Small Animal Medicine, Module 9

Gastroenterology 1 – The Liver and Pancreas

8th November 2005

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Diagnosis of hepatobiliary diseases – An overview

Underlying pathophysiology

Webster, CRL. History, Clinical Signs, and Physical Findings in Hepatobiliary Disease. In: Ettinger, SJ; Feldman, EC. (Eds.) *Textbook of Veterinary Internal Medicine, Sixth Edition*. St Louis, Mo: Elsevier/Saunders, 2005; 1422-1434.

The liver has many, diverse functions within the body and this is reflected in the many consequences of liver dysfunction. Like the kidneys, the liver has considerable functional reserve, so that significant hepatobiliary disease can exist before signs of dysfunction become evident. Clinical features of early liver disease are non-specific and include polyuria/polydipsia (PU/PD), vomiting, lethargy and inappetence. Findings that are suggestive of more severe hepatobiliary disease include: icterus, hyperammonaemia (leading to hepatic encephalopathy), hypoglycaemia, ascites and haemostatic disorders. Needless to say, there are many other causes of most of these clinical findings.

Pathophysiological 'explanations' of some of the possible clinical features of hepatobiliary disease are offered in concise form below:-

- **Icterus (jaundice)**: decreased uptake, conjugation and/or transport of bilirubin into the bile.
- **Microhepatica**: liver fibrosis or inadequate liver perfusion (as seen in portosystemic vascular anomalies, PSVAs).
- **Hepatomegaly**: infiltration of the liver with glycogen, lipid, amyloid or cells (e.g., inflammatory or neoplastic cells); congestion of the liver (right heart failure).
- **Peritoneal effusion**: hypoalbuminaemia, portal hypertension, right heart failure, excessive renal sodium and water retention, hepatic neoplasia, bile duct or gallbladder rupture.
- **PU/PD:** decreased production of urea by the liver, increased production and decreased hepatic metabolism of cortisol, primary (psychogenic) polydipsia, hypokalaemia, stimulation of thirst due to HE.
- **Pollakiuria/stranguria/dysuria**: ammonium biurate urolithiasis (occasionally seen as a consequence of portosystemic anomalous vascular shunting).
- **Dullness/lethargy/head pressing/decreased level of mentation:** HE, hypoglycaemia, vitamin B1 deficiency.

- **Vomiting/diarrhoea/melaena/inappetence**: gastroduodenal ulceration, steatorrhoea, portal hypertension (its effects upon the intestines), stimulation of the vomiting centre/CRTZ.

> **Case scenario**
>
> A seven year-old female spayed Doberman pinscher is presented to an emergency room in a coma. The owner reports some depression and 'vacancy' over the last several weeks. Faeces are black and tarry on rectal examination. PCV and TPP are both moderately low. There is moderate hypoglycaemia. A buccal mucosal bleeding time is markedly prolonged but the activated clotting time is within the normal range.
>
> Ultimately this dog turns out to be comatose as a consequence of advanced chronic hepatitis and gastrointestinal bleeding. Reflect upon this information and generate some plausible pathophysiological explanations for the clinical observations. Why wasn't the chronic active hepatitis detected earlier?

Signalment

Although many of the clinical features of hepatobiliary disease are non-specific, a consideration of the age, breed and sex of a patient will sometimes alert the clinician to the possibility that liver disease may be present. This is an example of the use of 'probabilistic reasoning'. Below is a list of some breed, age and sex associations in liver disease:-

- **Bedlington terrier**: inherited disorder of hepatic copper metabolism leading to marked copper accumulation in the liver.
- **West Highland white terrier, Skye terrier, Dalmatian, Siamese cat (plus, perhaps, many others)**: less well-defined copper-associated hepatopathies in which copper accumulation is probably not the primary factor.
- **Doberman pinscher (especially middle-aged females), English** and **American cocker spaniels (especially young males), Standard poodle, Labrador retriever**: chronic, idiopathic hepatitis.
- **Persian and Himalayan cats (often less than two years of age)**: portosystemic vascular anomalies.
- **Yorkshire terrier, Maltese, Dandie Dinmont terrier, Pug, Miniature schnauzer (often less than two years of age)**: extrahepatic portosystemic vascular anomalies.
- **Australian cattle dog, old English sheepdog, Irish wolfhound, Golden and Labrador retrievers (often less than two years of age):** intrahepatic portosystemic vascular anomalies.

- **Cairn terriers and many of the other breeds prone to PSS:** microvascular dysplasia.
- **Chinese Shar Pei; Abyssinian, Siamese and Oriental cats:** hepatic amyloidosis.

Tobias KM, Rohrbach BW. Association of breed with the diagnosis of congenital portosystemic shunts in dogs: 2,400 cases (1980-2002). J Am Vet Med Assoc. 2003; 223(11):1636-9.

Hoskins, JD. Liver disease in the geriatric patient. *Veterinary Clinics of North America. Small Animal Practice* 2005; 35: 617-634.

History

In addition to some of the features mentioned above under 'Pathophysiology', historical findings suggestive of hepatobiliary disease include:

- Stunted growth;
- Previous cystotomy for ammonium biurate urolithiasis (suggests PSS);
- Recent treatment with a potentially hepatotoxic drug;
- Anaesthetic intolerance;
- Drug intolerance;
- Recent, marked weight loss and anorexia in a previously obese cat (often after stress; suggests hepatic lipidosis).

Physical Examination

In addition to some of the features mentioned above, under 'Pathophysiology', poor body condition score is a physical examination finding found in many, but not all, patients with significant hepatobiliary disease. It is easier to palpate hepatomegaly (especially in cats) than it is to appreciate microhepatica. Discrete liver masses are often quite easily palpated, unless they are located dorsally (such as in the caudate lobe).

Hepatic encephalopathy (HE) arises as a consequence of the liver's failure to degrade various substances that enter the circulation from the intestinal lumen and act as inhibitory neurotransmitters. Usually, HE manifests with non-specific cerebral signs. The clinician may notice the patient showing dullness and 'staring into space' during the physical examination. In more severe cases, there may be head pressing, stupor, or even coma.

Stewart, CA; Cerhan, J. **Hepatic encephalopathy: a dynamic or static condition.** *Metabolic Brain Disease* 2005; 20: 193-204.

A rare dermatological finding in some patients with chronic hepatobiliary disease is termed 'hepatocutaneous syndrome' or superficial, necrolytic dermatitis. This condition is associated with a crusting, ulcerative dermatitis on the face and distal extremities. It is also observed occasionally in dogs with glucagon-secreting pancreatic tumours.

March PA, Hillier A, Weisbrode SE, Mattoon JS, Johnson SE, DiBartola SP, Brofman PJ. **Superficial necrolytic dermatitis in 11 dogs with a history of phenobarbital administration (1995-2002).** *J Vet Intern Med.* 2004 Jan-Feb;18(1):65-74.

Laboratory tests

Hall EJ, German AJ. **Laboratory evaluation of hepatic disease.** In: E. Villiers & L. Blackwood (Eds.) BSAVA Manual of Canine and Feline Clinical Pathology, Second Edition. Pp. 184-206.

Haemogram

Haemogram (i.e., complete blood count) findings are relatively non-specific and unhelpful in the diagnosis of most cases of hepatobiliary disease. Patients with liver disease may have anaemia. If the anaemia is regenerative, it is most likely to be a consequence of gastrointestinal bleeding. Non-regenerative anaemia is more frequently encountered in patients with hepatobiliary disease and is usually normocytic and normochromic. In most cases it is thought to be a manifestation of inflammation and iron sequestration, in other words 'anaemia of inflammation' (what used to be called 'anaemia of chronic disease' or 'anaemia of chronic inflammation'). Sometimes microcytic, hypochromic, non-regenerative anaemia is present. This may be a consequence of chronic gastrointestinal blood loss and iron deficiency. Alternatively, when observed in patients with portosystemic vascular anomalies, it may be a consequence of defective iron transportation. Target cells and variably shaped cells (poikilocytes) are sometimes seen in animals with liver disease. These changes are thought to be a consequence of abnormalities in red blood cell plasma membrane lipoproteins.

Serum Biochemistry

Liver enzymes

Serum activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase (γ-GT) are evaluated routinely when screening for the presence of hepatobiliary disease in dogs and cats. Increased activities are sensitive indicators of the presence of hepatobiliary disease but have poor specificity. Diseases outside of the liver and administration of various drugs can lead to elevations in the serum activities of these enzymes.

The magnitude of elevation of ALT and AST correlates reasonably well with the extent of recent damage but does not provide information about functional reserve or prognosis. Indeed, animals that have lost a great deal of liver tissue to fibrosis may have lower enzyme activities than other animals with much greater reserves of liver tissue and a better prognosis.

ALT

Serum ALT elevation is a sensitive indicator of hepatocellular damage (or 'leakage') in dogs and cats. Acute hepatocellular necrosis causes the highest elevations. It is relatively liver-specific, although serum activity may be increased when there is severe muscle disease. It may also increase in situations where the liver is injured or 'responds' to systemic or other extra-hepatic disorders (so-called 'reactive' hepatopathies, for example feline hyperthyroidism). The serum half life of ALT is reportedly several hours to several days and much shorter in cats than in dogs. Therefore small ALT increases are more significant in cats than in dogs (although still not indicative of *primary* hepatopathy).

Although ALT is classically considered a hepatocellular necrosis, 'leakage' enzyme, it also increases (more slowly) in cholestatic disorders. The accumulation of toxic bile salts that accompanies cholestasis damages hepatocytes and causes enzyme leakage. ALT elevations seen in association with hepatic neoplasia may be a reflection of leakage from abnormal tumour cells or tumour-related pressure necrosis.

It is well-known that several drugs can increase serum activities of ALP by enzyme induction, but less widely appreciated that this also seems to happen for ALT. In dogs, phenobarbital and glucocorticoids seem to induce ALT expression. However, the increases are not dramatic unless high, toxic doses of these drugs are used, or an idiosyncratic reaction develops. Potentially

hepatotoxic drugs reported to be able–in some patients–to cause elevation of serum ALT activity include griseofulvin, ketoconazole, sulphonamides, azathioprine, paracetamol, phenobarbital, halothane and many others.

Examples of 'secondary' causes of ALT elevation, in which primary hepatic disease is not present include:

- Primary gastrointestinal disease (intestinal permeability increases, allowing more 'toxins' to reach the liver and cause hepatocyte damage;
- Hyperthyroidism;
- Fatty infiltration of the liver secondary to a variety of endocrine and metabolic disorders;
- Liver tissue hypoxia secondary to anaemia;
- Systemic inflammation; and even
- Severe periodontal disease.

AST

This is another 'leakage' enzyme that, as well as being found in liver, is also found in substantial amounts in the cardiac and skeletal muscles. It is therefore less specific than ALT as a measure of hepatocellular damage. It seems to have few advantages over ALT, although some authors suggest it is a more sensitive indicator of hepatobiliary disease and a more specific marker of *severe* disease. If the AST level is disproportionately high compared with the ALT, muscle disease should be suspected.

Arginase

This is yet another marker of hepatocellular injury that is less prone than ALT and AST to elevations in 'secondary' hepatopathies. Levels of arginase decline to normal during recovery after injury. Persistent elevations, therefore, may have greater negative prognostic significance than do persistent elevations of ALT or AST.

ALP

Alternative abbreviations for alkaline phosphatase (ALP) include AP and SAP. ALP is a membrane-bound liver enzyme found on hepatocyte canalicular membranes and on the luminal surfaces of the cells lining bile canaliculi. It is released into the blood during cholestasis as a result of hepatocyte damage as well as increased synthesis. Elevation of serum ALP is a sensitive

indicator of cholestatic hepatobiliary disease but unfortunately this finding is quite non-specific, particularly in dogs. There are several isoenzymes of ALP produced in the liver, kidneys, bone, intestines and placenta. The most important ones that contribute to serum ALP activity in normal, healthy animals are the bone and liver isoenzymes. The others have short half-lives and do not contribute very much. One exception is that, in pregnant queens near full-term, the placental isoenzyme is a significant contributor to overall serum activity.

Glucocorticoids (including those administered topically to the eye, ear and skin) and anticonvulsant drugs such as phenobarbital induce the synthesis of a second, liver-derived isoenzyme in dogs. Glucocorticoids are particularly effective in this regard, so this drug-induced isoenzyme is often called 'corticosteroid-induced' or 'steroid-induced'. Cats do not produce this second, drug-inducible ALP isoenzyme in response to drug treatment. Another important difference exists between dogs and cats that means that mild-to-moderate elevations of serum ALP in cats are much more significant than in dogs. It concerns differences in the half lives of ALP in the two species. In dogs, the half life of both of the liver-derived forms of ALP is approximately 70 hours. In cats, the half life of the single liver-derived isoenzyme is only six hours. Consequently, an elevation of ALP to ~ 200U/L or more is far more significant in a cat than it would be in a dog.

The different isoenzymes of ALP can be distinguished using laboratory tests (one useful method involves the use of levamisole as a reagent). From the foregoing, it would be tempting to believe that it would be diagnostically useful in many clinical situations to quantitate the serum activities of the different ALP isoenzymes. However, this has not proved to be the case. One reason is that chronic, stressful illnesses (including hepatobiliary diseases) are thought to be able to lead to endogenous glucocorticoid production and induction of the drug-inducible isoenzyme. In many animals with liver disease the total serum ALP activity is comprised of a mixture of drug-inducible isoenzyme and liver isoenzyme.

γ-GT

γ-GT is another marker of cholestatic or biliary disease and another membrane-bound enzyme found in the biliary tree. Serum activity is mostly derived from the liver, although γ-GT is present in many other tissues. (It is also present at high concentrations in colostrum and milk so that serum γ-GT levels can be used in neonatal production animals as a way of judging whether sufficient colostrum has been ingested). Increases in serum activity of γ-GT in patients with cholestasis arise as a consequence of elution of the enzyme from hepatocytes and *de novo* synthesis.

γ-GT is not as widely used for diagnostic purposes by clinicians as is ALP. However, it does have some advantages. Since it is not so prone to drug induction, it is more specific (although less sensitive) for the detection of liver disease in dogs. In cats, γ-GT may be a more sensitive indicator of cholestasis than is ALP. One exception is feline hepatic lipidosis which tends to cause ALP elevation without γ-GT elevation. When ALP and γ-GT are used in combination for the detection of hepatobiliary disease, high specificity can be achieved.

Case scenario

An apparently healthy 14 year-old Beagle is presented for an annual health check. Physical examination reveals no significant abnormalities. Routine blood work and UA reveals an ALT of 312 U/L (ref. 8-60) but no other abnormalities. *What would be your approach?*

Some extrahepatic causes of serum liver enzyme elevation

Cause	ALT	AST	ALP	**γ-GT**
Glucocorticoid overexposure	+	+	+++	+/++
Anticonvulsant therapy	+	+	+/++	+
Feline hyperthyroidism	+		+	
Canine hypothyroidism			+	
Diabetes mellitus			+	
Muscle damage	+	++		
Young growing animal			++	
Late pregnancy (queen)			+/++	
Severe anaemia / hypoxaemia	++	+	-/+	-/+

Albumin / Globulin

Albumin is synthesized in the liver so hypoalbuminaemia can be a manifestation of liver failure. However, the liver has considerable reserve capacity for albumin synthesis. Therefore hypoalbuminaemia is a manifestation of severe, usually chronic liver disease. It is most often seen in patients with portosystemic vascular anomalies or end-stage, chronic liver disease (often associated with cirrhosis). Hypoalbuminaemia associated with severe liver disease may arise as a consequence of failure of hepatic synthesis, but can also be seen because of avid renal sodium and water retention or loss of albumin into a 'third space' body compartment such as a peritoneal effusion. Hypoalbuminaemia is certainly not a specific sign of liver disease. It can also be caused by protein-losing nephropathies and enteropathies, vasculitis, acute blood loss, cutaneous exudative lesions and systemic inflammatory processes. (Serum albumin is a negative acute-phase reactant, decreasing in a variety of inflammatory disorders, in parallel with increasing serum globulin). Concurrent evaluation of serum globulin concentration in hypoalbuminaemic patients may help to

limit the list of differential diagnoses. For example, protein-losing nephropathies typically cause selective hypoalbuminaemia whereas protein-losing enteropathies typically cause panhypoproteinaemia. In severe liver disease, hypoalbuminaemia may be associated with a high, normal or (uncommonly) low serum globulin concentration.

Many non-immunoglobulin globulins are synthesized in liver, so liver failure can lead to hypoglobulinaemia. However, in many hepatic disorders there is an increase in total serum globulin concentration, often as a consequence of both immunoglobulin and non-immunoglobulin contributions. Often, hyperglobulinaemia reflects inflammatory processes going on in the liver and elsewhere in the body. The diseased liver may not be able to filter portal blood properly, so that a degree of systemic inflammation can be a feature of many serious liver diseases. Hyperglobulinaemia is a regular feature of feline infectious peritonitis (FIP), the disease that often affects the liver.

Cholesterol

Serum cholesterol concentrations are frequently abnormal in patients with significant hepatobiliary disease, but measurement of serum cholesterol provides little specific information. Post-hepatic bile duct obstruction (usually expressed as *Extra*hepatic bile duct obstruction, EHBDO) is usually associated with an increase in serum cholesterol. Conversely, dogs and cats with portosystemic vascular anomalies (PSVA), and those with severe, end-stage liver disease, often have low serum cholesterol (about 2/3 of dogs and cats with PSVA are hypocholesterolaemic). Hypocholesterolaemia may be a consequence of decreased hepatic synthesis or increased incorporation into bile acids.

Glucose

The liver plays a central role in carbohydrate metabolism and, through glycogen storage and gluconeogenesis, serves to prevent fasting hypoglycaemia. As was the case for albumin synthesis, the liver has considerable reserve capacity for glucose production. Therefore, it is only in patients with liver failure (*e.g.*, PSVA or end-stage, chronic disease) that failure to synthesize sufficient glucose occurs. About one-third of dogs with PSVA are intermittently hypoglycaemic.

Another cause of hypoglycaemia that is occasionally encountered is hepatic neoplasia. Large primary liver tumours, more often encountered in dogs than cats, are frequently associated with severe hypoglycaemia, sufficient to cause clinical signs. If the tumour is difficult to palpate, an

initial, incorrect diagnosis of insulinoma may be made. However, abdominal imaging usually resolves the dilemma without difficulty. These large liver tumours are thought to produce hypoglycaemia by consuming glucose or—more likely, considering the severity and persistence of the hypoglycaemia despite i.v. glucose infusion—by producing insulin-like growth factors that inhibit gluconeogenesis and promote glycogenolysis.

Rarely, a clinician may encounter a glycogen storage disease (or glycogenosis) causing hepatomegaly and hypoglycaemia.

http://www.shilohgtf.com/Glycogen%20Storage%20Disease.htm

Urea

Urea is synthesized by the liver, so liver failure may be accompanied by a low serum urea concentration. This is most likely to be observed in patients with PSVA, occurring in approximately 2/3 of affected dogs and cats. A decreased serum urea is certainly not specific for liver disease. Low protein food, fasting, anorexia, intravenous fluid therapy and other causes of high renal tubular flow rates (via renal medullary washout) can all cause a relatively low serum urea concentration. Conversely, high protein food, gastrointestinal bleeding, dehydration and renal failure can all lead to serum urea elevation. Since severe liver disease can sometimes lead to gastrointestinal bleeding, it is possible for a patient with primary liver disease to have a high, rather than low, serum urea concentration.

Bilirubin

Bilirubin, a yellow-brown pigment, is a product of haemoglobin metabolism by the mononuclear phagocyte system (MPS). MPS cells are responsible for removing senescent red blood cells from the circulation and degrading them. Haemoglobin from senescent red blood cells is metabolized by MPS cells to bilirubin and then released. The bilirubin released by MPS cells is insoluble in plasma and reversibly bound to albumin. It is taken up by hepatocytes and conjugated with glucuronic acid, which renders it soluble in aqueous solution. This conjugated bilirubin is secreted by hepatocytes into the bile, against a concentration gradient. In the intestine, bilirubin is metabolized to colourless urobilinogen and then to brown-pigmented stercobilins. Some of the urobilinogen undergoes enterohepatic cycling and some is filtered by the glomeruli and appears in the urine.

If hyperbilirubinaemia develops and is sufficiently severe and long-lasting, clinically apparent jaundice (icterus) will develop. Icterus is partly due to staining of connective tissues. It is most readily detected in the sclerae and, particularly in cats, in the soft palate. When severe, it can be striking in the gums. Some, but not all, forms of liver disease are associated with icterus. For example, PSVA, glucocorticoid-induced hepatopathy, and metastatic hepatic neoplasia are rarely, if ever, associated with jaundice.

Hyperbilirubinaemia may be pre-hepatic, hepatic or post hepatic. Pre-hepatic hyperbilirubinaemia is due to excessive extravascular haemolysis, for example as a consequence of immune-mediated haemolytic anaemia. The amount of haemolysis taking place must be sufficiently extreme to exceed the considerable capacity of the liver to conjugate and secrete bilirubin into the bile. Patients with pre-hepatic hyperbilirubinaemia are invariably anaemic, and usually have severe or moderately severe anaemia. The anaemia, by causing poor oxygen delivery to hepatic tissues, may contribute to the inability of the liver to conjugate and secrete sufficient bilirubin in patients with pre-hepatic hyperbilirubinaemia.

Hepatic hyperbilirubinaemia is a consequence of impaired uptake, conjugation or secretion of bilirubin into the bile. Disorders that have severe intrahepatic cholestasis as a feature may be accompanied by hepatic hyperbilirubinaemia. An unusual form of hepatic hyperbilirubinaemia is '*cholestasis of inflammation*' or '*cholestasis of sepsis*'. In this condition, circulating inflammatory cytokines prevent hepatocytes from transporting bilirubin into the bile. The hepatocytes are temporarily 'paralysed' by the inflammatory process. Cholestasis of inflammation need not be associated with liver enzyme elevations whereas most other forms of hepatic hyperbilirubinaemia are.

Post hepatic hyperbilirubinaemia is a consequence of post hepatic bile duct obstruction or discontinuity (*e.g.,* traumatic rupture). Bile duct tumours, choleliths, biliary sludge, inspissated pus and external pressure from (for example) pancreatitis or tumours can all cause bile duct obstruction.

It is not usually difficult to distinguish pre-hepatic hyperbilirubinaemia from the other forms. However, it can be difficult to distinguish hepatic hyperbilirubinaemia from the post hepatic form. The most reliable way to distinguish causes of hepatic hyperbilirubinaemia from those causing post hepatic hyperbilirubinaemia is to use abdominal imaging, in particular abdominal ultrasonography. Dilated, tortuous bile ducts and distension of the gallbladder with loss of tapering of the neck of the gallbladder are features of post hepatic bile duct obstruction. Post hepatic hyperbilirubinaemia is

more consistently associated with hypercholesterolaemia than is hepatic hyperbilirubinaemia. However, this is not a reliable way of making the distinction.

The so-called Hijmans van den Bergh's test has been used in the past to distinguish conjugated from unconjugated bilirubin and measure their relative proportions. This test has little diagnostic value for reasons that are reminiscent of those previously described for the various isoenzymes of ALP. One might predict that the circulating bilirubin in patients with pre-hepatic hyperbilirubinaemia would mostly be unconjugated whereas, in patients with post hepatic hyperbilirubinaemia, most would be conjugated. In reality, conjugated and unconjugated forms of bilirubin are found in variable proportions in pre-hepatic, hepatic and post hepatic disorders and making the distinction is not usually helpful. Another important complicating factor that diminishes the value of the van den Bergh's test is the presence of variable amounts of bilirubin *irreversibly* bound to albumin (so-called biliproteins or delta-bilirubin) in some hyperbilirubinaemic patients. This delta-bilirubin, which is measured as direct-reacting, conjugated bilirubin in the van den Bergh's test, persists much longer in the body than do the conventional conjugated and unconjugated forms. Indeed, its half life approximates that of albumin. Thus, hyperbilirubinaemia may persist in some patients long after the underlying disease (e.g. pancreatitis) has resolved.

Urine analysis

Many patients with hepatobiliary disease have PU/PD and therefore a low urine specific gravity.

Some dogs and fewer cats with PSVA have detectable ammonium biurate crystalluria on urine sediment examination. This is a consequence of concurrent hyperuricaemia and hyperammonaemia. It may be necessary to examine several fresh urine samples in order to detect this crystalluria.

It is abnormal for cats to have any bilirubin in their urine because they have a high threshold for its renal excretion. Therefore, any bilirubin in the urine of a cat qualifies as hyperbilirubinuria and is indicative of excessive extravascular haemolysis or hepatobiliary disease. Conversely, it is normal for some dogs (particularly male dogs) to have some conjugated bilirubin in their urine. If a large amount is present (i.e. a strong dipstick reaction), this hyperbilirubinuria has the same significance as discovering any bilirubin in the urine of a cat.

Urobilinogen is a normal finding in the urine of healthy dogs and cats, although it is not invariably detected. An increased amount may be present in the urine of patients with hyperbilirubinaemia. Urobilinogen will be absent from the urine of animals that have pale, 'acholic' faeces as a consequence of complete post hepatic bile duct obstruction.

Serum bile acids

Bile acids are synthesized by hepatocytes, secreted into the bile and stored in the gallbladder. After a meal is ingested, bile is secreted into the intestinal lumen where bile acids aid in the emulsification of dietary fat. Under normal circumstances, >95% of bile acid molecules are reabsorbed from the gut and efficiently extracted from the portal blood by the liver. This highly efficient enterohepatic circulation means that individual bile acid molecules may recycle between liver and intestine many times per day. After digestion of a meal is completed, bile acids are efficiently removed from portal blood and stored in the gallbladder. In patients with PSVA, the enterohepatic circulation is disturbed and SBAs may be markedly elevated, particularly, post-prandial values.

The quantification of pre- and post-prandial serum bile acids (SBAs) for assessment of hepatobiliary function is, by now, quite well-established in small animal practice. Despite this, many questions and uncertainties remain in the minds of clinicians about SBA measurements. The following list of key points is not intended to provide an exhaustive coverage of this large and complicated topic. It is intended to be read in conjunction with a suitable textbook chapter, for example this one:-

Hall EJ, German AJ. **Laboratory evaluation of hepatic disease.** In: E. Villiers & L. Blackwood (Eds.) BSAVA Manual of Canine and Feline Clinical Pathology, Second Edition. Pp. 184-206.

- It is not usually helpful to measure SBAs in patients that are already icteric as a consequence of hepatic disease. Measurement of SBAs can be thought of as a rather 'subtle' diagnostic test that is superfluous when something obvious like icterus is already present.

- Measurement of total SBAs, as currently practiced, does not provide specific information about particular causes of hepatopathy. Although SBA quantitation is often used for diagnosis of PSVA, it is not a specific test for this purpose.

- The severity of disease does not correlate well with the magnitude of elevation of SBAs. SBA values should only be interpreted as 'normal' or 'abnormal'.

- There is some debate about what should be appropriate cut-off values (i.e. upper limit of normal) for use when measuring SBAs in dogs and cats. Some authors recommend cut-off values that are much higher than the original ones that were published. Obviously, the higher the cut-off value, the greater the specificity but the lower the sensitivity of this diagnostic test.

- There is some debate about the relative merits of measuring pre- and post-prandial SBAs. Some authors question whether it is necessary to feed a meal and measure both. You could consult your favourite small animal internal medicine specialist or clinical pathologist to devise a protocol for your practice.

- The effects of haemolysis and lipaemia are important and potentially confusing. If too large a meal is fed to the patient undergoing investigation, it may become lipaemic. Lipaemia, in turn, may cause some haemolysis. Lipaemia and haemolysis can interfere with the measurement of SBAs. The extent of any haemolysis that may be induced by lipaemia is very difficult, or impossible, to predict. For this reason, it is important to standardize and limit the amount of food given to stimulate cholecystokinin release. Some authors recommend 2 tsp of a defined food (for example, Hills canned d/d) be fed to dogs < 5 kg and 2 tbsp of the same food defective dogs over 10 kg. Unfortunately, for some dogs, this amount of food may be insufficient to stimulate gallbladder emptying. Consider devising a suitable test protocol in collaboration with your favourite clinical pathologist and/or small animal internal medicine specialist.

- In Australia, many Maltese dogs have apparently elevated post-prandial total SBA concentrations in the absence of detectable hepatobiliary disease and with normal ammonia tolerance. SBAs were measured using a conventional enzymatic spectrophotometric method. When high-performance liquid chromatography was used instead for SBA quantitation, lower values were obtained, suggesting the presence of interfering substance(s)

Tisdall PL, Hunt GB, Tsoukalas G, Malik R. **Post-prandial serum bile acid concentrations and ammonia tolerance in Maltese dogs with and without hepatic vascular anomalies.** Aust Vet J. 1995 Apr;72(4):121-6.

- Despite these several concerns, measurement of SBAs remains useful, particularly in the diagnosis of PSVA. In the future, measurement of specific acids, rather than *total* SBAs, may prove to be worthwhile and feasible. Measurement of urinary, rather than serum, bile acids has been investigated but has not so far been used widely.

Blood ammonia

Normally, ammonia produced by intestinal bacteria is transported in the portal blood to the liver where it is converted to urea. Animals with PSVA or sufficiently severe parenchymal liver disease may have abnormally high blood ammonia concentrations. Although 80-90% of animals with PSVA and 50% of animals with parenchymal liver disease have high fasting blood ammonia concentrations, use of an ammonia tolerance test (ATT) can increase sensitivity. In a conventional ATT, a 20mg/ml ammonium chloride solution is administered by stomach tube at a dose of 100 mg/kg (up to a maximum of 3g). This is done after a 12 hour fast and after a baseline blood sample has been taken. 30 minutes later, another blood samples taken and both are submitted for ammonia quantitation. This conventional oral ATT may cause vomiting and can worsen encephalopathy. It is not without risk. As a modification, a rectal ATT has been devised. A warm water enema is used to empty the rectum 12 hours before the test. After a baseline blood samples obtained, ammonium chloride solution (50mg/ml) is administered into the rectum, via catheter, at 2 ml/kg body weight. Blood samples are taken a 20 and 40 minutes afterwards. This test is safer, more convenient, less prone to cause vomiting but less sensitive than the oral test. Finally, a modified oral ATT has been described in which food, rather than ammonium chloride solution is used. This test is safe and has good sensitivity for the detection of PSVA but poor sensitivity for detection of parenchymal hepatocellular diseases.

A major limitation of all of these tests that require measurement of blood ammonia is that samples need to be handled very carefully. Blood needs to be drawn into cold heparinized tubes, held on ice and transferred promptly to the laboratory. Dry chemistry methods for detection of ammonia in veterinary practice have, unfortunately, been reported to produce unreliable results.

Coagulation profile

All coagulation factors, except Factor VIII, are synthesized by the liver. The vitamin K-dependent activation of factors II, VII, IX and X also takes place there. The liver synthesizes various fibrinolytic proteins and some important inhibitors of coagulation and fibrinolysis. Patients with liver disease may have mild thrombocytopenia and/or platelet dysfunction. It is therefore difficult to predict precisely what haemostatic consequences severe liver disease may have in a particular patient.

Vitamin K deficiency may arise in hepatobiliary disease because of failure to absorb this fat-soluble vitamin, or failure to store it adequately in the liver. Inadequate dietary intake is a less common cause. Relative or absolute vitamin K deficiency will first cause prolongation of the prothrombin time (PT) and later cause prolongation of the activated partial thromboplastin time (APTT). Another test for detection of vitamin K deficiency involves the detection of circulating, inactive forms of the vitamin K-dependent coagulation factors. These inactive factors are termed *proteins induced by vitamin K absence or antagonism (PIVKA)*. Some authors suggest that measurement of PIVKAs may increase the sensitivity with which we can detect animals with hepatobiliary disease that are likely to bleed at the time of biopsy. However, others are unconvinced of the value of PIVKA quantitation.

For safety's sake, it is certainly recommended to carry out buccal mucosal bleeding time (to assess primary haemostasis) and a coagulation screen (e.g. PT, APTT, platelet count ± FDPs) on patients immediately prior to hepatic biopsy. Given that vitamin K deficiency is relatively common in animals with severe hepatobiliary disease, some clinicians routinely inject a dose of vitamin K1 (*e.g.*, 2.5 mg/kg SC) 24 hours before carrying out a final coagulation screen and, all being well, carrying out biopsy. Unfortunately, bleeding may still occasionally occur despite normal coagulation values and vitamin K pre-treatment. Fresh frozen plasma should therefore be available on hand.

Imaging

Radiography

Plain radiography is excellent for assessing liver size, shape and radio-opacity. Normally, the liver is a homogeneous soft tissue structure present in the cranial abdomen, immediately behind the diaphragm. The stomach is normally immediately behind the liver and, in average-shaped dogs, the

gastric axis is approximately parallel with that of the overlying ribs. The axis is more vertical in deep-chested dogs. Usually there is enough gas in the stomach to allow its axis to be assessed. Diffuse hepatomegaly is associated with caudal displacement of the stomach and some caudodorsal displacement of the pylorus, so that the gastric axis becomes closer to horizontal. The caudal ventral margin of the enlarged liver (in the lateral projection) sometimes appears obviously rounded. Sometimes the shadow of the liver and the spleen merge in the lateral projection, so that it is wise to speak of 'hepatosplenomegaly' rather than, over-confidently assuming the enlargement is definitely liver.

Microhepatica is seen in patients with PSVA and severe, often end-stage liver fibrosis. The liver shadow may literally be a thin 'sliver' in the cranial abdomen. The pylorus of the stomach is displaced cranially and ventrally compared with normal, so that the stomach may be are orientated vertically, or even have the pylorus positioned cranial to the fundus in the lateral projection.

Gallstones (choleliths) and other calcifications and concretions within the biliary tree may appear as radiopaque structures superimposed on the liver shadow. Choleliths are usually seen as discrete, round, mineralized structures in the cranial, right, ventral liver. Other changes in radio-opacity that may be observed include diffuse hepatic mineralization and focal areas of mineralization (due to infection, granuloma formation, neoplasia, or resolving abscesses or haematomas).

PSVA can be diagnosed by contrast imaging of the portal venous system. The best method is termed 'operative mesenteric portography' and involves general anaesthesia, laparotomy and catheterization of a mesenteric jejunal vein. An aqueous iodinated contrast agent is rapidly injected and (preferably) several radiographs are made rapidly afterwards. Alternatively, fluoroscopy can be used.

Ultrasonography

Abdominal ultrasonography can be extremely useful in the investigation of hepatobiliary disorders. For example, it may be crucial in enabling the clinician to distinguish intrahepatic from post hepatic disease. It can be used to assess focal, multinodular or diffuse disease, so is often used to guide clinicians when taking liver biopsies.

Complete post hepatic biliary obstruction is associated with dilatation and tortuousity of bile ducts. The changes become more obvious and extensive as time passes after the obstruction.

Normal liver tissue appears homogeneous under ultrasound examination. The echogenicity of normal liver parenchyma is approximately the same as that of renal cortex. Hypoechoic tubular structures should be visible within the parenchyma; these represent hepatic and portal veins.

Disease processes that typically cause a diffuse increase in hepatic parenchymal echogenicity include: fibrosis, lipidosis, steroid hepatopathy, and various forms of neoplasia. Fibrotic livers will typically be smaller than normal whereas, in steroid hepatopathy, the liver may be normal-sized or large. Having said that, ultrasonography is not as reliable as radiography for determining liver size.

Disease processes that typically cause a diffuse decrease in hepatic parenchymal echogenicity include: suppurative inflammation, passive congestion and some forms of hepatic lymphoma.

Haematomas and abscesses have variable appearance depending upon their maturity. Both tend to begin as hyperechoic structures and mature to become hypoechoic and more clearly marginated.

Primary liver tumours are usually large, solitary and relatively well circumscribed. They typically distort and protrude beyond the normal liver outline. Hepatic lymphoma may appear as diffuse hyper- or hypoechogenicity of the liver parenchyma or as multiple 'targetoid lesions', in each of which there is a central area of hyperechogenicity surrounded by a ring of hypoechogenicity.

In expert hands, abdominal ultrasonography is an accurate way of detecting PSVAs. The liver is usually small with less prominent than normal vascular structures. The kidneys may be large and bladder calculi may be observed (ammonium biurate uroliths). In extrahepatic PSVAs, the abnormal shunting vessel may be directly visualized. This is more easily done if Doppler ultrasound is available, since high velocity turbulent flow may be observed in the abnormal, shunting vessel. The hepatic portal vein, if visualized, may be smaller than usual. Intrahepatic PSVAs can also be detected relatively easily by experts.

Scintigraphy

Per-rectal scintigraphy is used in dogs and cats for the detection of PSVAs. A small amount of radioactive ^{99m}technetium pertechnetate is administered via catheter to the animal's rectum. The animal is positioned over a gamma camera while this is done. From the rectum, the radioactive dye is absorbed rapidly and, in normal animals, appears first in the liver and then in the heart and lungs. In animals with portosystemic shunting, radioactivity is detected in the heart and lungs before or at the same time as it is first detected in the liver. Rectal scintigraphy does not distinguish congenital

from acquired shunts. Animals with microvascular dysplasia or parenchymal liver diseases without acquired shunts have normal scans.

Liver biopsy

The crucial importance of taking precautions to minimize the risk of haemorrhage when obtaining liver biopsies has already been emphasized.

Fine needle aspiration (FNA) of the liver and cytological examination of aspirates will occasionally provide diagnostically useful information (for example, it may yield a specific diagnosis of hepatic carcinoma or lymphoma). Unfortunately FNA agrees with 'proper' hepatic biopsy only in a minority of instances. In fact, it may yield partial information that misleads the clinician. For example, vacuolar hepatopathy (*e.g.*, due to hepatic lipidosis in a cat or steroid hepatopathy in a dog) may be the only finding on FNA when a full biopsy would have revealed further changes (*e.g.*, necrosis, active inflammation, infection; perhaps an underlying cause for the vacuolar changes). Nevertheless, there are some situations in which FNA is the only diagnostic option available to the clinician. It may be possible to increase the accuracy of FNA somewhat by taking several aspirates.

Wang KY, Panciera DL, Al-Rukibat RK, Radi ZA. **Accuracy of ultrasound-guided fine-needle aspiration of the liver and cytologic findings in dogs and cats: 97 cases (1990-2000).** J Am Vet Med Assoc. 2004 Jan 1;224(1):75-8.

Ultrasound-guided needle biopsies or wedge biopsies obtained at laparotomy are the kinds most commonly evaluated. Some practices are equipped to obtain biopsies at laparoscopy. Unfortunately, tiny needle biopsies obtained under ultrasound guidance do not provide results that correlate particularly well with those provided by much larger wedge biopsies. It is therefore particularly important, when taking or requesting ultrasound-guided needle biopsies, to obtain adequate tissue. Three pieces of liver tissue that more-or-less fill the cavity in a 16G or larger biopsy needle are needed. The use of 14G biopsy needles may increase diagnostic accuracy, but also increase the risk of haemorrhage. Alternatively, if laparoscopy is unavailable, a wedge biopsy can be obtained at laparotomy. Although this is more invasive and expensive, it allows collection of a larger amount of tissue and proper attention to haemostasis.

Cole TL, Center SA, *et al.* **Diagnostic comparison of needle and wedge biopsy specimens of the liver in dogs and cats.** *Journal of the American Veterinary Medical Association* 2002; 220: 1483-1490.

If an adequate biopsy is submitted for histopathological examination by an expert, it should be possible to establish the following:

- the category of disease process that is present (*e.g.*, neoplastic, vascular, vacuolar);
- the degree of severity of that disease process (*e.g.*, mild, moderate or severe);
- the degree of chronicity (*e.g.*, peracute, acute, chronic).

Unfortunately, even when a substantial piece of liver tissue is obtained and submitted for histopathological examination, pathologists may disagree about the diagnosis. In situations where the histopathological diagnosis does not fit well with the entire clinical picture, the clinician has ultimate responsibility to decide whether or not it is necessary to seek the opinion of a second, or a subsequent pathologist.

Collection and submission of liver biopsies for aerobic and anaerobic bacterial culture, rather than just for histopathological examination, is sometimes appropriate.

Treatment of hepatobiliary diseases – An overview

Surprisingly few studies have been done to evaluate the efficacy (or otherwise) of drugs used to treat hepatobiliary disease in dogs and cats. It would be ideal if randomized, double-blind placebo-controlled clinical trials formed the basis of many of our treatment choices. In reality, no such trials have been done and most of our clinical decisions are based upon small, non-randomized retrospective studies or extrapolations from human medicine based upon a reasonable understanding of underlying pathophysiology.

An international group of veterinary hepatologists is now in the process of standardizing nomenclature as a prerequisite for commencing multi-centre collaborative studies. It is to be hoped that, in the coming years, high-quality scientific studies will be carried out and published as peer-reviewed scientific articles, to allow a much more rational approach to therapy of hepatobiliary diseases, one based on high-quality evidence. However, that is for the future. Much of what follows is based upon rather flimsy evidence, but represents a summary of current practices.

Glucocorticoids

It is generally accepted that glucocorticoids have a strong, beneficial effect when used to treat many *chronic*, idiopathic hepatitides–especially in dogs–that are characterized in part by the presence of mononuclear and lymphocytic inflammatory infiltrates. In a published retrospective study, treated animals went into complete remission, did not relapse, and survived much longer than untreated animals. The clinical experience of numerous veterinarians further supports the use of glucocorticoids for treatment of chronic, idiopathic hepatitides (*e.g.,* prednisolone, 1-2 mg/kg SID initially, then decreased to EOD and tapered gradually while monitoring for relapse).

The apparent efficacy of glucocorticoids and the observed inflammatory cell infiltrates are consistent with the possibility that immune (perhaps autoimmune) pathomechanisms are operational in some animals with chronic, idiopathic hepatitis. It has been conjectured that an acute insult (*e.g.,* infection by a presently uncharacterized infectious agent) and consequent hepatic tissue damage may lead to exposure of autoantigens and subsequent autoimmune attack upon the liver. During the chronic phase of liver disease, the infectious agent may be long gone (*i.e.,* a hit-and-run disease mechanism may be operational).

Glucocorticoids should probably not be used to treat *acute* idiopathic hepatitides, since some affected animals may have as yet uncharacterized infections. Glucocorticoids are contraindicated in many infectious diseases and irrelevant in others. Supportive care is usually sufficient for management of acute, idiopathic hepatitides.

Although glucocorticoids have some anti-fibrotic and choleretic (*i.e.,* bile flow stimulating) effects, it has been suggested that there are other drugs that are more potent, if these effects are needed or desired.

Azathioprine

This immunosuppressant drug (1-2 mg/kg SID to EOD) may also be used for chronic, idiopathic hepatitis. It has the advantage that it does not cause many of the adverse effects of glucocorticoids (*e.g.,* PU/PD, panting, ravenous hunger, steroid hepatopathy). However, it can sometimes cause myelosuppression. It may be used in combination with prednisolone in dogs to allow the dose of glucocorticoid to be decreased somewhat. It is not recommended for use in cats, since it can cause more severe adverse effects in this species. Melphalan could perhaps be used instead.

Ursodiol (Ursodeoxycholic acid)

This hydrophilic bile acid is choleretic, i.e. it stimulates increased bile flow. It is administered orally (15 mg/kg PO SID or divided BID) and is recommended for use in patients that have chronic intrahepatic cholestasis *without* bile duct obstruction. Ursodeoxycholic acid, being hydrophilic, is a relatively harmless bile acid and is thought to displace more pathogenic, hydrophobic bile acids from the recirculating pool. Removal of hydrophobic bile acids from the recirculating pool is thought to diminish the 'detergent-like' action of hydrophobic bile acid excess that causes hepatocyte membrane injuries, oxidative damage and induction of apoptosis in hepatocytes.

Ursodiol is also used for many other forms of feline and canine liver disease, although it has not been proven to be effective in any of them. It has immunomodulating effects and increases the hepatic production of glutathione and metallothionein. It may thus serve as an antioxidant.

Lathyrogenic (anti-fibrotic) drugs

Probably the most effective way to slow the progression of liver fibrosis is to attack the underlying process (usually inflammatory) that is leading to the fibrosis. Thus, glucocorticoids and azathioprine may have anti-fibrotic effects in some patients. Colchicine (0.025-0.03 mg/kg/day;

benefit unproven) is a drug advocated for the purpose of diminishing hepatic fibrosis. It is thought to stimulate collagenase activity. Unfortunately, it has a reputation for causing nausea, vomiting and diarrhoea in dogs although the true extent of this problem is unknown. In humans, it can be very toxic and small, single overdoses have led to deaths. There is insufficient evidence that colchicine truly has an anti-fibrotic effect . Some authorities suggest that colchicine should not be used until evidence to support its use is published.

Drugs to combat copper accumulation and its effects

Various drugs have been used for the treatment of hepatopathies associated with copper accumulation. The best characterized of these copper-accumulation hepatopathies is the one found in Bedlington terriers. This is reported to be an autosomal recessive disorder that leads to the progressive accumulation of copper in the liver and eventually to liver damage. It was once believed that this Bedlington disorder was a perfect model for human Wilson's disease, but this has been disproven. Affected dogs accumulate copper in their livers gradually over time. Liver copper content may gradually rise to be as high as 12,000 ppm dry weight in affected Bedlington terriers. There is a progressive increase in copper accumulation until 8 years of age. An acute haemolytic crisis sometimes develops in affected dogs, as a consequence of copper release from the damaged liver.

Fuentealba IC, Aburto EM. **Animal models of copper-associated liver disease.** Comparative Hepatology 2003; 2(1):5.

This article is available for free from:
http://www.comparative-hepatology.com/content/2/1/5

Copper-accumulation hepatopathies are also seen in other breeds (*e.g.,* West Highland white terrier, Skye terrier, Dalmatian, Doberman pinscher, Turkish shepherd dog). In some of these, copper accumulation is thought to be a primary event and in others it is secondary to chronic cholestasis or other metabolic defects within the liver.

D-Penicillamine

D-Penicillamine is an orally administered chelating agent that binds copper and some other heavy metals. It is dosed at 10-15mg/kg PO BID and given 30 minutes before feeding or, if nausea develops, at the time of meals. It is the best characterised copper chelating drug and is still widely used and recommended. It must be given for several months to have any beneficial effects. It is capable of removing copper, gradually, from the liver. It does this by binding extracellular copper,

which is subsequently excreted in the urine. Free, intracellular copper then moves out of cells to equilibrate and gradually excess copper is cleared from hepatocytes.

2,2,2 tetramine tetrahydrochloride (Trientene)

This is an alternative copper chelating agent that is sufficiently potent that it may eventually cause copper depletion. It is dosed at 10-15 mg/kg BID, with meals. It may cause nausea and vomiting if given on an empty stomach.

Zinc gluconate or Zinc acetate

Zinc (10mg elemental zinc/kg BID, one hour before feeding) induces the expression of metallothionein in intestinal epithelial cells. This induced protein binds dietary copper and the complex is excreted (in sloughed enterocytes) in the faeces. Zinc can be thought of as a way of preventing further copper accumulation. In most animals with pre-existing copper accumulation, it is appropriate to treat with a chelator for about three months and then switch to the use of zinc. Chelators and zinc should not be used at the same time, since the chelator will bind to the zinc and render both drugs ineffective.

Other drugs

Free cytosolic copper induces oxidative damage in the hepatocyte, particularly to the mitochondria. Therefore, antioxidant medications may have a place in the management of some patients with copper accumulation hepatopathy. This is particularly true if a haemolytic crisis develops. Antioxidant medications are described in the next section.

Antioxidant drugs

Oxygen free radicals and so-called oxidative stress play an important role in initiation and perpetuation of many hepatobiliary diseases. For example, free copper within the cytosol of hepatocytes can lead to the production of free radicals and oxidative damage. The hepatotoxicities of paracetamol and Death Cap mushrooms (*Amanita phalloides*) centre upon oxidative damage. Free radicals are generated within hepatocyte mitochondria. Since hepatocyte mitochondrial membranes are damaged by elevated bile acid concentrations in many cholestatic disorders, cholestasis can lead to hepatic injury, in part, by causing oxidative damage. Activated macrophages also produce free radicals, so many inflammatory hepatic disorders are associated with oxidative damage.

The body has defence mechanisms against oxidative stress, including superoxide dismutase (SOD) and glutathione (GSH) peroxidase. These defences, however, may be overwhelmed in the face of severe oxidative challenge. Antioxidant therapy has been proved to be beneficial in paracetamol and Death Cap mushroom poisoning. It is very likely to be helpful in Bedlington terriers with haemolytic crisis. In many other hepatic disease situations, antioxidant therapy is a little more speculative, but may provide benefit.

Silymarin (extract of Milk thistle, Silybum marianum*)*

Silymarin is a collective term for a number of active compounds found in the milk thistle plant. Milk thistle has been used for centuries as a treatment for hepatobiliary disorders. Silymarin has been shown to be a potent free radical scavenger and it increases hepatocyte SOD levels. Several studies have shown that it has potent, sometimes life-saving effects when used in patients poisoned by Death Cap mushrooms or paracetamol. How long after such intoxications silymarin can be given, and still exert a life-saving effect, is uncertain. Silymarin may also have a useful role in treatment of copper accumulation hepatopathy although no studies have been done to demonstrate added benefit on top of chelator therapy. The potency of silymarin has not been directly compared with that of other antioxidants drugs such as the ones that follow immediately.

Vitaglione P, Morisco F, Caporaso N, Fogliano V. **Dietary antioxidant compounds and liver health.** Critical Reviews in Food Science and Nutrition 2004;44(7-8):575-86.

s-Adenosyl-L-methionine (SAMe)

SAMe is present in normal hepatocytes, being a precursor of cysteine, which in turn is a precursor of the tripeptide glutathione (GSH). GSH is very important in combating oxidative stress. GSH may be depleted in the face of overwhelming oxidative challenge. If SAMe production were compromised in the damaged liver, inadequate production of GSH might be a consequence. Therefore, administration of exogenous SAMe may help to restore GSH production and combat oxidative damage. One study has shown that in 45% of dogs and cats with liver disease GSH levels were sub normal. However, the efficacy of SAMe not been directly demonstrated in dogs and cats with liver disease.

Others

As well as its copper-reducing properties, zinc has antioxidant properties. For this purpose, lower doses are recommended (2-3 mg/kg/day elemental zinc). Ursodiol also seems to protect hepatocytes from oxidative injury by increasing hepatocyte levels of GSH and metallothionein. Vitamins E and C are well-known dietary antioxidants, although at high concentrations vitamin C can be pro-oxidant. Alpha-tocopherol (vitamin E; 15IU/kg/day) is a lipid-soluble, dietary constituent that is absorbed from the gastrointestinal tract and found membrane-bound in hepatocytes. It can protect against membrane peroxidation. Ascorbic acid (vitamin C) is a water-soluble antioxidant. It can reactivate oxidised vitamin E. Unlike humans, dogs and cats can synthesise their own vitamins C and E. There is no evidence that levels are deficient in canine and feline hepatobiliary diseases.

Medical management of hepatic encephalopathy (HE)

Rational management of HE is based upon an understanding of the underlying pathophysiology. Here is an article written fairly recently (2001) concerning HE in humans and available for free via the Web. The underlying pathophysiology in humans and animals is quite similar:-

http://www.postgradmed.com/issues/2001/02_01/assi.htm

If the underlying cause of HE can be resolved (for example, by surgical management of a PSVA) this is the most effective way of dealing with the problem. Temporary medical management is often necessary, even if surgical management is being planned. Since the source of ammonia and other compounds that cause HE is the gastrointestinal tract, many of the therapeutic interventions focus on changing the environment within the intestines.

A special diet with reduced total protein content and more substantial reduction of aromatic amino acids should be used. Sources of gastrointestinal haemorrhage (*e.g.,* parasites, ulcers) should be treated or removed, if possible. **Lactulose** (5-30ml PO TID until the stools are slightly soft), a synthetic disaccharide, should be given. This osmotic laxative will hasten gastrointestinal emptying, allowing less time for absorption of ammonia produced in the colon by intestinal bacteria. More importantly, fermentation of lactulose lowers intestinal pH, trapping ammonia (as ammonium ions) in the colonic contents, and changing the colonic bacterial flora favourably. An

antibiotic that is not absorbed from the intestinal tract and is active against urea-splitting bacteria (*e.g.*, neomycin) is also useful in some patients.

The use of benzodiazepine drugs is generally to be avoided in patients with HE, since endogenous benzodiazepine-like substances contribute to the pathogenesis of HE. HE is worsened by hypokalaemia, so attention should be paid to avoiding this electrolyte abnormality. Alkalosis is also to be avoided, because it can increase the likelihood of hypokalaemia developing (because potassium ions move intracellularly to replace hydrogen ions when these exit cells in response to alkalaemia).

Selected hepatobiliary conditions – key points

Inflammatory / infectious hepatobiliary diseases

Canine chronic hepatitis

- Strictly, ≥6 months' duration with hepatocellular necrosis and a predominantly lymphoplasmacytic inflammatory infiltrate. Typically progresses to fibrosis and cirrhosis. The cause may be evident (*e.g.,* primary copper accumulation), but most are idiopathic. Typically associated with persistent elevation of serum ALT and ALP until very advanced disease leads to decreasing enzyme levels. ALT is usually more impressively elevated than ALP (versus steroid hepatopathy). In severe, advanced cases icterus may be present.

- Female Doberman pinschers and male cocker spaniels are at increased risk. Other breeds reported to be overrepresented include Bedlington terriers, West Highland white terriers, Dalmatians, Skye terriers, standard poodles, Labrador retrievers, German shepherd dogs, Scottish terriers, and beagles. In some of these breeds, primary copper accumulation is likely to be the underlying cause.

- Typical clinical signs in advanced cases include lethargy, depression, inappetence, weight loss, PU/PD and vomiting. Disease may be detected before the signs become evident if a serum biochemistry profile is assessed for some reason.

- Definitive diagnosis requires a liver biopsy. Lymphoplasmacytic inflammation and piecemeal necrosis are essential features. Fibrosis is a feature of advanced disease. Bridging fibrosis[*] and nodular regeneration (i.e. cirrhosis) indicate very severe, advanced disease. Copper accumulation and vacuolar hepatopathy may be present.

- Treatment usually consists of glucocorticoids (± azathioprine), antioxidants and ursodiol. H-2 receptor blockers may be appropriate to help reduce gastrointestinal ulceration in some patients. If copper accumulation is severe enough, chelation therapy and or zinc therapy are indicated. Specific anti-fibrotic therapy (*i.e.,* colchicine) is suggested by some authors and considered contraindicated by others. Many of the other drugs mentioned above have anti-fibrotic activity.

[*] there are bridges of fibrous tissue extending between liver lobules. Bridging fibrosis may cause permanent distortion of the liver's architecture and be associated with regenerative nodules. This is called *cirrhosis*.

Doberman pinscher chronic hepatitis

Middle-aged, female Doberman pinschers are at increased risk to develop a severe form of chronic hepatitis with consequent cirrhosis. Sometimes this goes completely unnoticed until the dog suffers gastrointestinal haemorrhage at which point HE might develop. On other occasions, the diagnosis is made when dogs are investigated for PU/PD. Affected dogs may have high liver copper concentrations, but it is thought that copper accumulation is secondary to inflammation and cholestasis in this disease.

Copper accumulation in Bedlington terriers

The copper accumulation hepatopathy of Bedlington terriers is autosomal recessive and thought to be caused by a deletion of exon 2 in the *MURR1* gene. The Bedlington disease differs somewhat from true Wilson's disease of humans.

Favier RP, Spee B, Penning LC, Brinkhof B, Rothuizen J. **Quantitative PCR method to detect a 13-kb deletion in the MURR1 gene associated with copper toxicosis and HIV-1.** Mammalian Genome 2005; 16(6):460-3.

Affected Bedlington terriers gradually accumulate copper in their livers, with levels occasionally reaching a staggering 12,000 ppm of liver tissue. Above 2000 ppm, mitochondrial damage to hepatocytes is likely to occur with consequent inflammation and serum ALT elevation. When liver copper levels have risen sufficiently, modest stress is sufficient to induce acute hepatic necrosis and haemolysis. Renal failure may develop. In animals over eight years of age, liver copper content tends to decrease, probably because copper-laden hepatocytes are replaced by fibrous tissue.

Early detection offers the best chance of helping affected animals. Chelation therapy may be needed if sufficient copper has already accumulated. After that, lifelong zinc administration can be used to help affected animals live a normal life.

In some countries, selective breeding has dramatically decreased the prevalence of this disease. In future, a robust genetic test for detection of affected animals and carriers is likely to become commercially available. Meanwhile, liver biopsies are being taken at 6 and 15 months of age and used to distinguish normal animals from heterozygotes and homozygous affected animals. The liver copper concentration is high on the first biopsy and increases on the second biopsy in

homozygous affected animals. It is abnormally high on the first biopsy but decreases by the second biopsy in heterozygotes. It is, of course, normal in unaffected animals.

Infectious canine hepatitis

This acute viral disease is caused by *Canine adenovirus*. Largely as a consequence of widespread vaccination, it has become very uncommon in many parts of the world. It has been suggested that canine adenoviral infection may underlie some cases of chronic hepatitis in dogs, but there is little evidence to support the suggestion.

Leptospirosis

Some dogs with leptospirosis develop acute or subacute renal failure without jaundice, but in many the liver is involved. Fever, jaundice and increased liver enzymes in the dog that has concurrent renal failure suggest the possibility of leptospirosis. One serovar of *L. interrogans* (grippotyphosa) has been implicated as a possible cause of chronic hepatitis in dogs.

Feline Cholangitis / changiohepatitis complex

Caney SMA, Gruffydd-Jones TJ. Feline inflammatory liver disease. In: Ettinger, SJ; Feldman, EC. (Eds.) *Textbook of Veterinary Internal Medicine, Sixth Edition*. St Louis, Mo: Elsevier/Saunders, 2005; 1448-1453.

This is probably the most common primary liver disorder (or cluster of disorders) in British cats. Cases can be broadly categorized as either suppurative or lymphocytic.

Suppurative cholangitis and cholangiohepatitis

- Predominantly neutrophils infiltrating the bile ducts, which show necrosis and degeneration. Variable fibrosis. Thought to arise as a result of ascending bacterial infection. Mixture of enteric bacteria can usually be cultured from bile of affected cats.

- Often accompanied by mild pancreatitis, which can also be caused by ascending bacterial infection (N.B. the anatomy of the feline pancreatic & common bile ducts). Even more often accompanied by inflammatory bowel disease (IBD; usually lymphoplasmacytic, but sometimes suppurative). Hence (if all three entities present concurrently) the use of the term ***triaditis***. Maybe IBD → ascending infection → pancreatitis and cholangitis.

- 'Triaditis' usually manifests clinically as cholangitis.

- ***Clinical features:*** An acute onset disease of middle-aged to older cats (often >10 years). No sex or breed predilection. Anorexia, ±pyrexia, **icterus** (due to intrahepatic cholestasis ±sludge causing EHBDO), ± abdominal discomfort.

- ***Diagnosis:*** ↑ ALT and bilirubin. ± ALP, γ-GT and SBA elevations. Increased PIVKAs. Ultrasound reveals gallbladder distension ± thickening. Prominent ± thickened bile ducts. Sometimes cholelithiasis. Histopathology required for confirmation. Laparotomy allows biopsy of liver, intestine and pancreas; plus aspiration and culture of bile.

- ***Therapy:*** Amoxicillin-clavulanate pending culture results. Fluoroquinolone / metronidazole may be needed. 4-6 weeks of antibiotics. Ursodiol ±SAMe. Surgery if complete EHBDO. Supportive measures.

- ***Prognosis:*** In one study, half survived more than a year (median survival 29 months). Prognosis influenced by concurrent illnesses. Much worse if surgical anastomosis to deal with EHBDO is required.

Lymphocytic cholangitis

- Predominantly T-lymphocytic inflammatory infiltrates surrounding bile ducts and within portal areas. Suspected to be an immune-mediated disease.

- Bile duct proliferation, maybe with inflammation but no epithelial degeneration. Variable fibrosis, sometimes severe. Secondary nodular hyperplasia.

- Association with IBD and pancreatitis much less strong than for suppurative cholangitis.

- Considered possibly to be a sequel to suppurative cholangitis, ***but*** seen in younger cats, less associated with pancreatitis / IBD, no history of previous liver disease reported for most affected cats.

- ***Clinical features:*** >50% under 4 years old. Persians overrepresented. Much more common than the suppurative disease. Present as icteric cats or cats with worsening ascites; maybe both. Do not look very sick; indeed may be hungry. ±weight loss, ±palpable hepatomegaly.

- ***Diagnosis:*** Liver enzymes and bile acids elevated. ± hyperbilirubinaemia and hyperglobulinaemia. Lymphopenia. Ascitic fluid, if present, reminiscent of that in FIP. Histopathology required for confirmation and, sometimes, to distinguish from FIP.

- ***Treatment:*** Prednisolone 1-2 mg/kg BID gradually tapering over 6–12 weeks. ± other immunosuppressant drugs. ± Ursodiol, SAMe.

- ***Prognosis:*** Limited information available, but seems to be fairly good.

Metabolic and toxic liver diseases

Scherk MA, Center SA. Toxic, metabolic, infectious and neoplastic liver diseases. In: Ettinger, SJ; Feldman, EC. (Eds.) *Textbook of Veterinary Internal Medicine, Sixth Edition*. St Louis, Mo: Elsevier/Saunders, 2005; 1464-1478.

Canine vacuolar hepatopathy

As previously mentioned, the canine liver responds to exogenous glucocorticoid administration by induction of liver enzymes, particularly ALP. Morphological changes accompany or follow these enzymatic changes. Progressive accumulation of glycogen in hepatocytes occurs, leading over time to enlargement of the liver and obvious vacuolar changes visible on microscopic examination of routine H&E stained liver biopsies. This glycogen accumulation is reflected as a diffuse increase in overall echogenicity of the liver, when viewed using ultrasound.

Excessive endogenous production of steroids (such as glucocorticoids and sex steroids) can lead to an identical effect. Thus, the various forms of hyperadrenocorticism can cause vacuolar hepatopathy. However, not all dogs diagnosed with vacuolar hepatopathy are demonstrably Cushingoid. It is thought that the stress associated with a variety of non-adrenal illnesses can, in some animals, lead to sufficient excessive glucocorticoid secretion to cause vacuolar hepatopathy and (usually) serum ALP elevation. In other animals that have negative test results for hyperadrenocorticism, sex steroids produced by hyperplastic adrenal glands may be responsible for the vacuolar hepatopathy. Sex hormone profiles can be done before and after ACTH administration to assist in diagnosis of such cases. One author has suggested that mitotane treatment of affected animals should be considered, since vacuolar hepatopathy may occasionally progress to more severe disease and be associated with hepatocutaneous syndrome.

Feline hepatic lipidosis

This condition is common and very important in the United States but much less so in UK. Its pathogenesis is complex and incompletely understood. It is only described superficially here. Ill

cats tend to accumulate triglycerides in their hepatocytes leading to visible fatty vacuolation. This causes no significant problems until it becomes markedly severe. Obese cats that become anorexic are at greatest risk of developing hepatic lipidosis. In such cats, peripheral fat is mobilized and excessive fat is taken up by the liver but is not dispersed properly. A variety of defects in hepatic function may then come into play, hampering formation of very low-density lipoproteins and fat dispersion. L-carnitine deficiency, vitamin B_{12} deficiency (perhaps associated with intestinal disease), GSH deficiency and unavailability or failure to use SAMe have all been proposed to be relevant.

Cats of any age can be affected, especially those 4–15 years old. Clinical signs are initially non-specific: anorexia, lethargy, weight loss and vomiting. Icterus and hepatomegaly may be appreciated on physical examination. The serum chemistry profile reveals elevated ALP and ALT, but usually mild or no elevation of γ-GT. Bilirubin may be elevated. Hypokalaemia is common and should be treated, if present. Ultrasound usually reveals a diffusely hyperechoic liver parenchyma. FNA will typically reveal the vacuolar change. Diagnostic investigations may also reveal a distinct underlying cause for the hepatic lipidosis, although many cases remain idiopathic.

Treatment usually involves placement of a feeding tube (*e.g.,* gastrostomy, oesophagostomy) and provision of a balanced diet at 60 kcal/kg/day, often provided in multiple very small portions, or as a 'constant infusion'. Intravenous fluid therapy is provided with water-soluble vitamins added. Supplementation of potassium and phosphate may be necessary.

Vitamin K_1 (0.5-1.5 mg/kg SC BID), L-carnitine (250-500 mg/day), taurine (250-500mg/day) and antioxidants may also provide benefits and have been recommended for use.

Hepatotoxicities

Numerous drugs, herbal remedies and poisons can cause hepatic damage. The toxic effects of some of these agents are 'intrinsic' (*i.e.,* a direct effect, reliably to be expected) and, for others, toxicity is idiosyncratic, sometimes being immune-mediated. The distribution of lesions within hepatic acinar units can sometimes be informative as to the likely cause of a toxic insult.

You should aim to find and read one or two paragraphs of supplemental information about each of the hepatotoxicities caused by the following drugs or groups of drugs (Ettinger & Feldman is one good source of information):-

- Anticonvulsants (*e.g.,* phenobarbital)

- Antimicrobials (*e.g.*, trimethoprim-sulpha, ketoconazole)
- Diazepam
- Methimazole / carbimazole
- NSAIDs (carprofen, paracetamol)

Portosystemic vascular anomalies (PSVAs)

Mathews KG, Bunch SK. Vascular liver diseases. In: Ettinger, SJ; Feldman, EC. (Eds.) *Textbook of Veterinary Internal Medicine, Sixth Edition*. St Louis, Mo: Elsevier/Saunders, 2005; 1453-1464.

- PSVAs are congenital anomalies that may be intrahepatic or extrahepatic in location. In general, small breed dogs are prone to extrahepatic shunts and large breed dogs are prone to intrahepatic ones. Extrahepatic shunts are more common. Most extrahepatic shunts are single aberrant vessels. Many intrahepatic shunts represent patent ductus venoses that failed to close early in life.
- Clinical features are a consequence of portal blood circumventing the liver. The systemic circulation is exposed to toxins and bacteria that would normally be filtered by the liver. The liver is deprived of trophic factors and oxygenated blood.
- PSVAs are much less common in cats than in dogs. Most feline PSVAs are single and extrahepatic. Himalayans and Persians are predisposed to develop PSVAs. Clinical features observed in cats include staring into space, aggression, intermittent blindness and intermittent salivation.
- Partial attenuation of PSVAs, rather than complete occlusion in one procedure, is usually necessary to avoid life-threatening portal hypertension. A variety of surgical approaches has been advocated for gradual attenuation of extrahepatic PSVAs. These include cellophane bands and ameroid constrictor rings. Some surgeons advocate the use of a n intravenous catheter, extension set and water manometer during surgery, for measurement of portal hydrostatic pressure to help judge how much the aberrant vessel should be attenuated.
- Up to 3 days post-operatively, status epilepticus occasionally develops and can be life-threatening. This is reportedly more frequently observed in older animals, whose brain

chemistry has had time to adapt to the presence of benzodiazepine-like substances and perhaps other neurotoxins from the gut.

Exocrine pancreatic disorders – key points

Pancreatitis in dogs and cats

Watson P. Laboratory evaluation of exocrine pancreatic disease. In: E. Villiers & L. Blackwood (Eds.) BSAVA Manual of Canine and Feline Clinical Pathology, Second Edition. Pp. 226-240.

Williams DA, Steiner JM. Canine exocrine pancreatic disease. In: Ettinger, SJ; Feldman, EC.. (Eds.) *Textbook of Veterinary Internal Medicine, Sixth Edition*. St Louis, Mo: Elsevier/Saunders, 2005; 1482-1488.

Steiner JM, Williams DA. Feline exocrine pancreatic disease. In: Ettinger, SJ; Feldman, EC.. (Eds.) *Textbook of Veterinary Internal Medicine, Sixth Edition*. St Louis, Mo: Elsevier/Saunders, 2005; 1489-1492.

Pancreatitis is a relatively common diagnosis in dogs and is being diagnosed with increasing frequency in cats. The true incidence of pancreatitis in dogs and cats is uncertain. It is likely that many cases are missed and, conversely, pancreatitis may sometimes be diagnosed incorrectly in patients with other gastrointestinal diseases.

The fundamental mechanism of disease in pancreatitis is autodigestion of pancreatic tissue by digestive enzymes that are prematurely activated within the pancreatic acinar cells. Normally, pancreatic digestive enzymes are released from the pancreas as inactive zymogen granules. Trypsinogen within these granules is proteolytically cleaved and activated when it reaches the duodenal lumen by an enzyme called enteropeptidase (*prev.* enterokinase). The newly-formed trypsin is then able to activate other zymogens by proteolytically cleaving from each a small amino terminal peptide called the 'activation peptide'. In acinar cells, the developing granules are normally strictly kept separate from lysosomes. In many experimental models of acute pancreatitis, zymogen granules fuse abnormally with lysosomes inside acinar cells leading to inappropriate intra-pancreatic activation of the zymogens. Lysosomes contain proteases that, at low pH, are capable of activating the zymogens. For protection, the pancreas contains trypsin inhibitors and trypsin can autocatalyze its own degradation. However, the inhibitor present in zymogen granules is not active at the low pH present in lysosomes. If the zymogen activation process proceeds too vigorously, pancreatitis can result.

Pancreatitis can have severe, adverse systemic effects because activated proteolytic enzymes can circulate and cause damage distant from the pancreas. There are plasma protease inhibitors (*e.g.*, alpha-macroglobulins and alpha-1-proteinase inhibitor) that bind and inactivate circulating

proteases and lead to their rapid clearance from circulation by the mononuclear phagocyte system. Unfortunately, these plasma protease inhibitors can be consumed in severe pancreatitis. This is one reason why fresh-frozen plasma transfusions can sometimes be life-saving in severe pancreatitis.

Some of the ways in which pancreatitis can be reproduced experimentally include: 1). hyperstimulation of secretion; 2). obstruction of the pancreatic duct; and 3). retrograde, intraductal injection of bile or duodenal enzymes. These mechanisms may also be relevant in clinical situations. For example, in high-rise syndrome of cats retrograde flow of duodenal contents into the pancreatic duct may occur. Alternatively, blunt trauma to the pancreas may lead to ischaemic damage and consequent pancreatitis. In cats, viscous bile may lead to EHBDO. Remember that the pancreatic duct joins the bile duct before entering the duodenum in cats, meaning that biliary diseases more readily extend to involve the pancreas in this species.

In many patients with pancreatitis, the underlying cause for development of the disease is never defined. Some risk factors that are well-recognised, but not necessarily well understood, include:-

- Ductal obstruction;
- Hyperlipidaemia (*e.g.,* familial forms);
- Dietary indiscretion (*e.g.,* a recent very fatty meal);
- Physical trauma (*e.g.,* high-rise syndrome, blunt abdominal trauma, surgery);
- Hypercalcaemia;
- Ischaemia / reperfusion / hypoxaemia (*e.g.,* gastric dilatation-volvulus, profound anaemia);
- Various drugs and toxins (*e.g.,* organophosphates, azathioprine, L-asparaginase, tetracycline potassium bromide); and
- Infections / infestations (*e.g.,* Toxoplasmosis, FIP, hepatic fluke [*Amphimerus pseudofelis*]).

In cats, as previously mentioned, pancreatitis commonly accompanies cholangitis/cholangiohepatitis and IBD. In dogs, pancreatitis is thought to be more common in obese animals.

Diagnosis

Pancreatitis is most common in middle-aged and older dogs that are often overweight. In cats, a much wider age range may be affected. Dogs with acute pancreatitis usually have vomiting, abdominal pain, depression and sometimes fever and diarrhoea. Peracute disease may be associated

with stupor, collapse and rapidly progressive deterioration in haemodynamic status. Signs of DIC (*e.g.*, petechiae, ecchymoses) may develop within hours. In subacute or chronic cases, a cranial abdominal mass may be palpable after one or two days. This can sometimes be quite firm, and maybe associated with peripancreatic fat saponification.

Cats usually have less obvious clinical signs and dogs with lethargy, anorexia and weight loss predominating. The disease can also vary enormously in severity. Vomiting and abdominal pain are absent in a majority of affected feline patients.

Radiography may be helpful in dogs, but only in a minority of affected patients. There may be increased radiopacity and reduced contrast in the right cranial abdomen (with a so-called 'ground glass' appearance). The descending duodenum may be displaced to the right and have some gas in it. This gas may be persistently present on more than one radiograph. Sometimes the gas within the duodenum reveals a corrugated 'angry' appearance to the descending duodenum, or the impression of thickened duodenal walls. Similar changes may also be detected in the ascending/transverse colon.

Animals were severe pancreatitis may have a pleural effusion, more likely to be observed on the right side.

Ultrasonography can be highly specific for diagnosis of pancreatitis in the hands of an expert operator, but sensitivity is rather low. It ranges from 70% in dogs to as low as 30% in cats. Ultrasonographic diagnosis of pancreatitis is particularly challenging in cats because many have mild or chronic morphological changes. Contrast enhanced computed tomography in cats has been reported to be even less sensitive than ultrasonography for the detection of pancreatitis.

Peripheral blood neutrophilia, often with a left shift, is a common feature of pancreatitis. Thrombocytopenia, if present, may be evidence of developing DIC. Azotaemia may be present. It may be prerenal or renal, since pancreatitis can induce secondary acute renal failure. This form of acute renal failure can resolve if the pancreatitis is successfully managed. Liver enzymes are usually increased as a consequence of local inflammation and flow of toxins in venous blood from the inflamed pancreas to the liver. EHBDO may develop because of external pressure on the common bile duct. This can lead to hyperbilirubinaemia, hyperbilirubinuria and sometimes icterus. Cholestasis of sepsis may contribute to hyperbilirubinaemia and icterus in some patients. Hyperglycaemia may be present as a result of stress and, in some patients, islet-cell destruction. Hypoalbuminaemia and hypocalcaemia may develop. Low blood calcium may only reflect the

albumen concentration or may be a consequence of calcium consumption in peripancreatic soap. Hypoalbuminaemia may be a consequence of inflammation (remember, it is a negative acute phase reactant) or loss of albumin from blood vessels into the extracellular space and into 'third spaces' (*e.g.,* peritoneal cavity, oral cavity) as a result of pancreatitis-induced vasculitis. Hyperlipidaemia may be present despite anorexia and may interfere with a measurement of many other serum biochemical analytes.

Serum amylase and lipase have been used for many years in the assessment of suspected pancreatitis. Unfortunately, they far from ideal for this purpose. In one study, the sensitivity and specificity of elevated serum amylase for detection of canine pancreatitis were 62% and 57%, respectively. For elevated serum lipase the sensitivity and specificity were 73% and 55%, respectively. In pancreatitis, these enzymes may become depleted or their synthesis may be disrupted. This may explain the poor sensitivity values and also why the severity of clinical disease does not correlate well with the degree of enzyme elevation. The poor specificity values may be explained by sources of enzyme outside the pancreas, failure of clearance of serum enzyme in renal failure and glucocorticoid-induced increases in serum lipase activity, in the absence of pancreatitis. In contrast, glucocorticoids are reported to decrease serum amylase activity.

Measurement of amylase and lipase activities in peritoneal effusion fluid, or fluid obtained by peritoneal lavage, has been suggested and is used by many clinicians. Whether it provides advantages over measuring serum activities is uncertain.

In cats, measurement of serum amylase and lipase activities has no diagnostic usefulness.

Serum trypsin-like immunoreactivity (TLI) is familiar to many companion animal veterinarians because it is used in the diagnosis of canine (and more recently feline) exocrine pancreatic insufficiency (see later). Unfortunately, TLI is an insensitive way of assessing dogs and cats with naturally-occurring pancreatitis. Elevated levels were observed in less than 40% of dogs and 30-60% of cats with naturally-occurring pancreatitis. It has high specificity except in azotaemia cats.

A relatively new kind of test detects serum pancreatic lipase immunoreactivity in both cats (fPLI) and dogs (cPLI). Unfortunately these can only be measured in Texas, although British clinical pathology labs will forward samples. The reference range for serum cPLI is reportedly 2.2–102 µg/L. Using a cut-off value of 200µg/L, the test was 82% sensitive and 100% specific. In cats, fPLI detection is reported to be sensitive and specific in the diagnosis of pancreatitis.

Treatment

In severely affected patients this can be very challenging. Here as a summary list of things to consider in most cases:-

- Removal of any identified underlying cause
- Analgesia
- Intravenous crystalloid fluid therapy, with monitoring of electrolytes and acid-base status in severely ill patients
- Insulin if diabetic
- Plasma or whole blood transfusion in severely ill patients
- Control of vomiting
- Offer water and if vomiting does not follow, provide enteral nutrition with a fat-restricted, highly digestible food. In cats, tube feeding is likely to be necessary.

Exocrine pancreatic insufficiency (EPI)

Watson P. Laboratory evaluation of exocrine pancreatic disease. In: E. Villiers & L. Blackwood (Eds.) BSAVA Manual of Canine and Feline Clinical Pathology, Second Edition. Pp. 226-240.

Westermarck E, Wilberg /M, *et al.* Exocrine pancreatic insufficiency in dogs and cats. In: Ettinger, SJ; Feldman, EC.. (Eds.) *Textbook of Veterinary Internal Medicine, Sixth Edition*. St Louis, Mo: Elsevier/Saunders, 2005; 1492-1495.

EPI is uncommon to rare in cats and much better characterized in dogs. In cats, it is most often caused by chronic pancreatitis.

In dogs, EPI may arise because of selective loss of pancreatic acinar cells (PAA), chronic pancreatitis and, less commonly, pancreatic hypoplasia or pancreatic neoplasia. By far the most common cause is PAA.

PAA results from selective destruction or loss of the pancreatic acinar cells with consequent failure to produce and secrete pancreatic digestive enzymes. This results in clinical signs of voluminous stools, steatorrhoea, weight loss and (typically) ravenous hunger. Coprophagia may be a feature. Diabetes mellitus is not a feature.

PAA is most common in German shepherd dogs and, to a lesser extent, in Rough collies. In these breeds, lymphocytic infiltration of the pancreas has been detected before overt pancreatic insufficiency develops. It is therefore thought that this disease may be immune-mediated or, indeed, autoimmune. For this reason, the name PAA (which stands for pancreatic acinar atrophy) should perhaps be discarded and replaced with a name that more accurately describes the suspected underlying pathogenesis.

Diagnosis

The typical clinical picture is of a young German shepherd dog with pale, voluminous faeces, ravenous hunger and weight loss. Flatulence and intermittent diarrhoea may be reported. The hair coat may be dull.

Routine blood work does not provide a specific diagnosis. ALT is often elevated. This is thought to be a consequence of increased gastrointestinal toxins reaching the liver, perhaps as a consequence of small intestinal bacterial overgrowth (SIBO).

Measurement of serum trypsin-like immunoreactivity (TLI) has become the standard way of diagnosing EPI. And abnormally low level (<2.5ng/L in dogs) is found in affected animals. A fasting serum sample is required (12 hour fast) to avoid confusion that may be caused by release of small amounts of enzyme into the blood during feeding (if the animal has residual pancreatic secretory capacity). The test has excellent sensitivity and specificity and high positive and negative predictive values when applied to patients with a compatible clinical picture. Occasionally, a result will be obtained in the grey area (2.5–5.0 ng/L). Repeat evaluation is recommended in these cases. Sometimes such dogs go on to produce clearly positive results but more often the TLI level will subsequently be found to be normal. Sometimes such animals will remain persistently in the 'grey area'. These animals may have chronic, grumbling pancreatitis with marginal exocrine secretory capability. In a non-German shepherd dog with clinical signs strongly suggestive of EPI, a single normal TLI value cannot be used to rule out a diagnosis of EPI. Such dogs may have chronic pancreatitis causing EPI. Pancreatitis tends to cause elevation of serum TLI and EPI, of course, lowers it. These competing influences make it impossible to predict what TLI value will be obtained on any particular day.

There are some other diagnostic tests that can be used for diagnosis of EPI (*e.g.,* faecal proteolytic activity, faecal elastase activity), but these have been largely superseded by TLI. SIBO often complicates EPI. Serum cobalamin (vitamin B_{12}) can be measured and supplements provided it is

found to be low. Serum folate can also be measured or, alternatively, it may be appropriate to assume that SIBO is present and treat accordingly.

Treatment

There is no firm data to suggest that early treatment of dogs heading towards EPI (those with biopsy-proven lymphocytic pancreatic infiltration) using immunosuppressant therapy provide any benefit.

Enzyme replacement therapy is indicated for EPI. Various enzyme extracts are commercially available. Powdered, non-enteric-coated supplements are recommended (~ 1 teaspoon added to each meal). Enteric-coated forms are reported not to work so well, because they are retained in the stomach. Alternatively, in some countries, it is legal to purchase and use raw pancreas to treat this disease.

H2 receptor antagonists can be used if response to enzyme supplementation is poor. These antacid drugs may increase the amount of enzyme supplement that survives passage through the stomach. Preincubation of soft food with enzyme supplements has been advocated, but whether it provide any real benefit is uncertain.

A highly digestible, low fibre, moderate fat food may be helpful in some patients but many animals do not need to be fed a special diet. Fat restriction may be advisable because enzyme supplementation is insufficient to match normal lipase production.

Antibiotic therapy (*e.g.,* tetracycline, metronidazole) can be used in selected animals in which SIBO is demonstrated or strongly suspected. If response to enzyme supplementation alone is satisfactory, they should not be needed.

In some dogs with EPI, cobalamin deficiency can be demonstrated. Enzyme supplementation should not be expected to resolve this problem. Parenteral supplementation (250-500µg/dose) and monitoring of serum levels may be necessary.

Prognosis

There is usually a prompt response to therapy with improved faecal consistency, decreased polyphagia and weight gain. Treatment must be continued indefinitely and can be expensive some clients. Over the long-term, it has been reported that approximately 50% of dogs can be rendered essentially normal. 20% have are relatively poor response. Euthanasia is carried out in about 20%

of cases during the first year after the diagnosis is made. The cost of treatment and/or poor response to treatment are thought to be responsible.

Other pancreatic diseases of dogs and cats

There are numerous other kinds of pancreatic disease that are relatively uncommon. These include:-

- pancreatic pseudocyst;
- pancreatic abscess;
- exocrine pancreatic neoplasia;
- pancreatic parasites; and
- nodular hyperplasia.