## Chapter 5

# Ruminant Liver Disease

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## Introduction

The liver remains comparatively inaccessible to the clinician, despite advances in ultrasonography and contrast radiography, and this is particularly true in large animals, in which only the longest arms can palpate a small portion of the liver during rectal examination. This inaccessibility, coupled with the fact that clinical signs of liver failure often take the form of disorders of skin, blood or nervous system, explains why liver disease is often overlooked by veterinary clinicians, or mistaken for disease of some other system.

## What Should a Field Veterinarian Know About Liver Form and Function?

The liver is a large brown organ whose **FORM** (**size**, **shape** and **color**) is relatively constant for a given species. If clinicians are to recognize liver disease during field necropsy examinations, they must be confident about the gross features of normal liver. Likewise, knowledge of the range of **FUNCTIONS** carried out by the liver will reduce the chance of misdiagnosing significant liver disease.

**Size:** "Normal" liver mass is in fact the outcome of a balance between several factors. It has long been known that removal of more than half the liver mass by surgery or disease will result in vigorous regenerative attempts to replace the missing tissue. Regeneration will cease when the balance between these factors has been re-established, so there must be finely-tuned feed-back loops which regulate total liver mass.

The first of these factors is the animal's state of **nutrition**: severely malnourished animals of all species will have small livers, since the above-mentioned reserve capacity of the liver means that a considerable proportion of the functional hepatocyte cytoplasm can be catabolised as an emergency source of nutrition during severe starvation or debilitating illness. The second important factor is the presence in the portal venous blood of normal concentrations of **hepatotrophic factors** from the gut and pancreas. Some of these factors are absorbed nutrients from the gut, so some of the above-mentioned atrophy of starvation falls into this category, but there are in addition some humoral factors such as insulin and other hormones which help maintain normal liver mass. If their concentration in incoming blood falls (as happens in porto-systemic shunting), then the liver will undergo atrophy. Thirdly, normal liver produces **chalones,** and these substances keep mitotic activity of

hepatocytes in check. So if part of the liver is lost, circulating chalone levels decrease and this has the effect of stimulating hepatocellular proliferation. Fourthly, liver size may be uniformly increased by certain diffuse pathological processes which do not cause increase in hepatocyte **numbers.** The most common of these is **fatty liver,** but there are other diffusely distributed conditions such as generalised **hepatitis**, **diffuse neoplasia** and **amyloidosis**.

**Shape:** The most common cause of distortion of the liver is uneven deposition of scar tissue, or fibrosis. This can be due to a wide variety of infectious, parasitic and toxic insults, and when it is severe, results in compression of hepatocytes and restriction of blood flow to them. This has the effect of diverting blood and hence hepatotrophic factors away from the affected parenchyma, which in turn results in atrophy of this part of the liver, so the distortion is accentuated. When much liver has been lost in this way, circulating chalone concentrations diminish to the point where surviving hepatocytes are stimulated to proliferate. Because of the constriction by scar tissue and the uneven blood supply, uniform proliferation of hepatocytes is impossible, so the phenomena of nodular regeneration and lobar hypertrophy are seen.

**Colour:** Liver parenchyma in most species is normally a deep reddish-brown colour; this is due to the presence in the hepatocytes of high concentrations of oxidative enzymes such as cytochrome oxidase. These enzymes are also responsible for the brown colour of the renal cortex. Normal concentrations of cytochrome oxidase can only be maintained if the hepatocytes are healthy and have access to an adequate blood supply. Thus **pallor** of the liver is a very common observation in livers damaged by a wide variety of insults. Generalized pallor of the liver can also be caused by dilution of the enzymes by large amounts of **fat** in the cells, or by severe infiltration of the liver by inflammatory or malignant cells, which contain few oxidative enzymes. Note the considerable overlap between causes of diffuse liver **enlargement** and liver **pallor**.

The liver carries out a huge number of **FUNCTIONS** that may be broadly classed as: **synthetic** and **secretory** (*eg* production of glucose, bile acids and albumin and many other soluble macromolecules), **transformations** (*eg* oxidation, hydrolysis and conjugation of dangerous endogenous and exogenous compounds), and **excretory** (*eg* elimination of bile pigments, phylloerythrin, etc). What is critical to an understanding and rational management of liver disease is that the liver possesses a large **reserve** of live function. The most often-quoted example of this is the fact that 70% of the organ can be removed without causing liver failure (see below).

## What Must a Field Veterinarian Know About Failure of Liver Function?

Clinical signs may follow failure of any of the above liver functions. Unfortunately, these clinical signs will be very varied and may not be immediately referable to the liver by the casual observer. For example, failure of the liver to convert ammonia to urea (for excretion by the kidneys) will result in **nervous signs** due to the toxic effects of ammonia on the brain. These nervous signs may be exacerbated by the failure of the liver to remove other neurotoxic substances from the portal blood following their formation in and absorption from the lower bowel. These substances, secondary and tertiary amines and the like, are produced by bacterial action in normal animals and are removed from the portal blood by one passage through the normal liver. This prevents them from reaching the brain, where they may act as false neurotransmitters and cause a variety of nervous signs ranging from depression and somnolence to mania and generalised convulsions.

Failure of the liver to excrete/secrete bile pigments, bile acids and bile salts is called **cholestasis**. **Intrahepatic cholestasis** is the term used when the failure is at the hepatocellular level (failure of bilirubin conjugation, non-specific hepatocyte degeneration/death, etc). It produces the clinical phenomenon known as **icterus** (**jaundice**), which is yellowish discoloration of tissues by bile pigments. The intensity of this discoloration is dependent on two factors: firstly the *severity* of the cholestasis (quantitatively, how much bile pigment is being retained), and secondly, the *duration* of the cholestasis. It takes several days at least for tissues levels of bile pigments to equilibrate with those of the plasma. This may explain why an animal that has been suffering moderately severe cholestasis may be much more yellow than an animal which died after a short episode of complete liver failure.

Icterus can of course also be caused by **obstruction** of the extra-hepatic biliary vessels, and by the overproduction of bile pigments caused by **severe haemolysis**. Obstruction can be detected by palpation and expression of the biliary apparatus (provided you remember to do it before removing the liver!), while haemolytic disease is recognized by the presence of haemoglobin-stained kidneys and urine (in the case of intravascular haemolysis), or by significant splenomegaly in extravascular (sequestration) haemolysis. The gallbladder bile in both types of haemolysis should be deep greenish-black with excess bile pigment and will be thick, dark and even granular in texture. In animals suffering from intra-hepatic cholestasis, insufficient bile pigment reaches the biliary tract, so gallbladder bile is abnormally pale, and photosensitivity is more likely.

Failure of a damaged liver to remove phylloerythrin from the portal blood has particular significance for herbivores. This compound is produced in the digestive tract as a breakdown product of chlorophyll. It is photodynamic, which means that it is changed into very reactive chemicals by the action of visible light. So, after it has had time to

accumulate in pale, sparsely-haired skin which is exposed to sunlight, it will cause vascular and epidermal damage known as **secondary photosensitisation**. Since phylloerythrin excretion involves the same pathways as bile pigment excretion, **icterus** (jaundice) is a common (but not necessary) accompaniment of secondary photosensitivity. Because jaundice may be very mild in photosensitised animals, it is possible to mistakenly exclude liver damage from a diagnostic list because an animal with eczema of exposed skin has no clinical jaundice. Such animals, however, will always have some elevation of plasma bilirubin and/or bile acids, so these parameters must always be measured in such cases. If they are within normal limits, then consideration may be given to the possibility of **primary photosensitivity**, in which some component of the diet is directly photodynamic and for which there is no effective hepatic detoxification/excretion mechanism (hypericin intoxication, for example). Primary photosensitivity may also be caused by the accumulation of substances such as porphyrins due to inherited errors of metabolism (porphyria).

In animals suffering from haemolytic jaundice there will usually be no photosensitisation, since phylloerythrin is still being excreted, while photosensitivity is expected in the other causes of cholestasis.

If liver damage is sudden and severe, an early clinical sign may be **haemorrhage**. In acute necrotizing liver damage, a large proportion of the animal's blood volume is suddenly exposed to several $m^2$ of damaged parenchyma and sinusoidal endothelium. This will trigger the usual thrombotic cascade, which will in turn initiate compensatory **fibrinolysis**. The end result of this sequence will be rapid consumption of clotting factors which will be all the more profound because most of these are synthesized in the liver in the first place, and a severely damaged liver will not be able to produce them at the normal rate. Thus hemorrhagic diathesis will occur terminally in such animals, and be reflected at necropsy by widespread ecchymotic and petechial haemorrhages that may distract the observer from changes in the liver itself, which macroscopically may well be less spectacular.

Liver failure may be manifested by **hypoproteinaemic oedema**, due to failure of synthesis of albumin and other plasma proteins by the liver. This will result in oedema of dependent loose skin (submandibular and brisket). Hypoproteinaemic oedema, however, can also be caused by haemorrhage such as that caused by severe internal parasitism, and since oedema can also be induced by vascular permeability changes and by circulatory failure, oedema is just as likely to distract the clinician from a diagnosis of liver failure.

It is most important is to remember the huge **functional reserve** of the liver, which means that, once liver failure is clinically apparent, a huge proportion of liver must have been damaged or destroyed. This must always lead to a grave prognosis. Sometimes a favourable outcome may be hoped for when only one function is impaired, such as excretion of bile in toxic cholestasis, since the other important functions of the liver are still working, and removal from the toxin may allow the organ to recover.

## Responses of The Liver to the Various Classes of Liver Insult

There are four fundamental disease processes which may affect the liver as well as any other tissue. These are:

- **developmental (congenital etc) abnormalities**,
- **inflammation (acute, subacute and chronic)**, and
- **degenerative disease (includes toxic insult and necrosis)**,
- **proliferative/neoplastic disorders**.

It is usual for one more of the above basic disease processes to be combined with any of the others. Thus there is nearly always some **degeneration** (including necrosis) associated with **inflammation**, but it is helpful, when confronted with a confusing combination of gross changes in any organ, to at least try to identify the primary process and eliminate the least likely processes.

Sometimes it is difficult to separate true disease from physiological response; for example, the proliferation that takes place in a tissue as a result of increased demand, such as removal of part of the organ, may be regarded as beneficial and hence physiological.
Applying each of these basic disease processes to the liver, the following comments may be made.

### Developmental abnormalities

Developmental abnormalities of the liver have little or no clinical significance, unless they are the rare ones that result in failure of bile secretion (*e.g.*, biliary atresia). In this sense the liver differs from organs like brain, heart and eye, in which developmental anomalies often have catastrophic effects. The liver has no specialized substructure, so (unlike brain or heart) a few isolated malformations may not impair function at all, since any part of the liver can take over the function of a damaged portion.

### Inflammation

The processes of inflammation are essentially the same in liver as they are in other tissues. As far as **cause** is concerned, the most common stimulus is the lodgment in the liver of bacteria (or their spores) that have passed through the lining of the alimentary tract. This an extremely common event: probably the best example is the formation of liver abscesses as a result of bacteria getting into the portal vein blood as a result of rumenitis in ruminants on high grain diets. Bacterial infection is discussed further in a later section.

Inflammatory lesions in the liver may be **focal** or **diffuse**. In either case there will be increase in liver size (focally or overall) in the acute and the subacute stages: later with chronic inflammation (scarring) there may be shrinkage.

### Degeneration

Degeneration of the liver is of more importance since it includes **toxic** and **metabolic** diseases, which are of more clinical significance in ruminants. As mentioned above, degenerate liver usually becomes paler, unless the problem is **congestion** (see below), in which case of course it is dark red, especially in the early stages. The palest liver is produced by severe **fatty change**; this may be due to toxicity or to endogenous metabolic disorder. Severe fatty liver is always enlarged; this is one of the few examples where an organ becomes swollen as a result of metabolic or degenerative disease.

When a large proportion of the liver is damaged by degenerative disease, the special feature of the liver, its regenerative potential, comes into play if the animal survives long enough. This produces irregular, often nodular swellings separated by fibrous tissue; the former can sometimes lead the observer to suspect neoplasia (see below)

### Neoplasia

Neoplasia of the liver in ruminants in relatively rare; as in other species it can arise in the liver itself (from hepatocytes or from biliary tract) or metastasise to the organ from elsewhere. Metastatic disease most commonly originates from primaries in the gut, since the effluent blood from the entire alimentary tract must pass through the liver. It should be remembered that primary neoplasms may be much smaller than their metastases; this applies particularly to secondaries in the liver, which seems to permit their more rapid growth.

Mention has been made above of the fact that a scarred, shrunken liver may develop nodular swellings in its attempts to regenerate. These nodules can mimic certain forms of neoplasia. This confusion can be resolved by determining whether the liver mass overall is greater or less than normal: a nodular scarred liver will always be smaller overall than a normal liver (no matter how big the regenerative nodules), while neoplastic tissue added to liver will increase its size.

## Gross Evidence of Disordered Liver Circulation

Because the liver is such a large organ and contains such a large volume of sinusoidal blood channels, it is peculiarly prone to respond to changes in blood volume and pressure. In fact the liver is a more important short-term regulator of blood volume than is the spleen.

The liver responds in a rather predictable way to **chronic congestion**, whether this be due to **right-sided heart failure**, or to **compression of the posterior vena cava**. Blood flow through the liver slows dramatically as the hepatic venous pressure rises relative to the arterial and portal vein pressures. In this semi-stagnant situation, the

hepatocytes and sinusoids that are furthest from the incoming blood undergo atrophy and dilatation, respectively, while surviving hepatocytes closer to the portal triads accumulate fat and lose cytochromes (see above) and become pale. The effect of the resulting contrast in colours is that the cut surface of the liver assumes a characteristic reticulated pattern that has been likened to the cut surface of a nutmeg. However, this so-called "**nutmeg liver**" pattern (also known as **acinar pattern**) is not pathognomonic for chronic liver congestion unless it is obviously more pronounced in the subcapsular parenchyma than in the deeper parts of the organ. A more uniform nutmeg pattern can be seen in livers that have been acutely damaged by hepatotoxins (see below). Chronically congested livers usually have a slightly thickened, slightly irregular pale gray capsule, sometimes with fresh or organizing fibrin adherent to it, and there is usually a great excess of watery clear abdominal fluid (**ascites**). As soon as these features are noticed at necropsy, great care should be taken in examining the heart, since congestive heart failure is by far the most common cause of passive congestion of the liver. However, sometimes in cattle a large hepatic abscess or a tumour may cause passive congestion by compressing the posterior vena cava as it passes through the dorsal part of the liver.

Sometimes at necropsy of young animals which have been chronically unthrifty (sometimes showing nervous signs as well), the liver will be very noticeably smaller than normal. If at the same time it is normal in colour, consistency, shape and texture, then there is the possibility of a congenital porto-systemic venous shunt. These are more commonly associated with companion animals but they have been found in cattle. The liver is uniformly small because it has been perfused with lower than normal concentrations of hepatotrophic factors. If the possibility of a porto-systemic shunt is not recognized early in the necropsy, the shunt will probably be destroyed in the subsequent dissection and the diagnosis will not be able to be confirmed.

## Biochemical Assessment of Liver Function and Damage

The significance of changes in circulating levels of bilirubin and bile salts has been discussed above.

There are several intracellular enzymes that are only found in significant concentrations in hepatocytes of the various domestic species, therefore when their levels in plasma are elevated, there is a likelihood of significant active liver disease. Unfortunately, different enzymes are "liver-specific" in this manner in different species. Alanine aminotransferase (ALT) for example, while widely used as an indicator of liver damage in carnivores, is essentially useless for this purpose in ruminants, whose hepatocytes are poorly furnished with it. Arginase and sorbitol dehrydrogenase are more useful liver-specific enzymes in ruminants, but their assay is a bit more complicated and expensive.

Gamma glutamyl transferase (GGT) is concentrated in canalicular and bile duct membranes; also in renal tubular epithelium. GGT levels in plasma are usually elevated in ruminants suffering from cholestatic liver disease, and such disease should be strongly suspected when there is concomitant elevation of plasma bile acids or bilirubin.

Clearance of injected exogenous chemicals (usually dyes such as bromsulphthalein and indocyanine green) can give accurate assessment of liver function, but these procedures are rarely appropriate for clinical practice because of their expense and time needed.

### How about the use of liver biopsy?

Liver biopsy of ruminants is a relatively simple procedure. The equipment is simple *(see Fig.1)* and can be made from stainless steel rod and tube by local workshops. Appropriate anaesthesia is easily achieved by using paravertebral local anaesthethic injection behind ribs 10-13, with xylazine sedation as necessary. A cruciform stab incision through the skin will facilitate insertion of the trochar-cannula combination. While in the animal, the trochar must be kept within the cannula at all times to lessen the chance of pneumothorax occurring. Rapid removal of the cannula-retracted trochar combination will provide sufficient negative pressure to keep the liver core within the cannular lumen. Retrieval of good cores will be facilitated by sharpening the cannula before use, and remembering to twist the cannula when advancing it into the liver. Livers that are diffusely fibrotic or scarred may yield hardly any liver tissue, but in these cases, experienced operators will recognize the altered texture of the liver, and at least a diagnosis of liver fibrosis will be indicated.

The advantage of a 7mm core liver biopsy is that it provides enough tissue for good histological assessment, as well as enough for biochemical analysis (Cu, etc)

## Insights Into Some Specific Liver Diseases of Ruminants

### Acute hepatotoxicities

There are widely differing sources of hepatotoxins which are acutely fatal for ruminants. These range from the cyanobacteria (blue-green algae) through numerous genera of higher plants, to the larvae of certain insects, and these will be covered elsewhere in this course.

While these substances range in chemical formulae from atractylosides to toxic octapeptides, the clinical signs and pathology of these intoxications are remarkably similar; almost stereotyped. Attention should be drawn to the mysterious condition known as "acute bovine liver disease" in the southern Australian states: it occurs unpredictably and in outbreak form in both dairy and beef cattle, and sheep seem not to be affected. Rough Dog's tail grass (*Cynosurus echinatus*) has been loosely implicated:

charges have been laid but there have been no convictions to date. This condition is interesting for the pathologists because it is one of the rare acute hepatopathies in which periportal tissue is preferentially destroyed, and, while regeneration of destroyed liver cells can occur in survivors, cholestasis is more severe and prolonged than it is after other acute hepatoxicities in which periacinar tissue is targeted.

**Clinical signs** rarely include jaundice or photosensitivity because of the acuteness of the disease, although these signs may develop later in surviving affected animals. The most severely affected animals are either found dead, or show an unpredictable range of clinical **neurological signs** such as generalized convulsions, aggression, tremor and stupor; these signs may be exhibited alternately and unpredictably in the one affected animal. If a blood sample is drawn from such a case, the bleeding and coagulation times should be carefully measured, since **clotting factors** are usually exhausted in these cases (see above). Recovery is most unusual in a ruminant showing bleeding disorder and nervous signs due to acute liver damage: the animal is usually dead by the time serum enzymology has been performed. This one condition in which liver biopsy as described above, while likely to give a diagnosis, will probably shorten the animal's life, since fatal haemorrhage is likely due to the bleeding disorder. But one can argue that the animal would very likely have died, anyway.

So the clinical signs are fairly non-specific. Clinical chemical results will include spectacular elevations in levels of liver-specific enzymes such as arginase and sorbitol dehydrogenase, but these results will probably come too late for clinical diagnosis, so it is most important for the field veterinarian to be able to recognize the **macroscopic** features of acute hepatotoxicity **at necropsy** in the field. The carcass is unlikely to be jaundiced (see above), nor will there be severe photodynamic dermatitis. The carcass overall will often be in good nutritional condition because the animals which ingest most toxin will often be the dominant members of the herd. There will usually be petechial and ecchymotic haemorrhages on serosal surfaces (especially the epicardium). There will be slight excess of peritoneal fluid; yellow, clear and with some free fibrin in it. The liver itself may be relatively normal in gross appearance, although a distinct **acinar pattern** will nearly always be evident on cut surfaces. Often it is swollen and dark red due to the blood trapped in the corrupted sinusoids. The gall bladder wall will usually be somewhat oedematous.

Only rarely will the gross inspection be diagnostic; the liver damage should always be confirmed by the submission of liver samples for histopathological examination. Brain should be similarly examined, especially in cases that showed nervous signs before death. Liver failure in ruminants often leaves characteristic histological changes in white matter tracts, which can be helpful in cases where the liver has autolysed. The rumen may contain recognizable fragments of the culprit ingesta, but this is rare because rumenal fermentation makes botanical recognition extremely difficult, even for experts.

If acute hepatotoxicity is suspected on the basis of the above case features, then immediate efforts should be made to deny surviving stock access to the suspected source.

Not much can be done to treat affected animals, other than supportive provision of shade, shelter and fluids.

## Chronic hepatotoxicities

Once again, the range of chemicals capable of causing chronic liver damage in ruminants is large, but the range of clinical features shown by affected animals is relatively small. The most helpful of these is **photosensitivity**, or photodynamic dermatitis (see above). If the death rate is low but photosensitivity appears suddenly in 20% or more of the flock, then cholestatic liver disease is very likely, the rare exceptions being the ingestion of plants such as ***Hypericum perforatum*** (containing a **primary photosensitiser**; see above) or the even rarer cases of **congenital porphyria**.

### Chronic non-fatal hepatotoxicity

Liver disease that is primarily cholestatic will not necessarily be rapidly fatal, since the other vital liver functions may be relatively unimpaired. The classic example of this is poisoning by Lantana camara. It is possible to treat affected animals with activated charcoal and fluids to remove the toxin (lantadene A) from the alimentary tract, but it is expensive. The reason for the success is that these livers are not fibrotic, so the organ can recover.

Similarly, poisoning by steroidal sapogenins may not be fatal unless neglected cases die from the secondary effects of severe photosensitivity (blindness, thirst, starvation, etc). These cholestatic compounds have been shown to be potent cholestatic agents, causing primary inhibition of bile salt excretion and as a consequence of that, phylloerythrin retention. Antemortem diagnosis may be made on liver biopsy if the liver contains the characteristic sapogenin crystals associated with cholangitis, but it is important to remember that, in may cases, clinical photosensitivity precedes the crystal-associated cholangiopathy. Careful appraisal of grazing history, aided if possible by total plasma bile acid determination, may be needed to make a provisional diagnosis.

At necropsy the liver looks surprisingly normal. Gallbladder bile should be collected for examination for the characteristic rhomboidal crystals of sapogenin, which can be provisionally identified microscopically.

It is now emerging that steroidal sapogenins can be elaborated by a wide variety of plants, some of them valuable pasture species such lucerne, in grasses in the genera Panicum, Brachiaria and Pangola, and in weeds like Tribulus terrestris. Because the conditions that favour such accumulation are poorly understood, outbreaks of hepatogenous photosensitivity in animal grazing these plants tend to be unpredictable.

Sporodesmin toxicity ("facial eczema"), on the other hand, can be predicted with a little more accuracy, since the botanical substrate and weather conditions predisposing to the overgrowth of Pithomyces chartarum are rather better understood.

Since the biliary tract, rather than the hepatocyte, is the principal target for sporodesmin, it is usual for affected animals to show signs of cholestasis (photosensitivity) without other signs of liver failure, as for sapogenin and Lantana poisoning. Unlike the latter conditions, at necropsy one expects to see macroscopic oedema/fibrosis of the biliary tract. Since chronic cholangitis eventually causes left lobe atrophy in the livers of ruminants, a sheep or bovine liver in which the right lobe is enlarged while the left is pale, thin, tough and small should always signal the possibility of chronic sporodesmin poisoning or chronic liver fluke damage (or both).

***Chronic fatal hepatotoxicities***

*Pyrrolizidine alkaloid (PA) poisoning:*

Cattle are much more susceptible to these alkaloids than are sheep: in Australia Echium plantagineum is known as "Paterson's Curse" by cattle graziers, whereas sheep owners call it "Salvation Jane", because it can sustain sheep in times of nutritional stress. The age of exposed animals is also critical to the outcome. The genera Senecio, Heliotropium and Crotolaria are more widely recognized throughout the world as the most important sources of this class of toxin.

By the time affected animals show specific clinical disease, they are running out of reserve total liver function, so clinical signs may include nervous signs as well as photosensitivity. But the syndrome may be only a vague and non-specific problem of depression, ill-thrift and wasting. When such cases die or are killed for necropsy, the liver may be quite unspectacular (no marked scarring or nodularity). It will, however, be small, its capsule thick and grey and the cut surface tougher than normal and mottled and greenish-yellow. The atrophy is due to a combination of malnutrition and the antimitotic effect of the toxin. Because of the atrophy and diffuse fibrosis, there will usually be portal hypertension due to impedance of portal vein flow. This will produce sometimes spectacularly severe ascites, and oedema of mesenteries and bowel wall. Lower bowel oedema is thought to be responsible for diarrhoea, and tenesmus (sometimes leading to rectal prolapse) which may be part of the clinical syndrome.

The histopathology of affected livers is fairly characteristic, so this condition may sometimes be diagnosed by liver biopsy if necropsy is not an option. However, it should be noted that the pathology of aflatoxin poisoning (see below) can be essentially identical to that produced by pyrrolizidine alkaloids

A major advance in diagnosis of PA poisoning has been the ability to detect bound pyrroles in liver and blood for at least several weeks after exposure has ceased (provided you can find a lab which is prepared to do the test in this era of economic "reform").

(see below for association between PA and chronic copper poisoning in sheep)

*Phomopsin poisoning:*

This mycotoxin is traditionally associated with mouldy lupin stubble, but other substrates may be the source. The clinical syndrome and gross pathology can almost completely overlap that of PA poisoning, but fortunately there are usually characteristic histological changes (bizarre mitoses) in the liver which promote the use of liver biopsy for diagnosis in live animals (see below for association between phomopsin and chronic copper poisoning in sheep).

*Aflatoxin poisoning.*

This mycotoxicosis produces fairly non-specific changes in the liver which to a large extent overlap those produced by PAs. The range of clinical signs is pretty well indistinguishable in all these chronic fatal hepatotoxicities. In more acute cases of aflatoxicosis it is possible to detect the toxin in the liver for quite a few days after exposure, but the techniques involved are sophisticated and expensive (GCMS). Aflatoxicosis is traditionally associated with mouldy peanuts, but it must be borne in mind that substrates as diverse as citrus pulp and milk replacer have been implicated as sources of the mycotoxin for cattle.

*Chronic copper poisoning:*

Sheep are much more susceptible than cattle to this intoxication (in contrast to PA poisoning), and there are marked differences in breed susceptibility. The pathogenesis involves slow asymptomatic accumulation of copper in hepatocytes, followed by an acute haemolytic crisis as the copper-loaded liver self-destructs and releases enough copper into the plasma to destroy erythrocytes. The crisis as far as the liver is concerned occurs when the death rate of copper-loaded hepatocytes exceeds their replacement by mitosis: until then, the new hepatocytes manage to take up the copper spilling from dying hepatocytes. Understandably, exposure to the anti-mitotic effects of pyrrolizidine alkaloids or phomopsin (lupinosis) will bring forward the crisis. So, although the disease is a chronic intoxication, it usually presents as an acute syndrome or as sudden death.

Because death is due to a combination of liver failure and severe haemolytic disease, the classic gross findings at necropsy are severe jaundice combined with the presence of reddish-brown urine in the bladder. The kidneys will be deeply stained throughout with haemoglobin. The most revealing feature of the liver grossly is the presence in the gall bladder of dark, concentrated bile. Photosensitisation does not have time to develop.

The above findings in members of a flock of British breed sheep would justify a provisional diagnosis of chronic copper poisoning and institution of control measures while awaiting laboratory confirmation of the diagnosis, since cohort animals must be at risk. Samples for diagnosis must include whole kidney, since only after the haemolytic crisis do kidney copper levels rise, whereas clinically healthy sheep in the same flock may have higher liver copper concentrations because they have not yet begun to tip the copper out into the blood.

### What about diagnosing significant liver fluke infestations these days?

Diagnostic enzyme-linked immunosorbent assay (ELISA) techniques have been developed to detect antibodies against *Fasciola hepatica* in serum of sheep and cattle. These tests have improved in specificity and sensitivity, to the point that they should become a useful tool for determining the fluke status of herds and for control of the disease.

Determining the significance of liver damage by fluke at necropsy is difficult, particularly in cattle. Many a prime beast has come to slaughter with a frightful-looking fluky liver. The organ may be dramatically distorted with the left lobe reduced to a fibrotic leaf-like appendage and the right hugely hypertrophied in compensation, and bile ducts thick, tough and partly calcified. Yet this animal passed ante-mortem inspection and its carcass makes profitable product. Severely fluky sheep, on the other hand, are more likely to be unthrifty and anaemic.

### Echinococcosis (hydatids)

A recent abattoir survey of bovine offal in Queensland revealed that hydatid lesions were the most common cause of downgrades and condemnation of livers. Since these hydatids were without exception sterile and degenerate, they pose no health risks to man or pet, yet the loss borne by the industry is considerable. Control seems unlikely as foxes seem to be involved, yet not much work seems to be done on the problem. The gross pathology in the liver can mimic cancer and tuberculosis and actinobacillosis, which causes diagnostic confusion.

### Bacterial liver disease

It seems that bacteria are perpetually gaining access to the portal blood from the gut. This is understandable, given the masses of organisms separated from intestinal capillaries by only a few cells, most of which are dedicated to absorbing stuff and some of which are actively involved in sampling particulate antigens from the bowel lumen (M-cells of the Peyers patches).

So bacteria often attack the liver and liver abscess has been mentioned above. The most dramatic examples are the clostridial infections black disease (necrotic hepatitis) and bacillary haemoglobinuria. The spores of *Clostridium novyi* or *C. haemolyticum* are filtered out of the sinusoidal blood in the liver and presumably remain in Kupffer cells until activated by liver damage. The resulting focus of necrotic liver has a yellow crumbly appearance that may easily be missed: the most telling feature is the intense red line that marks the edge of the lesion. The necrotic foci can be remarkably small and easy to miss unless the liver is sliced diligently: I once missed one hiding under the gall bladder. If the triggering agent was fasciolosis, then of course that pathology may confuse things.

The filtering role of the sinusoidal macrophages suggests that the liver will always be a good site for sampling in cases of suspected generalised bacterial infection. Well, yes; but remember that post-mortem invaders have been looking forward to the time when they can race up the portal vein from the gut and revel in the riches of the liver, so appropriate caution must be applied to interpreting results of bacterial culture of the liver, particularly when the post-mortem interval is more than a couple of hours.

### Fatty liver

The commonest abnormal finding in ruminant liver is pallor of greater or lesser severity caused by triglyceride (fat) accumulation in hepatocytes. The causes of fatty liver range from poor circulation and severe metabolic upset (*e.g.* ketosis) to physiological increase in lipid processing which is seen in heavily-lactating dairy cows or heavily pregnant cattle and sheep. In these latter circumstances, fatty liver is really physiological, rather than a pathological manifestation of true clinical disease. Unfortunately for the field or abattoir veterinarian, it is often difficult to differentiate confidently between the physiological and pathological states.

The most spectacular cases of fatty liver in ruminants are seen in **ketosis**, whether this be primary or secondary. But any condition that stops a fat ruminant from eating will lead to increase in net triglyceride in the liver, since it is much easier to get mobilized body fat into the liver than it is to export it as lipoprotein. So some degree of fatty liver will be seen in any animal whose liver function is compromised, since only mild disorder will turn the liver into a bottleneck as far as fat metabolism is concerned. It follows, therefore, that fatty liver is a common and usually non-specific finding at necropsy, particularly in high-producing adult females.

**Ovine white liver disease** is often a disease of younger sheep, which seem to require more cobalt/vitamin $B_{12}$ than do older animals. The cause of this condition has been controversial because some outbreaks have been associated with sudden change in feed, and it was thought that some nutritional/toxic factor might be involved as well. That may be the case sometimes, but the condition seems to have been reliably reproduced experimentally by simple induction of cobalt deficiency. The livers are pale and fatty, and in chronic cases become quite firm as delicate fibrosis is initiated. This can be helpful in gross diagnosis, since fatty liver is usually more friable than normal.

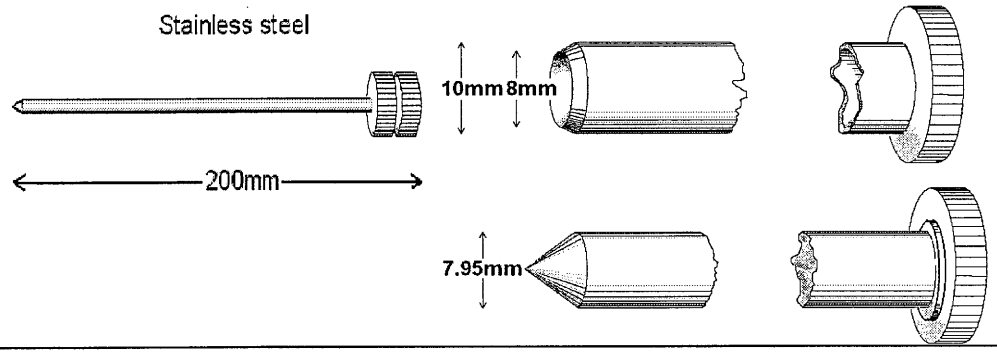


**Fig.1 Specifications for trochar and cannula for liver biopsy of cattle and sheep**

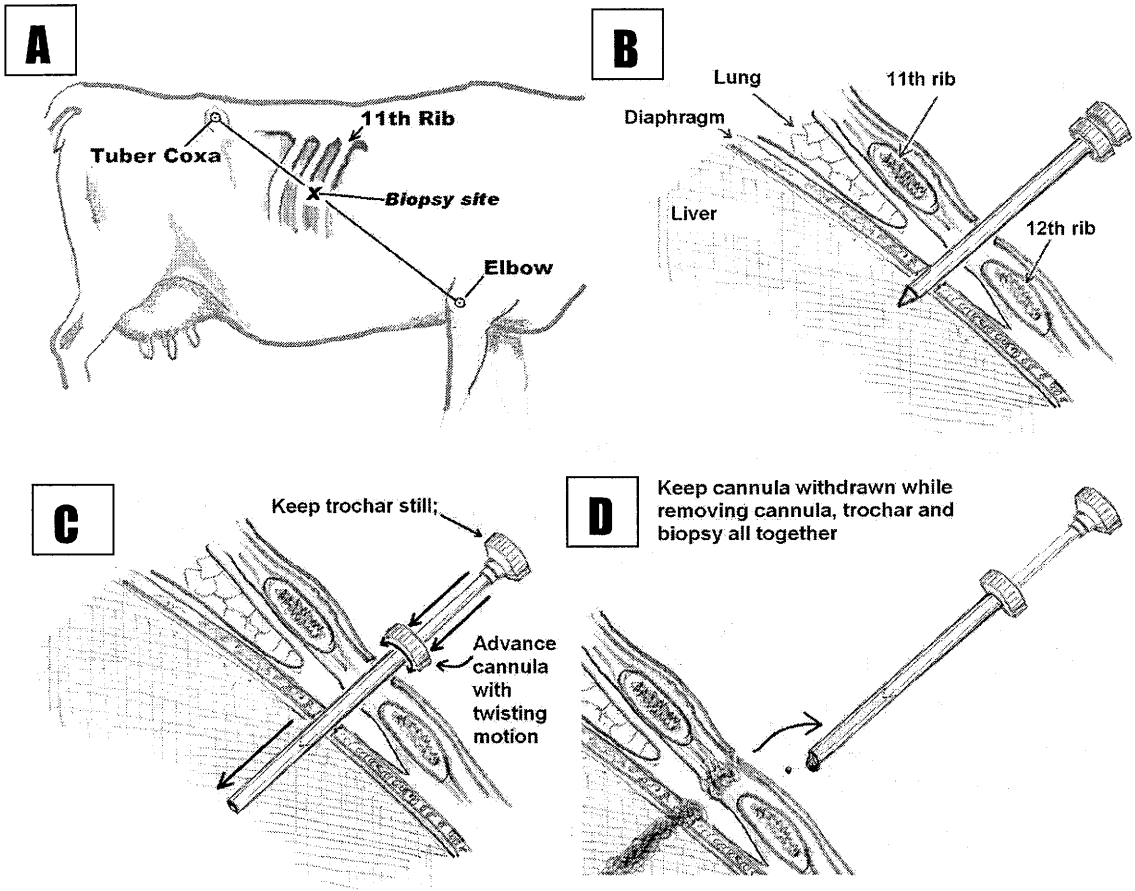


**Fig.2 Liver biopsy technique for ruminants**

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