EQUINE VETERINARY EDUCATION
Equine vet. Educ. (1999) **11** (2) 87-96

Tutorial Article

Liver disease in the mature horse

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Introduction

This article describes the approach to diagnosis, various conditions in which the liver is involved as a primary organ, and the treatment of liver disease in the horse.

Diagnosis of liver disease

Since the liver has a limited number of ways to respond to various insults, the clinical and laboratory changes are similar regardless of cause. It is useful first to determine if the horse has liver disease and then to attempt to identify the aetiology. The liver cannot be seen, heard, smelled, tasted or palpated in the live horse and **liver disease is usually diagnosed by identifying signs produced by failure of some of its functions**.

As with other organs, there is often liver disease prior to failure of function, but laboratory tests may detect disease before there is actual failure. The **liver has about an 80% reserve** and this must be surpassed before some of the functions fail. **Some functions fail before others and this dictates the progression of clinical signs** (Parraga *et al.* 1995). In the mature horse, failure to:

- compartmentalise enzymes
- convert ammonia to urea
- conjugate bilirubin

These usually occur before failure to produce clotting factors or albumin.

Clinical signs

The most common signs of liver disease in the horse are icterus (**Fig 1**), behavioural change and weight loss. **Other signs include** photosensitisation, inspiratory stridor, and occasionally diarrhoea. Tenesmus and ascites that occur in cattle are uncommon in horses, and haemorrhage and low albumin are near-terminal events. Obviously none of these signs are pathognomonic for liver disease and none are consistently present in every case (Pearson 1996). **Icterus** is produced by the liver's inability to take up, conjugate and excrete bilirubin. In the horse it can also be produced by overproduction of bilirubin in haemolytic events, blockage of bile flow, or just anorexia (Engelking 1989). If a horse is jaundiced, **it is wise to differentiate between these 4 categories** by examining the blood for haemolysis and performing liver function or excretion tests (Pearson 1982).

Weight loss may be due to impaired liver metabolic functions, but is more commonly caused by poor teeth, inadequate nutrition, parasites or chronic diseases, such as neoplasia, chronic inflammation or failure of other organs. Gastric impaction secondary to ragwort poisoning has been reported in ponies (Milne *et al.* 1990).

Hepatic encephalopathy is common in liver disease in horses. Signs may be very subtle and manifest only by depression. Some horses become more friendly than usual, whereas others become vicious. In advanced cases, ataxia, dysmetria, circling, continued walking and head pressing can be observed. Yawning is frequently seen in these horses (**Fig 2**). Eventually the depressed horse goes into a

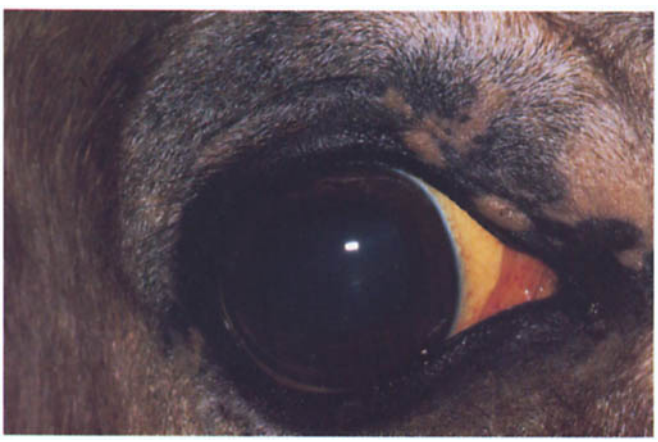

Fig 1: Horse with severe icterus. *If icterus is present* ***the clinician must consider bile obstruction, haemolysis and anorexia,*** *in addition to liver disease.*

Fig 2: Yawning horse. Frequent yawning in a horse could be a subtle sign of hepatic encephalopathy.

TABLE 1: Tests for liver disease discussed in text

Excretion	Usefulness	Normal range
Serum total bile acids	Sensitive, remains elevated in hepatocellular disease, blockage of bile, and portal systemic shunts	<15 μmol/l
Total bilirubin	Inconsistent, also elevated in anorexia, bile obstruction and haemolysis	6.8–34.2 μmol/l
Direct bilirubin	More sensitive than total to bile blockage or hepatocyte damage	0–6.8 μmol/l
BSP (sulphobromophthalein) clearance	Competes with bilirubin so increased if jaundiced, tests excretion function	T 0.5 = <3.5 min
Enzymes		
Gamma glutamyl transferase (GGT)	Source is duct epithelium, elevated in cholistasis, remains elevated in chronic liver disease and post transient disease	8–30 iu/l
Alkaline phosphatase (ALP)	Not specific, in bone, placenta, macrophages, intestine; remains elevated in chronic liver disease	73–194 iu/l
Sorbitol dehydrogenase (SDH)	Specific for liver, not as stable, may not remain elevated in chronic liver disease	0–8 iu/l
Glutamate dehydrogenase (GLDH)	Specific for liver, sensitive, more stable than IDH, may not remain elevated in chronic liver disease, analysis not available in many laboratories	<3.5 iu/l
Lactate dehydrogenase (LDH)	Not specific, in most tissues, may not remain elevated in chronic liver disease	162–412 iu/l
Aspartate amino transferase (AST) SGOT	Not specific, in muscle and heart, elevated with hepatocellular damage	150–270 iu/l
Arginase	Specific, elevated with hepatocellular damage	Not available
5' nucleotidase		1.2–2.4 μiu/l
Alanine amino transferase (ALT) SGPT	Low levels in herbivore liver, not sensitive	Not available

stupor or even recumbent in coma. In ponies inspiratory distress with loud sounds heard from the pharynx and larynx has been reported (Pearson 1991). It is thought this pharyngeal paralysis is part of hepatic encephalopathy.

Pathogenesis

The **pathogenesis of hepatic encephalopathy remains controversial** with an abundance of uninhibited speculation. Blood ammonia levels are elevated in horses with hepatic encephalopathy (Morris and Henry 1991) and CSF glutamine, the product to which ammonia is detoxified, is increased. However, clinical signs cannot be produced in normal animals by injecting them with similar amounts of ammonia (Maddison 1992). It is thought other toxic products that by-pass the malfunctioning liver may work along with ammonia to produce clinical signs.

Horses with hepatic encephalopathy have an increased ratio of aromatic to short branch chain amino acids, and improve when infused with short branch chain amino acids (Gulick *et al.* 1980). It was theorised that there was an increase in inhibitory neurotransmitters such as gamma amino butyric acid (GABA) and L-glutamate due to the excess aromatic amino acids, but this has not been proved. Ammonia is also believed to be involved in the metabolism of GABA in the brain. More recently it has been proposed that neuroinhibition is due to increased endogenous benzodiazepine concentrations (Morris 1991; Maddison 1992)

Laboratory indicators

There are a number of laboratory indicators of liver dysfunction, but many are nonspecific, and others are not manifest either early or late in the disease. Since the liver is so important to metabolism, it is expected that the concentration of a number of metabolites would change. A few horses are hypoglycaemic because of the failure of gluconeogenesis or depletion of the glycogen stores, but this occurs more often in foals than in mature horses. Ammonia increases, as does the ratio of aromatic to branched chain amino acids, but these compounds are not easily measured by most laboratories. All of the serum albumin is produced by the liver, but the

TABLE 2: Source of liver toxins, their location and resulting lesions/clinical signs resulting

Source (plants)	Location or circumstance	Lesion or clinical sign
Pyrrolyzidine alkaloid	See above	Hepatomegaly, biliary hyperplasia, cirrhosis
Horsebrush *Tetradymia* spp.	Rangeland, Western US	Hepatic necrosis
Puncture vine *Tribulus terrestris*	Europe, N. Am., Australia	Biliary cirrhosis, necrosis
Alsike clover *Trifolium hybridum*	Cultivated, pasture	Portal fibrosis, biliary hyperplasia
Mouldy alfalfa	Wet cultivated fields	Biliary hyperplasia and necrosis, periportal inflammation, degeneration
Blue green algae *Microcystis, Nodularia* spp.	Bloom on ponds	Hepatic necrosis, dissociation
Some poisonous mushrooms *Amanita, galerina* spp.	Species varies worldwide	Hepatic necrosis, neurological signs
Lupine *Lupinus* spp.	Mycotoxin from *phornopsis*	Hepatic necrosis, cirrhosis
Panic grass *Panicum* spp.	Australia, Africa, South America, Southern U.S.	Biliary fibrosis, necrosis
Cycad palm *Cycas/Zamia* spp.	South America, Australia	(not described)
Source (chemicals and drugs)	**Dose or circumstance**	**Lesion or clinical sign**
Carbon tetrachloride	10–40 mg/kg	Fatty degeneration, centra lobular necrosis
Carbon disulphide	Botacide	Hepatocellular necrosis
Iron	Injectable or young animal	Portal necrosis, >iron content
Copper	Excess supplements, or lack of molybdenum	Haemolytic crisis, portal necrosis, vacuoles
Mycotoxin Aflatoxin B, etc.	Mouldy feed ingestion	Centralobular necrosis, biliary hyperplasia, megalocytosis
Isoniazid	Medication	Active hepatitis, cirrhosis
Rifampin	Medication	Cholistasis, reversible
Halothane	Anaesthetic	Active hepatitis, cirrhosis, necrosis
Fluothane	Anaesthetic	Active hepatitis, cirrhosis, necrosis
Dantrolene	Medication	Active hepatitis, cirrhosis
Phenothiazine tranquillisers	Sedation	Cholistasis, icterus

half life of albumin in the horse is about 19 days and the liver has a great reserve for its production, so low serum albumin is usually a near-terminal event. Most horses with low serum albumin are suffering from parasites, chronic inflammation, protein loss in the gut or sequestering of protein in fluid of the body cavities. **Total protein is almost never low in horses with liver disease because there is an increase in beta globulins** concurrently with the decrease in albumin (Paragara *et al.* 1995). Clotting factors may be decreased.

Increased concentrations of endogenous or injected compounds that are excreted by the liver may indicate liver disease or impaired bile flow. **Bilirubin** is the main bile pigment and is produced from heme in the macrophage system when erythrocytes are broken down. **Unconjugated bilirubin** is transported to the liver bound to albumin. This is taken up by the liver, conjugated, and excreted into the bile. **Increased serum concentrations occur** with increased production (haemolysis), hepatocellular disease, blockage of bile flow or anorexia. Fasting in the horse will increase the unconjugated bilirubin concentration by 2-to 3-fold (Engelking 1989).

In horses with liver disease, increased concentrations of indirect reacting (unconjugated) bilirubin is most

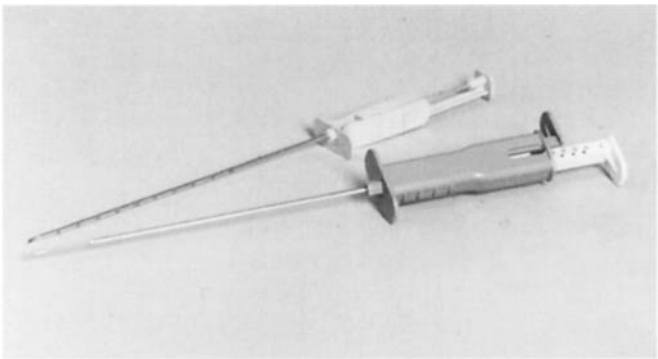

Fig 3: Needles used for percutaneous liver biopsy. The needle at the top is the BD Precision Cut[1]. Needle on the bottom is the Monoject ABC activated biopsy cutting needle[2].These are 14 gauge needles that will cut a piece of liver tissue about 1.5–2 cm long.

pronounced, although increases in direct reacting bilirubin may be the most sensitive indicator of hepatocellular disease. Direct to total bilirubin ratios of >0.3 usually indicate obstruction to bile flow (Pearson 1982).

Serum total bile acid concentration is a sensitive test for liver dysfunction (West 1989b). Bile acids are produced in the liver from cholesterol, conjugated and excreted in the bile. After they function to form fat micelles for fat absorption, 95% of them are reabsorbed by a specific transport system in the ileum, and recirculated a number of times each day through the enterohepatic circulation. If the liver cannot remove most of the bile acids on first passage, serum concentrations increase outside the portal system. **Increased serum bile acid concentrations indicate blockage to bile flow, hepatocellular damage or shunts from the portal system to the vena cava** (Pearson and Craig 1992). Changes in bile acid concentration occur fairly early in liver disease, and continue through the terminal stages. Serum bile acid concentrations are also a good prognostic indicator and may detect some diseases in their early stages (Mendel *et al.* 1988). Bile acids are relatively stable at room temperature.

Various dyes that are excreted by the liver can be injected i.v. into the horse, and the concentrations of the dyes in the serum measured to determine the efficiency of the liver's excretion. **Sulphobromopthalene (BSP) is the dye used most commonly in horses because of the cost of the other dyes, indocyanine green and rose Bengal**. A BSP clearance test can be conducted by injecting about 2 mg BSP/kg bwt i.v. into the animal. Blood samples are taken prior to the injection and 2–4 times 5–12 min following the injection. These samples are analysed for BSP and a half-life determined. Normal BSP clearance half-life in the horse is less than 3.5 min.

Serum enzyme concentrations have been used in recent years to evaluate the liver. A number of enzymes are produced by the liver and increase in the serum with hepatocellular damage, bile duct inflammation, or blockage of bile flow. **Table 1** lists the serum enzymes most commonly used to diagnose liver disease in horses along with some problems with each and their normal reference range for mature horses. **Gamma glutamyl transferase (GGT) is one of the more useful enzymes** (West 1989a; Divers 1993). **It is present in most duct tissue** so is high in liver, pancreas, kidney, and the udder. In kidney disease the enzyme usually escapes into the urine. Pancreatitis is uncommon in the horse and increased serum concentrations usually indicate liver or bile duct disease. Serum concentrations of GGT become elevated after a few days of liver damage and remain elevated until the terminal phase (Craig *et al.* 1991).

Alkaline phosphatase (ALP) is present in bone, intestine, placenta and macrophages in addition to the liver and is not very specific. However, it is a fairly sensitive indicator of cholistasis and remains elevated late in the disease (Reed and Andrews 1986).

Several of the dehydrogenases increase in the serum with hepatocellular damage but some, such as **lactate dehydrogenase (LD)** are not specific for liver damage since they are present in many tissues. **Sorbitol dehydrogenase (SDH)** is very specific for liver (Asquith *et al.* 1980; Bernard and Divers 1989), but it has a relatively short half-life outside the animal, and serum concentrations return to normal when the cells near the portal triad are destroyed, often before the animal becomes ill with chronic liver disease. **Glutamate dehydrogenase (GLDH)** is also specific for liver, but the analysis is more difficult, and it also returns to normal in chronic liver disease (Craig *et al.* 1991). **Aspartate amino transferase (AST)** is present in muscle as well as liver and is not therefore specific. It is best to analyse for 2 or 3 enzymes at the same time because some may not be increased at the time of sampling or are increased due to disease in other organs.

Serum enzymes, bile acids and **bilirubin concentrations** along with **clinical signs** may indicate hepatic damage, but give little help as to aetiology. **Liver biopsy** is much more useful in determining aetiology and prognosis (Pearson and Craig 1980). This is a relatively safe and inexpensive procedure and can be performed on the standing horse with local anaesthesia and minimal sedation. A notch cutting percutaneous biopsy needle such as the BD Precision Cut[1] or the Monoject needle[2] (**Figure 3**), can be used. The site used by the author is the **14th intercostal space on the right side at a line drawn between the *tuber coxae* and the point of the shoulder**. Some operators use the 13th intercostal space somewhat more ventral but above a line drawn from the *tuber coxae* to the point of the elbow.

The skin is prepared for aseptic insertion of the needle, a local anaesthetic agent injected under the skin, and a stab made with a No. 15 Bard-Parker blade. The biopsy needle is inserted slowly through the skin wound, intercostal muscles, pleura, sometimes a little lung, diaphragm and liver capsule into the liver. Directing the needle slightly (30°) cranial and ventrad keeps it in the parenchyma of the liver and away from the larger vessels on the visceral surface. The tissue should be placed in 5–10% buffered formalin and submitted for histopathology examination. A bacterial culture of part of the fresh liver tissue may reveal significant infection in cases of cholangiohepatitis.

Ultrasound can be used to examine the texture of the liver tissue and to guide a biopsy if adequate liver tissue cannot be obtained using the blind approach as described

Fig 4: Tansy ragwort. *This is a field with the second year growth of* Senicio jacobaea, *tansy ragwort.* ***Note*** *the yellow flowers and characteristic shape of the leaves. The first year growth of the biannual is a rosette that grows close to the ground.*

above. It can identify abscesses and tumours of the liver and stones in the bile ducts, but these are not common in the horse. Scintigraphy of the equine liver has also been described (Theodorakis *et al.* 1982), but is costly.

Liver diseases

Pyrrolizidine alkaloid poisoning, (P A)

Pyrrolizidine alkaloid (PA) is present in a number of plants including: *Senecio jacobeae* (tansy ragwort) (**Fig 4**), *Senecio vulgaris*, *reddellii*, or *douglassi* (groundsel) (**Fig 5**), *Senecio trianularis* (tar weed), *Senecio alpinus* (Alpenkreuzkraut), *Amsinkia intermedia* (Fiddleneck), *Crotalaria spp.* (Rattlebox), *Echium plantaquineum* (Salvation Jane), *Heliotropium europeaum* (Common heliotrope), *Cynoglossum officinale* (Hounds tongue) and several others. When plants containing pyrrolizidine alkaloids are ingested, the alkaloids are broken down to pyrrols in the liver. These metabolites cross link with DNA preventing regeneration in addition to inhibiting enzymes and protein synthesis (McLean 1970). **Most cases of pyrrolizidine alkaloid poisoning are chronic and delayed.** In some experiments, ponies did not become ill until a year after the consumption of the alkaloid was stopped (Craig *et al.* 1991). This makes obtaining an accurate history difficult since it may have been a year previous that the alkaloid was in the feed.

Horses with pyrrolizidine alkaloid poisoning present with **signs of liver disease as described above.** Weight loss, icterus, and a depressed behaviour are the most common presenting complaints. Liver enzymes become elevated before the animal shows clinical signs of disease (Lessard, *et al.* 1986; Mendel *et al.* 1988), but the dehydrogenases, SDH and GLDH, may return to normal or below normal levels before clinical signs are detected. For this reason **serum GGT, ALP and total bile acid concentrations are more sensitive indicators of this chronic condition.** A liver biopsy shows histological changes compatible with this condition and rules out some of the others.

Fig 5: The plant shown here is* Senecio vulgaris, *groundsel. It also contains Pyrrolizidine alkaloids, *but is not as well recognised as tansy ragwort.* ***Note*** *the yellow flowers and fluffy seeds, and the shape of the leaves.*

On *post mortem* examination the liver is small, friable, and dense. It is more difficult to cut because of the increased amount of connective tissue, and may be irregular or knobby on the surface. Some of the histological changes are characteristic and can be detected on biopsy specimens as well as *post mortem* tissue. The first changes are in the nuclei which may contain vacuoles or invagination of the cytoplasm (Craig *et al.* 1991). The nuclei then become enlarged and there are many cells containing 2 nuclei. **Hepatic megalocytosis** has been the hallmark of PA poisoning. Large hepatocytes with large nuclei are found throughout the liver lobule. This is also seen in mycotoxicosis, but with PA poisoning there is no regeneration. Biliary hyperplasia is apparent before cirrhosis. There are **increased numbers of bile ducts** in each portal triad, and an increase in bile duct epithelium. Cirrhosis starts in the portal areas and spreads centrally and to other portal regions (**Fig 6**). As the disease progresses, dead hepatocytes surrounded by inflammatory cells can be seen throughout the lobule; and connective tissue is eventually laid down in these areas. In the terminal stages there are very few normal hepatocytes and the liver tissue has been mostly replaced by connective tissue.

Most cases cannot be treated successfully once severe signs occur. A poor prognosis is indicated if there is bridging fibrosis found on histological examination, GGT and bile acids are elevated, but the dehydrogenases have returned to normal, or the albumin or clotting factors are low. In the early stages, before severe fibrosis but with elevated enzymes, some of the animals can be saved by removing the feed containing PAs, and supporting liver function as described at the end of this article (Lessard *et al.* 1986).

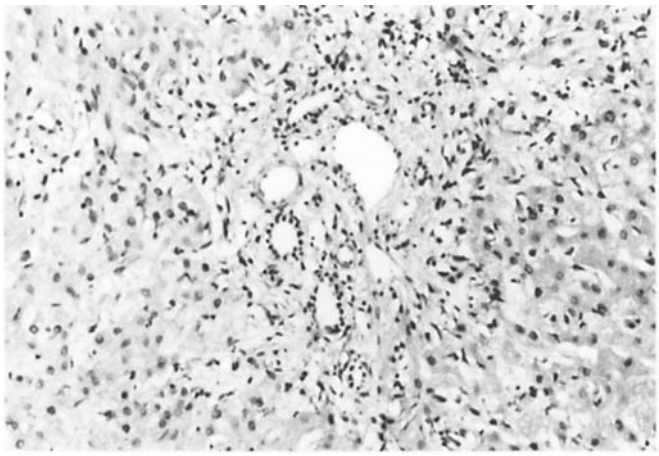

Fig 6: This is a histological section of the liver of a pony with tansy ragwort poisoning. *The pony died of the condition one week after this biopsy tissue was taken.* ***There is great reduplication of bile ducts (A) and bile duct epithelium (arrow),*** *portal cirrhosis (B) and loss of hepatocytes. H&E 50.4x*

Other hepatotoxins

Many other compounds are toxic to the liver **including other plants, chemicals** and even **drugs administered by veterinarians**. Clinical signs and laboratory changes will not distinguish between these toxins. In most cases a diagnosis of liver disease or liver failure is made and then the clinician starts looking for possible causes. **Table 2** gives some of the more common agents that can be toxic to the liver; and circumstances surrounding toxicity and liver lesions associated with each.

Acute hepatitis (serum hepatitis, Theilers disease)

Acute hepatitis in horses is now most commonly associated with the administration of tetanus antitoxin, although there are cases with no history of equine serum administration. The aetiology is unproven but some infectious agent is suspected because it can be transmitted by large transfusions of blood in some but not all attempts (Hjerpe 1964). The disease is somewhat seasonal with more cases in the summer and fall suggesting a possible insect vector. There are cases which develop in horses that have not been administered equine serum products, but exposed to horses which have (Tennant 1978).

The onset of clinical signs is acute and, if tetanus antitoxin has been administered, it is usually 4–10 weeks previously. Most cases are sporadic, but epidemics where several animals are involved have been reported (Guglick *et al.* 1995). Lactating mares which receive tetanus antitoxin at parturition seem to be more susceptible (Messer and Johnson 1994; Guglick *et al.* 1995) It is uncommon for foals given tetanus antitoxin at the same time to get the disease. **The presenting complaint is often lethargy, icterus and anorexia**. Most of the horses have signs of hepatic encephalopathy (Messer and Johnson 1994; Guglick *et al.* 1995).

The urine is a dark colour because of the high bilirubin concentration. Since this disease is acute, weight loss is not a common complaint as it is in chronic liver disease, **but any of the other signs attributable to liver failure may be seen**. It is not always easy to differentiate these cases from PA toxicity or other chronic hepatitis with clinical signs and laboratory work alone, especially if there is no history of tetanus antitoxin administration (Tennant 1978).

Diagnosis of acute hepatitis is made by the abrupt onset of clinical signs and laboratory tests to indicate liver disease. If there has been a history of administration of a product containing equine serum it will further incriminate serum hepatitis. Any of the liver-derived serum enzymes could be elevated. The acute release dehydrogenases such as SDH and GLDH remain elevated along with GGT, AST, and ALP. Serum total bile acid concentration will also be increased above 20 μmol/l. Serum total bilirubin concentration is usually in the range of 12–20 mg/dl; most of this is in the unconjugated form (Divers 1997). A liver biopsy which reveals characteristic histopathological changes is usually necessary to differentiate acute hepatitis from other forms of liver disease.

The **mortality rate** is high in acute hepatitis, and ranges from 50–88% (Hjerpie 1964; Guglick 1995) Aspartate amino transferase (AST) levels above 4000 u/l (Divers 1997) or prolonged prothrombin times indicate a poor prognosis. **At *post mortem* examination** the carcass is extremely icteric and the liver is small. The surface of the liver is tan, and the lobular pattern is more prominent than usual. **Histologically** there is hepatocellular necrosis in the central and mid lobular areas and, occasionally, the entire lobule. This location may help differentiate it from PA toxicity which has predominantly periportal changes in the earlier stages. There may also be proliferation of bile ducts, and infiltration of mononuclear cells into the portal areas.

There is **no specific treatment for acute hepatitis**, but supportive treatment of the liver as described at the end of this article could be helpful. Continuous administration of i.v. fluids containing dextrose has been recommended (Guglick 1995). If the horse becomes uncontrollable, due to hepatic encephalopathy, sedation will be needed.

Cholangiohepatitis

Cholangiohepatitis is severe inflammation of the bile passages and adjacent liver. It can be caused by an ascending intestinal infection, or migration of parasites such as flukes. In horses ***Salmonella* sp.** is the most likely infection to do this, and the organism is often cultured from the liver. The clinical signs may be more related to colon damage than that in the liver, but liver-derived enzymes are increased, and bilirubin and total bile acid concentrations may be disproportionately high.

A definitive diagnosis would be made by histopathological examination of liver biopsy tissue and culturing a pathogenic organism from a fresh biopsy specimen. **Histologically** there will be bile duct proliferation, inflammatory cells surrounding the bile ducts, and early signs of periportal fibrosis (Thornburg and Kintner 1980; Schulz *et al.* 1989).

In **treating cholangiohepatitis,** an antibiotic to which the organism is susceptible should be given systemically. It seems logical that an antibiotic that would be excreted in the bile would be most beneficial, but this has not been proved. In addition to antibiotics, support of liver function as described at the end of this article and supplying fluid replacement if colitis is present is also necessary.

Chronic active hepatitis

Chronic active hepatitis is a histological diagnosis of a sustained inflammatory process within the liver. It has been described more in man and dogs than in horses and, although some pathologists do not recognise it in the horse, certain cases fit well into this category. Some of the cases are diagnosed histologically as cholangiohepatitis because the inflammatory process is located mainly in the periportal areas (Carlson and Vivrette 1989). The exact aetiology is not known and probably involves multiple agents and pathways. Ascending infections, continuous exposure to toxins and, at least in man and dogs, immune-mediated processes are thought to be involved.

Clinical signs may occur abruptly even though there is histological evidence of chronic liver disease. Horses with chronic active hepatitis present with signs similar to other types of chronic liver disease. Marked depression and neurological signs are common (Carlson 1992). Fever may be present if there is a bacterial cholangitis (Pearson 1996). Icterus may be present, but not as consistently as with some other liver diseases. Some horses have a moist exfoliative dermatitis at the coronary bands due to a vasculitis (Carlson and Vivrette 1989). Occasionally, areas of dermatitis or skin sloughing will be present on other parts of the body. Horses begin to lose weight and signs of concurrent abdominal disease may be present (Carlson 1992). Serum concentrations of liver-derived enzymes and bile acids are increased and will confirm the presence of liver disease. Prolonged BSP clearance times and elevated blood ammonia levels have been described (Byars 1983). It is difficult clinically to differentiate these horses from those with PA toxicity. **For a diagnosis a liver biopsy is necessary and should demonstrate an ongoing but chronic hepatitis.**

On *post mortem* examination the liver is small firm pale tan to green in colour, and the cut surface may have prominent irregular markings. Histologically most of the lesions are present in the periportal areas. There is hepatocyte damage, infiltration of inflammatory cells which are predominantly mononuclear cells into the periportal areas. Bile duct hyperplasia is common, and there is a variable amount of fibrosis in the portal area depending on the duration of the illness (**Fig 7**). **The lesions differ from PA toxicity** since there are no megalohepatocytes seen here; and PA toxicity does not usually have as much inflammatory cell infiltration, but the differences are sometimes subtle.

Many horses with chronic active hepatitis that are detected early before bridging fibrosis occurs can be saved. General treatments to support liver function, as described below, should be used. There have been favourable results following the use of corticosteroids in a number of these cases (Carlson and Vivrette 1989; Pearson 1996). The use of steroids remains controversial and they perhaps should not be used in horses with a fever, or bacteria isolated from the liver biopsy tissue. Initial treatment should be 20–40 mg dexamethasone injected for 3–5 days. If treatment is needed for a longer period of time the horse should be switched to prednisolone at 400–600 mg/day or every other day (Carlson 1992). If a fever is present, bacteria are isolated from the biopsy tissue, or large numbers of neutrophils are present in the portal areas, systemic antibiotics should be used similar to those used for cholangiohepatitis. In some cases a favourable response, improved attitude and appetite, is seen within a few days, but it will take longer for the serum concentrations of some of the liver enzymes to be returned to normal.

Hyperlipaemia, hepatic lipidosis

Hyperlipaemia is probably not a primary liver disease, but a metabolic disease seen during a negative energy balance in which body fat is mobilised at such a rate that it is increased in the serum and deposited in the liver (Naylor *et al.* 1980). The fatty infiltration of the liver can be reversed if the process can be stopped at an early stage. In most cases, this negative energy balance is secondary to other diseases or conditions such as fetal growth, lactation, environmental chilling, work, pituitary adenomas, and febrile diseases, which cause increased metabolism of energy and/or a decreased appetite (Moore *et al.* 1994). It may be worse in an animal with excess fat stores because there is more fat to be broken down. There is an abnormal very low density lipoprotein (VLDL) which contains a greater triglyceride content (Watson *et al.* 1992). Ponies and miniature horses seem to be more susceptible, and it is seen more in pregnant or lactating animals in the winter.

Clinical signs of hyperlipaemia are variable, not specific, and not necessarily related to failure of liver function (Naylor 1982). Depression, weakness and anorexia are commonly observed. Some ponies may develop diarrhoea and, if the disease persists weight loss will be noted. **Diagnosis** is based on finding white-to-yellow opacity of the serum caused by the high lipid content. Triglycerides are increased in the plasma to >5.65 mmol/l (Moore *et al.* 1994). Cholesterol is also increased indicating an increase in lipoprotein. Free fatty acids or nonesterified fatty acid (NEFA), which measures the fat broken down from tissue to be carried to the liver, are elevated above 0.5 mmol/l. Serum concentrations of liver-derived enzymes such as SDH, GGT and ALP, along with bilirubin may be increased as fat is deposited in the liver. Liver biopsy will reveal increased fat content of the liver but is not usually necessary for a diagnosis. ***Post mortem* examination** reveals a fatty liver and sometimes also a fatty infiltration of the kidney. Lesions of the primary disease inducing the negative energy balance can often identified and the carcass is usually icteric.

Treatment must be intensive to save these animals. **Several principals are involved**: treat the primary disease, eliminate the negative energy balance, and decrease the mobilisation of fat at the same time as increasing its utilisation by the tissue. The primary disease,

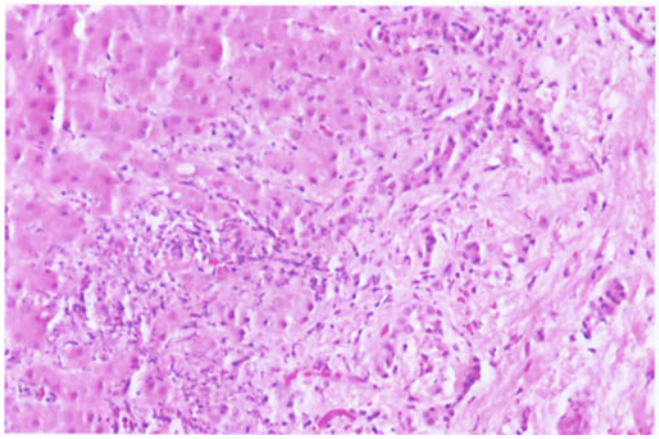

Fig 7: This is an haematoxylin and eosin stained section of liver from a horse with chronic active hepatitis. *Biliary fibrosis is present indicating some chronicity, but there is also an infiltration of inflammatory cells (lymphocytes) indicating active inflammation.*

Fig 8: The Cinnabar moth is used to control tansy ragwort. The caterpillar shown here eats *only Senecio. It will start at the bloom of the second year growth and eat down towards the roots. The population of moths is greatly reduced when the tansy is under control.*

if present, must be addressed immediately or the negative energy balance will continue in spite of treatment. Increased nutrients must be provided. This can be achieved by enteral feeding, putting a gruel that is high in energy into the stomach via a nasal-gastric tube 3–6 times/day. Some commercial preparations are available[3], or home-made mixtures containing glucose or galactose, corn starch, powdered whey and alfalfa meal can be used. In some cases, parenteral nutrition with at least glucose and amino acids is necessary, but giving glucose too rapidly may invoke a metabolic acidosis. This can be treated with bicarbonate, and some of the glucose replaced with galactose.

Insulin is useful because it blocks hormone-sensitive lipase activity in the adipose tissue, therefore reducing the hydrolysis of fat to free fatty acid and glycerol. A dose of 20 iu protamine zinc or ilitin insulin[d] has been recommended for the 200 kg pony (Maas and Pearson 1996). Others have used 1 iu insulin/100 ml parenteral fluid containing 1 kcal/ml. The author has used even higher doses without a problem. Heparin will stimulate the lipoprotein lipase, therefore increasing the peripheral utilisation of triglycerides (McCann *et al.* 1995). Subcutaneous administration of 100–250 iu/kg twice a day is suggested (Naylor 1982). Improvement takes an average of 7 days even with intensive therapy (Moore *et al.* 1994).

Haemochromatosis

Haemochromatosis is a condition in which there is cirrhosis or fibrosis of the liver with **increased iron stores**, primarily in the parenchymal cells of the liver, but also in other organs (Grace and Powell 1974). In horses it appears there is cirrhosis of the liver with secondary iron overload since there are no familial factors, and the total iron binding capacity of the blood is not saturated (Pearson *et al.* 1994). These horses **present with signs of chronic liver disease** and increased levels of liver enzymes and bile acids in the serum. When a liver biopsy is performed, a large amount of brown pigment is observed in the hepatocytes as well as Kupffer cells (Pearson *et al.* 1994) This pigment takes on specific iron stains and the iron content of the liver is increased by as much as 20-fold above normal horses. Serum iron and ferritin may be increased, but the total iron binding capacity is not saturated. Treatment has not been successful in horses, but in man repeated phlebotomy is used to reduce total body iron. Desferrioxamine is given to some human patients to induce a negative iron balance, but its use has not been reported in horses.

Choledocholithiasis

Since the horse does not have a gall bladder, stones in the bile duct are much less common in horses than in man, but have been described (Gerros 1996; Traub *et al.* 1982). The cause of these stones in the horse has not been prove, but alterations in the concentration of cholesterol and other salts in the bile as occurs in man has been suspected. Sometimes foreign bodies or parasites occlude the common bile duct (Gerros 1996). Horses with stones or other obstructions in the bile duct present with intermittent colic, fever, and icterus. Bilirubin, especially direct reacting bilirubin, and bile acids are greatly increased in the serum because they cannot be excreted. Serum activity of some of the liver enzymes such as ALP and GGT may also be increased.

At present, **ultrasonography is the best noninvasive tool for diagnosing cholelithiasis**. Hepatomegaly and bile duct dilation are seen and the echogenicity of the hepatic parenchyma increases when compared to normal horses. The bile ducts are thick and distended, and may appear as dilated channels adjacent to the portal veins. The cholelith itself may be seen as a hyperechoic shadow, or be somnolucent, depending on its composition. Cholelithiasis can be diagnosed by ultrasonography in at least 75% of cases (Reef *et al.* 1990).

At ***post mortem*** **examination** the liver is firmer than normal and varies in colour from red to green-brown. The hepatic ducts and common bile ducts are dilated and may contain calculi. **Treatment** of cholelithiasis by

choledocholithotomy and choledocholithotripsy has had limited success in the horse. Useful dietary or pharmacological treatment has not yet been determined for horses with choleliths.

Treatment of liver disease in the horse

Therapy for liver disease in general will be more successful in acute cases before excessive fibrosis develops and in cases with livers still capable of regeneration. The liver has a great capacity to regenerate, but must have the basic lobular architecture preserved. Fibrosis which bridges from lobule to lobule will eventually prevent regeneration and antimitotic toxins, such as pyrrolizidine alkaloids, prevent regeneration.

As with most diseases, **the first principle is to eliminate the cause**, whether it is a toxin, infectious agent or metabolic disturbance. However, eliminating the cause after irreparable damage or inhibition of regeneration has occurred cannot salvage the case. Some horses with hepatic encephalopathy may need to be **restrained chemically if they are violent or excitable**. Xylazine or Acepromazine is effective in most cases, but the **dose may have to be reduced because the liver is incapable of metabolising the drug. Diazepam should be avoided** because it enhances the effect of gamma aminobutyric acid on inhibitory neurons and its effect does not last very long (Divers 1997). Physical rest to lower the metabolic rate is also important.

One of the most important steps is to manage the diet. Adequate calories must be provided so that the liver is not overwhelmed with gluconeogenesis or glycogen breakdown. More frequent feedings with readily digestible carbohydrates may help keep the blood glucose levels up. Some cases may need i.v. glucose administration by slow continuous drip if the blood glucose level are reduced. Protein should be limited, but of high quality, so the amino acids are not used for energy which **increases the amount of ammonia produced**. Excess protein may lead to hyperammonemia and hepatic encephalopathy, but some protein is needed for regeneration of the liver and to produce lipoprotein to mobilise fat from the liver.

Diets high in branch chain amino acids, leucine, valine, and isoleucine could improve the attitude of horses with hepatic encephalopathy, but may not increase survivability. Pastes containing branch chain amino acids have been recommended or diets prescribed that contain feedstuffs that are high in these amino acids compared to aromatic amino acids (Gulick *et al.* 1980). Some feeds high in branched chain amino acids are **Sorghum, beet pulp, bran** and **Milo**. Since there may be increased oxidation supplying additional vitamin E or selenium could be beneficial. Fat is not usually a problem in large herbivores, but should not be increased greatly to supply energy, because an excess would need to be metabolised by the liver and could lead to fatty infiltration.

Reducing the amount of ammonia produced and absorbed has been a concern in most animals with liver disease. In small simple stomached animals that do not depend on bacterial fermentation to supply a large portion of their energy, neomycin is given *per os* (Divers 1997). Although recommended at 30 mg/kg bwt *per os* 4 times a day, it has not been scientifically tested in the horse, and could inhibit bacterial digestion in the caecum and colon, and **results have been disappointing**. **Lactulose** is reported to acidify the colon and reduce ammonia absorption in most species. In healthy horses 333 mg/kg bwt significantly reduced the concentration of blood ammonia, even though the faecal pH was not reduced significantly (Scarratt and Warnick 1998). Metronidazole at 15 mg/kg bwt *per os* 4 times a day can also be used to decrease ammonia producing bacteria.

Colchicine and cyclosporine have been used to suppress cirrhosis of the liver in man and dogs (Leveille and Arias 1993) but have not been adequately tested in horses and have proved to be ineffective in cases of pyrrolizidine alkaloid toxicity. Pruritus in man due to bile acid build-up in biliary cirrhosis patients has been treated with rifampin, but there are no reports of its use in horses (Ghent and Carruthers 1988). Anabolic steroids, such as Boldenone undecylenate[5], have been proposed but efficacy not tested. In cases of cholangiohepatitis where bacteria are involved, antimicrobial therapy is indicated. Some cases of chronic active hepatitis respond to corticosteroid therapy. Other complications, such as ascites, disseminated intravascular coagulation (DIC) or renal failure of cellular structure, especially lipid membranes, by peroxides when liver disease is present, may need to be treated symptomatically.

Prevention of liver disease may be as important as therapy since treatment of some liver conditions, such as Pyrrolizidine alkaloid poisoning, is not very rewarding. Several steps can be taken to reduce the exposure of horses to hepatotoxic plants. Senecio (tansy) can be controlled by cultivation, herbicide sprays, pasturing with sheep who are only slightly susceptible, or using biological control such as the cinnabar moth (**Fig 8**). Some of the other plants may not be consumed at toxic levels if there is adequate forage available. Mares should not be given tetanus antitoxin after foaling; it is better to vaccinate them with tetanus toxoid during pregnancy. The veterinarian should make sure toxic doses of drugs, which could damage the liver, are not used for long-term treatment of other diseases.

Manufacturers' addresses

[1]Becton Dickinson, Rutherford, New Jersey, USA.
[2]Sherwood Medical, Ballymoney, Northern Ireland.
[3]Ken Vet, Ashland, Ohio, USA.
[4]Lilly, Indianapolis, Indiana, USA.
[5]Solvay, Mendota Heights, Minnesota, USA.

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