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## Copper Toxicosis in Sheep

Copper is one of the oldest metals known to man. Brass, bronze, gun metal, and money metal are important alloys that contain copper. These alloys are often used in construction, electrical products, transportation equipment, industrial machinery/equipment, coins, and consumer products. Copper compounds are also commonly used for fungicides, fertilizers, and nutritional supplements for humans and animals. Acute copper toxicosis may occur in any species (ruminants or non-ruminants) associated with the use of these various compounds. The most common cause of copper toxicosis is usually caused by chronic exposure to diets containing either excessive amounts of this common metal or improper copper:molybdenum ratios. Since copper is an essential trace element, its role in electron transfer reactions make this metal vital for connective tissue cross-linking, antioxidant defense, cellular respiration, and catecholamine biosynthesis. However, copper is also responsible for toxicity at excess accumulations through free radical production and direct oxidation of cellular components.

There is significant variation in susceptibility to copper toxicosis among domestic animal species. Sheep are the species most susceptible to copper poisoning, due to reduced biliary excretion of copper. Chronic copper toxicosis in sheep usually occurs as a result of three environmental factors. First, excessive copper intake may occur as a result of contaminated water sources (either from natural sources or the use of copper piping) or pasture/prepared feeds. Second, increased copper accumulation may also occur as a result of increased availability of dietary copper. This condition may occur when dietary levels of molybdenum are low. Molybdenum, in the presence of sufficient sulfur metabolites, will form insoluble complexes with copper in the gastrointestinal tract and liver, decreasing bioavailability and absorption. For example, some species of clover growing in southern Australia are relatively deficient in molybdenum. Several British breeds of sheep are therefore more prone to copper toxicosis than other breeds. The third environmental factor that may predispose sheep to copper poisoning is concurrent hepatotoxicity from other toxic substances. The most important of these are the pyrrolizidine alkaloids.

Copper toxicity in sheep usually results from the accumulation of copper in the liver over a period of a few weeks to more than a year with no clinical signs. Most of the copper is sequestered in hepatocellular lysosomes, where it does little damage at concentrations of up to 200-300  $\mu\text{g/g}$ . As the copper concentration rises, lysosomal membranes lose their integrity, allowing the copper and lysosomal enzymes to damage the remaining cytoplasm. Once the hepatic copper concentrations have reached 300  $\mu\text{g/g}$  or more, single cell apoptosis within aggregates of neutrophils indicates increased cell turnover. At even higher levels, the rate of apoptosis increases and all hepatocytes become swollen and their nuclei vesicular. The rate of mitosis increases to keep pace with the accelerated rate of cell turnover and loss of hepatocytes. Large macrophages may also appear in the sinusoids and stromal spaces surrounding

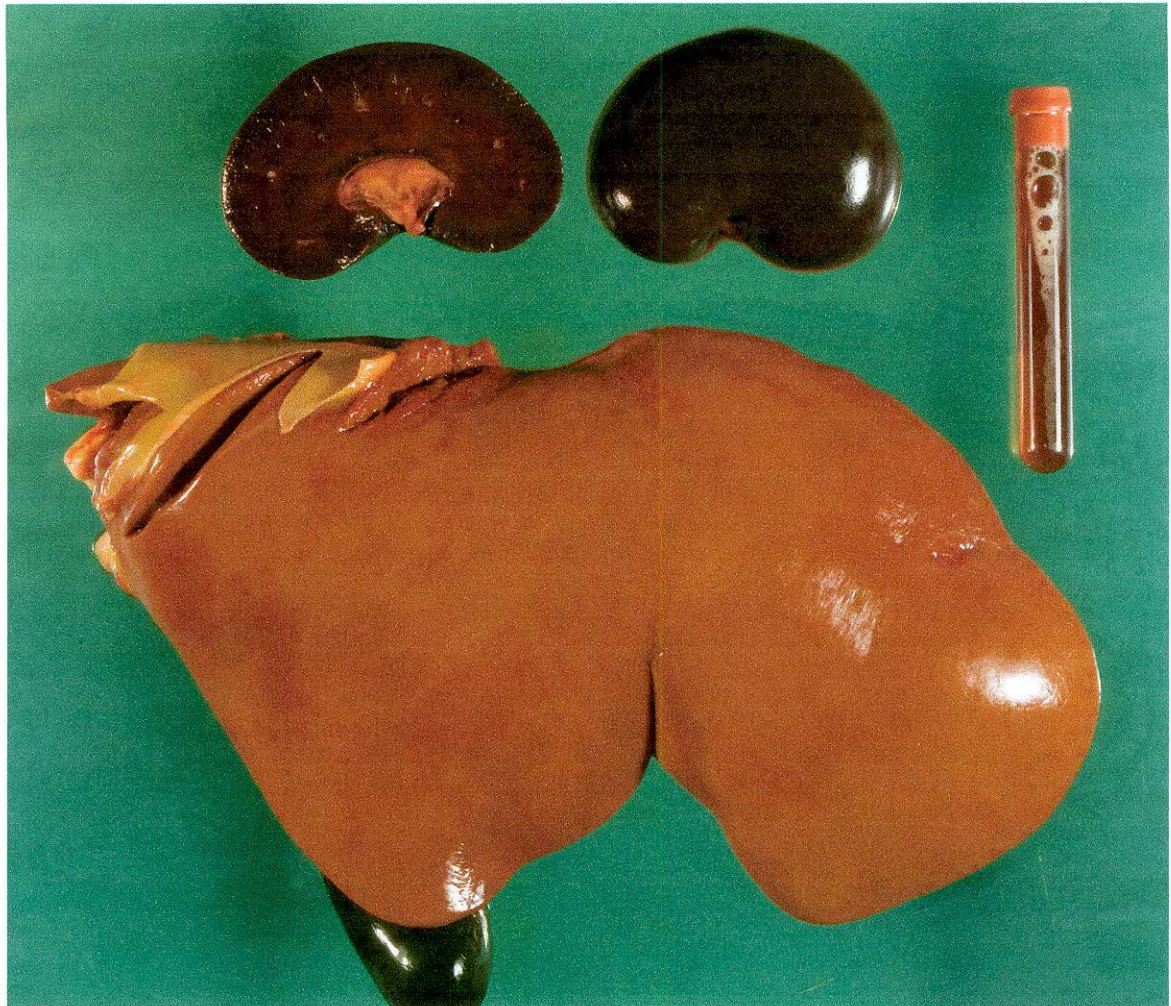
the vessels. These macrophages often contain eosinophilic or brown, granular debris consistent with copper-containing lipofuscins.

Sheep with copper accumulations greater than 1000 µg /g are clinically and hematologically normal if the mitotic rate can produce enough hepatocytes to replace dying cells and take up the copper these cells release. When the mitotic rate cannot keep up with the rate of hepatocellular death, plasma copper levels can rise to high enough levels to damage circulating erythrocytes. Excess copper in the blood oxidizes erythrocyte membranes and increases their fragility, thus resulting in intravascular hemolysis. The lethal clinical syndrome is then characterized by intravascular hemolysis and liver failure.

Sheep with severe, chronic copper toxicity may pass from apparent good health to death in as little as 6 hours. Stress, including brief periods of starvation, may also precipitate the lethal crisis in susceptible animals due to unknown mechanisms. During the hemolytic crisis, some of the copper may exit the liver and pass into the urine. Kidney copper levels may rise as high as 1000 µg /g or more. Therefore, blood or kidney copper levels may give a truer indication of a prior hemolytic crisis due to chronic copper poisoning than elevation of liver copper concentrations alone.

Diagnosis of copper toxicity in sheep is often based upon the presence of compatible clinical signs, chemical analysis of blood and various tissues, and necropsy findings. Clinical signs of acute hemolytic crisis related to acute anemia include: weakness, depression, anorexia, fever, icterus, pale mucous membranes, tachypnea, dyspnea, recumbency, and rumen stasis.

Lesions found upon necropsy examination are primarily found in the liver, kidney, and spleen. The carcass is often diffusely yellow in coloration due to generalized icterus. The spleen is often engorged, dark, and soft which is indicative of hemolysis. The kidneys are deep red-brown to black ("gunmetal kidneys") and the urine may be deep red (as a result of oxidation of hemoglobin to methemoglobin) and concurrent icterus. The liver is often slightly soft and swollen and deep orange in color. Hepatic atrophy and fibrosis may be present after long-term liver injury. Evidence of liver necrosis may also be present due to hypoxia, heart failure, or shock.



-Photo courtesy of Dr. Frank

Microscopic lesions may include: swollen and necrotic hepatocytes, hepatocyte vacuolation, periportal fibrosis, renal tubular necrosis, hemoglobin casts in renal tubules, and excessive fragmentation of erythrocytes within the spleen. Hemosiderin-laden macrophages may also be present in these tissues. Intracellular copper deposits within the liver may also be identified by special stains.

Laboratory examination is also important for definitive diagnosis of copper toxicosis. Hepatic enzymes such as AST, LDH, and SDH are often elevated, suggestive of hepatic necrosis. Hyperbilirubinemia, hemoglobinemia, or hemoglobinuria may also be present. Serum or whole blood copper levels greater than 1.5ppm are considered diagnostic of copper toxicosis. (The reference range for blood copper is considered to be between 0.2 and 1.0ppm). During the acute hemolytic crisis, blood copper concentrations may reach levels of 2.4 to 20ppm. Liver concentrations associated with copper poisoning are usually greater than 150ppm on a wet-basis, whereas kidney concentrations are usually greater than 15ppm. Fecal copper levels may be as high as 8,000-10,000ppm.

Prevention of copper toxicity is the most practical method of dealing with copper toxicosis as treatment is limited. Maintaining a proper copper:molybdenum ratio in the diet is very important for the prevention of feed-related toxicosis. This requires complete feed analysis of both copper and molybdenum in the diet. Feed rations formulated for sheep should have a maximum copper:molybdenum ratio of 6:1. Molybdenum addition should always be less than 5ppm of the total diet. Sheep diets can also be supplemented with zinc at 100ppm to reduce copper storage in the liver. In addition, do not feed swine or poultry feed to sheep. These feeds contain high levels of copper. Communicate with feed companies or suppliers carefully before purchasing their product (especially if these providers also handle swine feeds). Test feeds and forages for copper, molybdenum, and sulfur levels regularly. Avoid grazing sheep on pastures where swine or poultry waste is applied. Reduce access to plants that may cause hepatic injury (such as pyrrolizidine alkaloids).

-by Whitney Camp, Class of 2009

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