ASVP DIAGNOSTIC EXERCISE NO. 28 **Roger Kelly**

History:
Capsular and cut surfaces of the liver of a full-mouth Merino-Border-Leicester-crossbred wether. One of about ten percent of a flock of 300 animals on a Victorian Riverland farm that had died during December. Sudden onset of dullness and other nervous signs, and inappetance, followed by death in a day or so.

This liver was judged to be small in relation to the size of the carcass.

Decscription:
This liver is slightly paler than normal overall, and its capsule appears less smooth than it should. The capsular and cut surfaces bear randomly distributed small (up to 3mm) pale nodules that project slightly from surrounding tissue; these appear to be uniformly fleshy on section.

Interpretation:
Of the 4 basic disease processes, only a proliferative process (hyperplasia/neoplasia, or proliferative inflammation) would add nodules such as these to a normally uniform tissue. Focal degeneration (including necrosis) could produce pallor but not the nodules, and a developmental disorder seems intuitively improbable. The absence of any suggestion of hyperaemia or scarring or exudate within or around the nodules lessens their likelihood of being inflammatory in origin, so we are more or less left with a proliferative response.

The organ is described as being smaller than expected, and this is borne out by the fine wrinkling of the capsule between the nodules, which suggests that the organ has lost mass to the extent that the capsule is no longer under normal tension. If the nodules had been added to an otherwise normal liver, such as might happen with metastatic cancer, the organ would be expected to be slightly enlarged, if anything.

Pathological diagnosis:
Bearing in mind the capacity of liver to regenerate after significant loss of parenchyma, the appearance and circumstances favour the likelihood that this is randomly distributed nodular hyperplasia occurring in a liver that has undergone atrophy. So a combination of degeneration (atrophy) and subsequent nodular hyperplasia is preferred over metastatic neoplasia or multifocal hepatitis. Hepatic fibrosis might be present throughout, but this cannot be ascertained from these images without information about the texture of capsular and cut surfaces. Some toughening of the parenchyma will occur during parenchymal atrophy, simply by condensation of native stroma (hence the apparent thickening of the capsule in this case), but it is misleading to classify this as fibrosis; this term is better reserved for the formation of new collagen.

It is tempting to use the term cirrhosis as a catch-all for this sort of liver disease. Unfortunately, this term seems mean different things to different people. To me it is shorthand for distortion of the liver by a combination of atrophy, fibrosis and nodular regeneration, and discoloration by various degrees of fatty change and bile retention. Because of the doubt about fibrosis in this case, I am reluctant to call it cirrhosis.

Aetiology:
A number of hepatotoxins might cause chronic liver disease characterised by atrophy, fibrosis and nodular degeneration. Pyrrolizidine alkaloids, phomopsin and aflatoxins are all compounds whose metabolites can persist in hepatocytes and produce these changes as well as more specific histological features. The PAs, however, because of their powerful antimitotic effects, are particularly effective at producing hepatic atrophy, to the point that liver failure occurs. Some groups of hepatocytes may escape the mitotic inhibition, and are stimulated to proliferate by the insufficient hepatic mass; these produce the nodules.

So pyrrolizidine alkaloid poisoning is preferred over lupinosis and aflatoxicosis because of the history; geographic location, and prominence of the nodular regeneration relative to fibrosis.

Diagnostic confirmation:
Histological examination would help resolve the diagnosis. Diagnosis of pyrrolizidine alkaloid poisoning tends to be based on the presence of so-called megalocytes, but it must be remembered that hepatocytes become enlarged in many chronic degenerative liver conditions, and I have seen sections of bovine aflatoxicosis that were indistinguishable from PA poisoning. The absence or extreme rarity of hepatocellular mitosis is a better indicator of PA intoxication.

Pyrrolic metabolites are bound to hepatocytes and other tissues for long periods, and there are qualitative analytical methods for their detection that have specific diagnostic utility. Finding a laboratory that is prepared to keep the service going, however, will be a challenge. Moreover, until more research has been done with residue half-life in experimentally-intoxicated animals, the mere demonstration of pyrrolic residues alone will not confirm a diagnosis in the absence of concordant liver pathology.

Case management:
Unless asked for it, pathologists should steer clear of offering advice on specific case management, however some indication as to the general irreversibility of PA poisoning might be appropriate, in the event of the submitter being unaware of it. Perhaps a reference such as: *Pyrrolizidine alkaloid poisoning of sheep in New South Wales J. T. SEAMAN Australian Veterinary Journal 64:164-167 (1987)* would be appropriate.