesophageal reflux may be potentiated by or even caused by esophagitis (which may be caused by reflux in the first place). Thus, there may be a positive feedback loop which can be hard to break (i.e., esophagitis causes more reflux which causes more esophagitis which causes more reflux which causes ...). Rarely there can be spontaneous inflammation, as seen with eosinophilic esophagitis in dogs. Brachycephalic dogs seem to have an increased incidence of gastroesophageal reflux, esophagitis and perhaps hiatal hernia. Finally, esophageal foreign bodies typically cause varying degrees of esophagitis. The esophagus is far more susceptible to pressure necrosis from a foreign body than are the stomach or intestines.

You should seek to prevent further gastroesophageal reflux by keeping the stomach as empty as possible by using prokinetics such as metoclopramide or, preferably, cisapride. Studies in people show that cisapride is clearly more effective than metoclopramide. The only real advantage of metoclopramide is that it can be given by injection; a useful fact in animals that are regurgitating profusely. In addition, gastric acid secretion should be minimized and preferably abolished. H-2 receptor antagonists (e.g., cimetidine, ranitidine, famotidine) suppress gastric acid secretion, but they do not eliminate it. This is because they are competitive inhibitors. That means that there is constantly some degree of competition between the H-2 receptor antagonists and the stimuli for acid secretion. Omeprazole, lanosprazole,
Pantoprazole and esomeprazole are non-competitive inhibitors of gastric acid secretion. Therefore, these drugs can be noticeably more effective and for much longer than the H-2 blockers. You can try to achieve greater efficacy with the H-2 receptor antagonists by doubling or tripling their dose, but the proton pump inhibitors are usually more effective.

Sucralfate is of uncertain value in patients with esophagitis. Unless there is some gastric acid reflux into the esophagus (which you are desperately trying to stop in the first place), it is doubtful that the sucralfate is of much use. If you use it, it should be administered as a slurry.

A combination of omeprazole and cisapride seems to be the most effective medical treatment regime. Antibiotics are used to treat secondary infections, but nobody really knows if they do anything in this regard. Glucocorticoids have been thought to help retard fibrous connective tissue proliferation and cicatrix, but their effectiveness is uncertain (and they might predispose to infection). Placing a PEG tube seems to have some real advantages in patients with very severe disease. First, we will then know that the cisapride and omeprazole tablets will reach the stomach. Second, we will also know that the animal will receive its caloric and protein needs, and hopefully with less irritation to the esophagus than would have occurred otherwise.

If there is severe esophagitis, cicatrix may form and obstruction develop subsequently. Diagnosis of stricture is best accomplished by esophagoscopy IF the operator is familiar with such obstructions. It is surprisingly easy to pass a slender endoscope through a stricture and never recognize the stricture. It is also surprisingly easy to miss a partial obstruction due to a stricture with a barium esophagram. If you suspect a stricture and must use a barium esophagram to make the diagnosis, use barium mixed with solid food. Balloon-dilatation or bouginage is recommended if a stricture has occurred. Many animals need to have 2-6 dilatation procedures (all the while being treated for esophagitis), although some only need one procedure and some need more than 15. Do not try to resect the stricture unless you have had prior dilatation procedures fail.

Cicatrix (i.e., scarring) may occur after an episode of severe esophagitis from any cause (including foreign objects). It is particularly easy to miss this problem on a barium swallow if only liquid barium is used. If radiographs using liquid barium are nonrevealing, repeat the study using barium mixed with food, which is more likely to stop at a partial obstruction. Endoscopy is very good at finding these lesions; however, you must keep in mind the size of the patient as you evaluate the esophageal lumen. A partial stricture will be very obvious in a 10 lb dog or cat but may not be apparent in an 85 lb animal. Balloon-dilatation or bouginage is usually effective; it is also more likely to be successful than surgery and resection of the affected area. In
general, surgical resection should be a last ditch resort and only used if esophageal ballooning or bouginage has failed despite repeated dilatations. However, you must use proper esophageal balloons because Foley catheters and endotracheal tubes with inflatable cuffs will often not allow you to dilate a dense or mature stricture. More difficult cases (i.e., those with extensive strictures or with concurrent severe esophagitis) may benefit from a couple of techniques. Endoscopic administration of intralesional steroids may help minimize reformation of the stricture. Typically we put 1-2 ml of Vetalog at the site of the stricture either before or after ballooning. Another technique is to make 3-4 equidistant cuts into the stricture using an electrocautery device (i.e., either a snare or a knife) prior to ballooning. This helps the stricture to “break” open at multiple spots with the idea that there will be 3 or 4 smaller, less deep lacerations at the stricture site instead of one major, deep laceration which is more likely to restructure. However, you should not attempt to use cautery through an endoscope unless you have some training less you cause too much trauma to the tissues or destroy your endoscopic equipment.

Another technique is to “paint” the site where the stricture was broken down with Mitomycin C (NOT mithromycin C, there is a difference). A 5 mg bottle is reconstituted and soaked up into a gauze sponge. Then this sponge is endoscopically placed on the site where the stricture was broken up for 5 min. Then it is flushed off with 60 ml of water.

Finally, for particularly difficult cases, stents may be placed in the esophagus. These must be sutured in place. The major point to remember is that if an animal starts to have problems days to weeks after anesthesia, consider strongly the possibility that an esophageal stricture has developed secondary to esophagitis. If you are treating an esophageal stricture, remember that you may need to do 1-15 dilatations. If esophagitis is diagnosed, you need to treat it aggressively in order to help prevent the stricture from recurring quickly.

Hiatal hernias may be more common than suspected. Shar Pei’s seem to have a relatively high incidence of hiatal hernias. They can be difficult to diagnose unless you know how to look for them. Sometimes seen on plain radiographs and simple barium contrast radiographs, the more occult cases sometimes need more aggressive diagnostics. Sometimes one must manually put pressure on the abdomen during film exposure to try to push the stomach through the hernia and into the chest so that it can be diagnosed radiographically. Endoscopic diagnosis is not always straightforward. You may need to put the endoscope into the stomach and retroflex it in order to see the abnormality. Even when found, the big question is whether the hiatal hernia is causing a problem or is an “innocent bystander”. In particular, if you have an older dog or cat (i.e., > 1-2 years old) that just started having clinical signs, you
should strongly consider that the hiatal hernia is a fortuitous finding that is not responsible for the clinical signs.