Red Maple (Acer Rubrum) Poisoning

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Cause Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horses</td>
<td>1 - 6 days</td>
<td>Days; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

Red Maple (Acer Rubrum) Poisoning

Images

- Red Maple, Acer Rubrum - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org.

Source and Description

- Red maple is native to the entire eastern United States.
- Tree - Up to 120 feet tall.
- Growth Form - Medium size tree; trunk diameter up to 3 feet; crown oval or rounded.
- Bark - Gray and smooth when young, becoming darker and scaly.
- Twigs - Slender, mostly smooth, more or less reddish, usually with pale lenticels; leaf scars opposite, U-shaped, with 3 - 7 bundle traces.
- Buds - Rounded, reddish, usually hairy, up to 1/4 inch long.
- Leaves - Opposite, simple; blades up to 6 inches long, nearly as broad, palmately 3- to 5-lobed, the edges of the leaves sharply toothed to nearly toothless, pale green and smooth on the upper surface, white or gray and either smooth or hairy on the lower surface; leafstalks smooth or finely hairy, up to 4 inches long.
- Flowers - Staminate and pistillate borne separately, but sometimes on the same tree, in short dense clusters, bright red or yellow, opening in February and March before the leaves begin to unfold.
- Fruit - Borne in pairs, composed of an erect wing (or 2 wings) with a seed at the base, red or yellow, up to 1 inch
long.
- Wood - Heavy, close-grained, light brown.
- Uses - Furniture, gun-stocks.
- Habitat - Swamps, low woods, upland slopes, bluff tops.
- Range - Newfoundland across to Ontario, south to eastern Texas, east to Florida.
- Distinguishing Features - The Red Maple is characterized by its white lower leaf surfaces and its shallowly lobed leaves. The similar Silver Maple has very deeply lobed leaves.

**Toxic Principle and Mechanism of Action**

An, as yet, unidentified toxin creates an acute hemolytic anemia associated with methemoglobinemia and/or Heinz body formation.

**Toxicity**

- Wilted or dried red maple (*Acer rubrum*) leaves are especially toxic.
- Overnight freezing and prolonged (4 weeks) storage does not destroy the toxic material.
- Ponies given dried red maple leaves at a dose of 3.0 gm/kg body weight became ill and died 1 - 5 days after administration.
- Ponies given dried leaves collected before September 15 became ill with a hemolytic crisis and died within 3 - 5 days. Ponies given dried leaves collected after September 15 died by 18 hours. This suggests there is a slight increase in the levels of toxin during the autumn.

**Signs**

- Depression, anorexia, dehydration.
- Icterus.
- Cyanosis.
- Slight increase in heart rate and respiration.
- Slight to severe anemia.
- Brown discoloration of blood (methemoglobin).
- Hemoglobinuria.
Red Maple (*Acer rubrum*)

Clinical Pathology

- Decreased packed cell volume.
- Increased white blood cell count.
- Methemoglobin.
- Heinz bodies.
- Increased SDH, bilirubin and CPK.
- Urinalysis.
  - Hemoglobin.
  - Increased protein.
- Methemoglobinuria.

Lesions

- Generalized icterus.
- Increased pleural and pericardial fluid.
- Ecchymoses on serosal surfaces.
- Splenomegaly.
- Hepatomegaly, pale centrilobular areas.

**Differential Diagnosis**

- Equine Infectious Anemia - Anemia.
- Babesia infection - Anemia.
- Phenothiazine poisoning - Heinz body formation.
- Cultivated and wild onion poisoning - Heinz body formation.
- Nitrite toxicosis - Methemoglobinemia.

**Diagnosis**

History of exposure and appropriate clinical signs. Recorded cases occur primarily from July to October, but may occur later.

**Treatment**

- Whole blood transfusion if necessary.
- IV fluids to prevent shock and dehydration.
- Continued saline diuresis may be necessary to prevent renal tubular nephrosis from the released hemoglobin. Added bicarbonate may facilitate this goal.
- Monitor renal function and serum electrolytes. **Note:**
  - Methylene blue may be contraindicated if methemoglobin exists and oxidation to Heinz bodies has already occurred. Methylene blue has been shown to be relatively ineffective in accelerating methemoglobin reduction in equine erythrocytes and also can cause significant Heinz body formation.
  - Ascorbic acid seems a logical therapy, but there are no known reports evaluating its use in *Acer rubrum* poisoning.

**Prevention**

- Prevent boredom and provide adequate nutrition (especially in fall and winter). This may decrease leaf eating.
- Remove trimmed branches or fallen limbs immediately after a storm.
- Prevent accumulation of leaves that fall or blow into horse pastures.

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**Onion (*Allium*) Poisoning**

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Cause Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs, cattle, other species</td>
<td>Hours to days</td>
<td>Days; potentially lethal</td>
<td></td>
</tr>
</tbody>
</table>

**Images**

- *Allium* spp.. Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org.
Sources and Description

- The genus *Allium* includes various species of onion and garlic, including cultivated varieties.
- Cultivated (*A. cepa*) or wild (*A. validum*) onions as well as other species of onions (*A. canadense*), Egyptian garlic (*A. ampeloprasum*), and chives (*A. schoenoprasum*) have been implicated in poisoning of various species of animals.
- Ingestion of wild onion seldom causes signs of toxicosis.
- Livestock may be fed cull onions in areas where they are grown commercially. Often this can be done with few problems provided that they are mixed with ample amounts of other vegetable wastes or other feed components.
- Sometimes cool spring weather may delay growth of grass, whereas wild onions may readily propagate, making them the most readily available vegetation.
- A 12-kg dog was apparently poisoned after consuming the contents of a 3.5-oz jar of minced onions.

Toxic Principle and Mechanism of Action

- n-propyl disulfide is reported to be the toxic principle of *Allium* spp. and its only effects are on erythrocytes. The principle effects are related to hemolysis. This is believed to be secondary to oxidant-associated effects, and Heinz bodies may sometimes be evident.
- Other compounds are believed to be responsible for the lacrimator and antithrombotic effects associated with onions and garlic. Various sulfur-containing metabolites are probably responsible for the odors associated with ingestion of onions and garlic.

Susceptibility of Various Species

Cattle are more susceptible to onion poisoning than are horses, and sheep are even less susceptible, with goats being the least susceptible. In some cases, sheep may eat onions and show nothing more than slight hemoglobinemia. Poultry, rats, and rabbits have been experimentally poisoned.

Signs

- Discolored urine varying from port wine to almost black may be seen. Weakness, rapid breathing, and a rapid heart rate may be noted in hemolysis is sufficiently severe. Some animals may be icteric and/or have a characteristic onion odor to the breath.
- Loss of weight and appetite may occur. Severe toxicoses may be lethal.

Clinical Pathology

- Hemoglobinemia, hemoglobinuria, marked reductions in PCV. Heinz bodies sometimes reported.
- Evidence of damage of parenchymatous organs may be evident secondary to hemolytic anemia.

Differential Diagnoses

Include but are not limited to zinc toxicosis, copper toxicosis, autoimmune hemolytic anemia, and hemolytic blood parasites and bacterial infections.
Treatment

- Whole blood transfusion if necessary.
- IV fluids to control shock and dehydration.
- Saline diuresis with added bicarbonate (at least in animals with an acid urine) to limit hemoglobin-associated nephrosis.
- An empirical therapy to limit oxidant-induced damage of erythrocytes is ascorbic acid. There are no known reports of its use in this syndrome, however.
- Under some circumstances, methylene blue may be harmful to the horse (see section on Red Maple [*Acer rubrum]*) as well as to the dog. It is rarely recommended for felines. Low doses of methylene blue (1.5 mg/kg) have recently been reported to be beneficial to cats with nitrite-induced methemoglobinemia. Methylene blue especially when given in the absence of pre-existent methemoglobinemia) may cause methemoglobinemia and Heinz body formation.

Cultivated Onion.
The young green onion is shown on the left; the flower and seed stalks in the center; the enlarged flower, fruit, and seed in the upper right; and the onion bulb in the lower right of the drawing of this common food-seasoning plant.

Copper Toxicosis

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Cause Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper</td>
<td>Sheep, cattle, certain breeds of dogs</td>
<td>Hours to chronic</td>
<td>Days; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

Susceptibility
Because of major differences with regard to the sensitivity to copper toxicosis and the influence of molybdenum, this section
is subdivided between species and syndromes. The most common and serious problem is copper toxicosis-molybdenum deficiency in sheep: an acute syndrome which suddenly occurs after chronic dietary exposure to an excessive copper to molybdenum ratio. Cattle are sensitive to an excessively low dietary copper to molybdenum ratio. Goats are 3 - 4 times more tolerant of copper than sheep. Genetic defects in some dog breeds (Bedlington terriers) cause excessive storage of copper in the liver eventually resulting in liver damage. All species are sensitive to excessive copper intake and are potentially affected by acute or subacute copper toxicosis.

1. Acute Copper Toxicosis

An acute syndrome of copper toxicosis results from ingestion or administration of copper containing formulations at a highly toxic dose.

Sources of Copper-Containing Compounds

- Anthelmintics
- Foot baths used for livestock (see below)
- Pesticides including fungicides and algicides

Toxicity

- There are marked differences among species in their ability to tolerate high levels of copper:
  - 30 - 50 ppm copper in the diet may be toxic to ruminants.
  - Dietary copper in excess of 250 ppm is required to cause toxic effects in swine and rats.
  - Sheep accumulate copper in the liver in proportion to intake.
  - Many nonruminants maintain normal liver copper levels until extremely excessive dietary levels are reached.
  - Copper sulfate added to diets at 125 ppm or higher may be lethal to rabbits.

Mechanism of Action

Possible coagulative necrosis of the gastrointestinal mucosa.

Signs

- Vomiting.
- Hypersalivation.
- Signs referable to abdominal pain.
- Diarrhea, often greenish tinged.
- Collapse and death sometimes occurs within 2 days.

2. Copper Toxicosis in Nonruminants

- Horses are comparatively tolerant of copper.
- Swine are comparatively tolerant of copper.
  - Dietary concentrations generally must exceed 250 ppm to cause toxicosis.
  - High dietary iron and zinc protect swine somewhat from the adverse effects of high copper levels. Similarly, deficiencies of these elements increase susceptibility.
  - Signs seen include anorexia, weight loss, weakness, melena, and death.
  - Lesions observed are pale livers with centrilobular necrosis, gastric ulcers, pale musculature, and "watery" blood.
  - Liver copper concentrations may be diagnostic.
- Poultry:
  - More resistant to copper toxicosis than most mammals.
    - Turkey poults reportedly tolerate 767 ppm in diet for 21 days.
    - Chickens: MLD of copper sulfate on mg/kg BW basis.
Signs observed in toxicosis included weakness, anorexia, lethargy, anemia.

Dogs.

See Bedlington Terriers.

3. Chronic Copper Poisoning in Bedlington Terriers and Sometimes Other Breeds

Sources

Autosomal recessive defect causes increased copper retention in the liver which results principally in liver damage.

Mechanism of Action

Dark granules are observed in the liver, comprised of lysosomes containing copper and melanin. When the lysosomal capacity is overwhelmed, liver injury occurs.

Clinical Signs

Three syndromes occur:

Young dogs, 6 years of age and less may exhibit:

- Anorexia.
- Vomiting.
- Weakness.
- Lethargy.
- Dehydration.

These effects are believed to be due to active liver disease.

Older dogs, 6 - 12 years of age, may exhibit a chronic syndrome characterized by:

- Anorexia, weight loss.
- Occasional vomiting, diarrhea.
- Jaundice.
- Ascites.
- Hepatic encephalopathy, death.

The third form is comparatively rare and consists of sudden, severe, hemolytic crisis and anemia.

Lesions

- Hepatomegaly or small liver.
- Prominent cytoplasmic granules in hepatocytes; focal hepatitis; focal cirrhosis; chronic, active hepatitis; generalized cirrhosis.

Diagnosis

Breed - Bedlington terrier, West Highland white, Skye terrier.
Lesions (liver biopsy).
Affected dogs have liver copper concentrations usually of greater than 1,000 ppm on a dry weight basis and frequently over 2,000 ppm. The concentrations may increase with age up to a point and then decline but remain above normal.
Normal liver copper in dogs (also on a dry weight basis) is approximately 90 - 350 ppm.
Values above 350 ppm are considered diagnostic.
The increase in SGPT occurs late and reflects hepatocellular injury.
There is generally no increase in serum copper in affected dogs, except during an acute hemolytic episode.
Treatment

- Penicillamine (Cuprimine®), chronic administration.
- Glucocorticoids for lysosomal stabilization in acute disease.
- Ascorbic acid, 500 - 1,000 mg/day, to enhance urinary excretion of copper.
- 2,3,2-tetramine has been used as a chelator for copper in Bedlington terriers.

4. Subacute Copper Poisoning in Lambs

Sources

- In copper-deficient areas such as Florida, other southeastern coastal areas, and areas west of the Rockies, lambs are sometimes treated with copper-containing medications to prevent deficiency. A copper compound administered via oral drenching will often provide copper at a level adequate for several months. Single injections of copper-calcium EDTA or copper-methionate products may also be used.
- Even at the recommended rate of 50 mg copper, toxicosis may occur, especially in undersized lambs.

Lesions

- Gastrointestinal hemorrhage.
- Pulmonary edema.
- Ascites.
- Liver damage.
- Generally no icterus or hemolytic crisis.

Diagnosis

- Elevated serum, whole blood, liver, and/or kidney copper concentrations.
- History, lesions.

5. Copper Toxicosis/Molybdenum Deficiency
(Sometimes called chronic copper toxicosis. Primarily affects sheep and to some degree, young calves; much less often adult cattle).

Sources and Susceptibility

- Copper is routinely added to livestock mineral supplements and is a GRAS (generally recognized as safe by the FDA) feed additive.
- Molybdenum is not recognized by the FDA as an essential and safe element and its addition to feeds is thereby prohibited.
- Feeding to sheep of complete feeds intended for cattle or poultry can provide copper levels toxic to sheep.
  - Cattle can tolerate somewhat excessive copper and low molybdenum ratios, but sheep cannot.
- In the upper Midwest and Great Lakes states, diets containing the GRAS concentration of 15 ppm copper are often low in molybdenum so that 1 - 5% of sheep, may develop hemolytic crises.
- When a vitamin-mineral supplement is added to a ration, the copper concentration may be increased to 30 ppm or more.
- Natural molybdenum concentrations in rations are often 2 ppm or less.
- Consumption of forage plants naturally low in molybdenum and high in copper or confinement of sheep without green forage containing adequate molybdenum will skew the copper: molybdenum ratio.
- Complete rations for horses may be too high in copper for sheep.
- Consumption of plants contaminated by copper in pesticides such as bordeaux mixture (contains 1 - 3% copper sulfate) which is sometimes used in orchards.
- Water from ponds treated with copper containing algicides can cause toxicosis.
- Copper sulfate used as an anthelmintic or in solutions to treat infectious pododermatitis in ruminants can be a source...
of toxic levels of copper.
- Soils and vegetation contaminated from mining or smelting operations.
- Grazing on pastures amended by poultry or swine waste from animals fed copper-containing growth promotants.
- Grazing on vegetation growing on soils contaminated by copper mining or smelting operations.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Copper Concentrations in Mineral Supplement Samples Submitted to the University of Illinois Veterinary Diagnostic Laboratory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Number</td>
<td>Copper Concentration (ppm)</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>28</td>
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<td>5</td>
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<td>6</td>
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<tr>
<td>7</td>
<td>73</td>
</tr>
<tr>
<td>8</td>
<td>76</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Copper Concentrations of Corn, Hay, and Complete Feed Samples Submitted to the University of Illinois Veterinary Diagnostic Laboratory. Results reported as parts per million (ppm).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Number</td>
<td>Corn</td>
</tr>
<tr>
<td>1</td>
<td>1.9</td>
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<tr>
<td>2</td>
<td>2.8</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
<td>3.5</td>
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<tr>
<td>5</td>
<td>4.0</td>
</tr>
<tr>
<td>6</td>
<td>4.2</td>
</tr>
<tr>
<td>7</td>
<td>8.0</td>
</tr>
<tr>
<td>Mean</td>
<td>4.0</td>
</tr>
</tbody>
</table>
Note: The mean naturally occurring molybdenum content of feedstuffs is approximately 2 ppm or less.

<table>
<thead>
<tr>
<th>Sample Number</th>
<th>Mineral</th>
<th>Corn</th>
<th>Hay</th>
<th>Complete Feed</th>
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<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.17</td>
<td>0.18</td>
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<td>2</td>
<td>1.2</td>
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<td>0.65</td>
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<td>3</td>
<td>1.7</td>
<td>0.62</td>
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<td>1.6</td>
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<td>4</td>
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<td></td>
<td>1.8</td>
</tr>
<tr>
<td>5</td>
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<tr>
<td>9</td>
<td></td>
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<td>4.0</td>
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</tr>
<tr>
<td>Mean</td>
<td>1.6</td>
<td>0.80</td>
<td>1.10</td>
<td>2.3</td>
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</tbody>
</table>

Table 3
Molybdenum Concentration of Mineral Supplement, Corn, Hay, and Complete Feed Samples Submitted to the University of Illinois Veterinary Diagnostic Laboratory. Results reported as parts per million (ppm).

Table 4
Copper: Molybdenum Ratios of Samples Submitted to the University of Illinois Veterinary Diagnostic Laboratory

<table>
<thead>
<tr>
<th>Sample</th>
<th>Copper:Molybdenum Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Feed</td>
<td>18:1</td>
</tr>
<tr>
<td>Hay</td>
<td>8:1</td>
</tr>
<tr>
<td>Corn</td>
<td>5:1</td>
</tr>
<tr>
<td>Mineral Supplements</td>
<td>68:1</td>
</tr>
</tbody>
</table>

Toxicity

- The proper dietary ratio for sheep is 6 parts copper to 1 part molybdenum. Ratios in excess of 10:1 often result in clinical copper toxicosis in sheep.
- When normal dietary copper concentrations of 8 - 10 ppm and excessively low molybdenum concentrations of 0.5 ppm or less are present, an excessive buildup of copper and eventual hemolytic crisis may also occur.
- Copper sulfate is somewhat less toxic than many other copper salts, perhaps because of a sulfate-enhanced excretion of copper.
- Horse chow has been lethal to ewes.
- Copper in dry forages may be more available than copper from green forages.
- Toxicosis is often brought on by stress.

Absorption, Distribution, Metabolism and Excretion (ADME)

- Absorption:
  - Copper absorption takes place in the small intestine and, at least in sheep, considerable absorption also occurs in the large intestine.
Absorption varies as a function of the chemical form of the copper, the makeup of other minerals and organic materials in the diet, and the acidity of the intestine.

Most of the ingested copper is not absorbed and is therefore passed in the feces.

Copper absorption is poorly understood, but it is thought that a complex of copper with a protein, and another organic compound or another metal may be formed.

Zinc and copper may compete for the same carrier protein for transport across the intestinal mucosa into the blood.

Once absorbed, about 90% of the copper is firmly bound to a serum protein called ceruloplasmin and is loosely bound to albumin and amino acids.

**Copper in the blood:**
- Copper bound to ceruloplasmin is not as readily available for exchange or transfer as is free copper.
- Copper in red blood cells exists primarily in 2 forms: 60% is in a superoxide dismutase enzyme called erythrocuprein and the remainder is loosely bound to other proteins.

**Copper in the liver:**
- When copper reaches the liver, the primary organ influencing its disposition, it is largely incorporated into the mitochondria, endoplasmic reticulum, nuclei, and cytosol of hepatocytes. The copper is either stored in these sites or released for incorporation into erythrocuprein, ceruloplasmins, or various copper containing enzymes.

**Copper elimination:**
- Copper is secreted into the bile and excreted into the intestine. Fecal excretion is the primary route of elimination, although most fecal copper is comprised of unabsorbed copper.
- Small amounts of copper are also excreted in the urine.

**Influence of molybdenum on copper disposition:**
- *In vivo*, copper forms a complex with molybdenum in a molar ratio of 4:3, and the copper in this complex is biologically unavailable.
- The copper-molybdenum complex may not prevent the intestinal absorption of copper, but it reduces copper accumulation in the liver.
- The liver metabolizes considerable copper without ill effects provided that molybdenum and sulfate are present. Increased dietary concentrations of molybdenum and sulfate increase urinary and biliary excretion of copper. Molybdenum excretion is also promoted by sulfate. Molybdate inhibits the reduction of sulfate to sulfite, while copper antagonizes this effect of molybdenum.

**Influence of liver damage:**
- Plants or other toxicants that cause hepatic necrosis may impair the metabolism and excretion of otherwise tolerable amounts of copper.

**Mechanisms of Action**

- After copper builds up to about 150 ppm or more in the liver of sheep, the acute clinical syndrome of "chronic" copper toxicosis is initiated by the sudden release of copper from the liver into the blood. This may occur spontaneously, but it often seems to occur after some stress such as reduced feed intake, handling, or vigorous exercise. The copper content of blood is generally within the normal range until 24 - 48 hours before the onset of clinical signs, although an intermediate stage with a slight increase in blood copper may occur prior to the extreme release of copper.

- Generally, a sudden hemolytic crisis occurs, but not all animals that die of chronic copper toxicosis experience either hemolytic crisis or jaundice.

- Associated with the hemolysis is a marked reduction in red blood cell glutathione concentrations and an increase in methemoglobin, indicating that copper may, in some way, promote oxidative reactions that result in red blood cell destruction.

- Because of hemolysis, death may result from hemoglobin-induced renal damage and anemia.

**Summary of the Mechanism of Action of Copper Toxicosis-Molybdenum Deficiency:**

Copper buildup in liver from excess copper intake
(low molybdenum and low sulfate increase copper buildup)

Liver damage

+
Usually some stress factor
↓
Sudden release of copper
↓
Hemolysis, icterus, hemoglobinemia, hemoglobinuria
↓
Renal failure
↓
Collapse and death in 24 - 48 hours in most sheep

Clinical Signs

- Often excessive exposure has occurred for weeks or months before the onset of acute signs.
- Frequently a period of stress precedes the onset of signs.
- Sudden onset of weakness, trembling, anorexia, hyperventilation, hemoglobinuria (red or coffee-colored urine), and icterus are usually present.
- Occasionally only pale mucous membranes without icterus and hemoglobinuria are seen.
- Low morbidity generally (usually less than 5%), but mortality in affected animals is high (usually over 75%).
- If the syndrome progresses to death, the course generally lasts only 24 - 48 hours after the initial signs.

Clinical Pathology

- Liver enzymes such as SGOT, LDH, sorbitol dehydrogenase, arginase, and glutamic dehydrogenase may be increased for 6 - 8 weeks before the hemolytic crisis. The serum activities of these enzymes often return to near normal values 1 - 2 weeks before the hemolytic crisis, but increase to very high values shortly before or during the crisis.
- The enzyme activities do not correlate with copper concentrations in the blood.
- An increase in methemoglobin concentration may be seen.
- Hemoglobinemia, hemoglobinuria.
- Increased plasma bilirubin.
- Reduced PCV.
- Increased WBC, normal platelet counts.

Lesions

- Well before the hemolytic crisis, liver biopsies may show swelling and necrosis of isolated hepatocytes with swollen Kupffer's cells, rich in acid-phosphatase and containing PAS-positive, diastase-resistant material, and copper.
- Prior to the hemolytic stage, extensive proliferation of lysosomes is noted at the ultrastructural level in the hepatocytes of copper-dosed sheep.
- After the death of affected sheep, gross lesions usually include:
  - Generalized icterus.
  - Greatly enlarged gun-metal colored kidneys that sometimes are mottled with hemorrhage.
  - Slightly enlarged, friable, yellowish liver (or small, firm, pale liver).
  - Gallbladder distension with thick, greenish bile.
  - Splenic enlargement with a blackberry jam consistency and brown to black color in the parenchyma.
- Histologic changes include:
  - Cytoplasmic vacuolation and necrosis.
  - All liver lobules may contain clusters of necrotic cells.
  - Portal fibrosis begins early.
  - Renal tubules are clogged with hemoglobin with degeneration and necrosis of both tubular and glomerular cells.
  - The spleen is crowded with fragmented RBCs.
  - Status spongiosis has been reported in the white matter of the central nervous system.

Diagnosis
• Appropriate clinical history, signs, and lesions.
• Normal concentrations of copper in the blood range from 0.75 - 1.35 ppm. Concentrations above this range are often associated with copper poisoning. Often the concentrations are much higher at the onset of hemolysis.
• Normal liver copper concentrations in sheep range from 10 - 50 ppm (wet weight basis). Liver copper concentrations associated with copper toxicosis are usually greater than 150 ppm on a wet weight basis, whereas kidney concentrations are generally greater than 15.0 ppm.
• Complete sheep rations containing 25 ppm or greater with 2 ppm or less molybdenum may produce copper toxicosis. As noted under Toxicity, lesser amounts of copper may also be associated with toxicosis.
• In cattle, higher dietary copper concentrations may be necessary to induce toxicosis.

Treatment

• The prognosis for animals in the hemolytic phase of the disease is often poor. Usually the most benefit is derived via efforts to alleviate copper buildup in the rest of the flock.
• Urinary copper excretion is increased 10 - 20 times by the chelation agent, D-penicillamine, at 52 mg/kg/day for 6 days, although it may be prohibitively expensive for treating on a flock basis.
• Individual animals may benefit from alkalinization of the urine to decrease renal damage from hemoglobin. Animals may also improve in response to blood transfusions if serious anemia is present.
• Intravenous ammonium tetrathiomolybdate at 100 mg 2 times per week has been used to treat or prevent hemolytic crisis, minimize tissue damage, and decrease liver copper deposition.
• Supplementation of sheep rations with 2 - 16 ppm molybdenum has been efficacious in reducing the incidence of hemolytic crisis and in decreasing liver copper retention when sheep were fed copper at up to 45 ppm in the diet.
• Ammonium molybdate at 50 mg per head per day with 0.3 - 1 gram of thiosulfate daily for 3 weeks may help to prevent chronic copper toxicosis.
• Molybdenized superphosphate (at 4 oz molybdenum per acre) increases molybdenum content of pastures and reduces copper retention.
• Alternatively, molybdenized licks comprised of 190 lb salt, 140 lb finely ground gypsum, and 1 lb sodium molybdate may be used.
• Zinc may play a preventative role since supplementation of the ration with 250 ppm zinc as zinc oxide reduced liver copper buildup in lambs fed a ration containing copper at 40 ppm in the ration. The effect was synergistic with that of added sodium molybdate. Zinc at 175 - 375 ppm has also been shown to prevent hemolytic crisis in lambs fed copper at 29 ppm.

6. Excess Molybdenum-Deficient Copper (also see Molybdenum, Toxicants Affecting the Skin).

Cattle are more susceptible than sheep.

Sources

• Contamination of soils and forages in the vicinity of certain mining or smelting operations in which molybdenum containing ores are heated to high temperatures.
• Industrial contamination of farmland near metal alloy production plants.
• Contamination of soils with molybdenum containing fertilizers.
• In areas of Florida, other southeastern coastal regions, and in some states west of the Rocky Mountains (California, Oregon, Nevada), excessive molybdenum and/or deficient copper in soils and associated forages and grain may result in problems in cattle and, much less often, sheep.
• The critical copper to molybdenum ratio in cattle feeds is 2:1.

Toxicity

• When the ratio of copper to molybdenum in feed drops below 2:1, molybdenum toxicosis can be expected in cattle.
• Morbidity averages about 80% of the herd.
• When copper concentrations in feeds and forages are in the normal (8 - 11 ppm) range, cattle may be poisoned by molybdenum concentrations above 5 - 6 ppm, and sheep may be poisoned when molybdenum concentrations are greater than 10 - 12 ppm.
• However, the 2:1 ratio is not absolute even in cattle because increasing the copper concentration of the diet even 5 ppm above normal to 13 - 16 ppm will protect cattle against 150 ppm molybdenum.
• Calves may be poisoned by milk from cows on high molybdenum diets.

**Mechanism of Action**

• Copper and molybdenum form an *in vivo* complex with a molar ratio of 4:3.
• Molybdenum excretion is enhanced by increasing dietary inorganic sulfate.
• Increases in dietary molybdenum and sulfate increase urinary excretion of copper.
• Copper is an important metal component (often at a catalytic site) in many enzymes including: tyrosinase, lactase, ascorbic acid oxidase, uricase, monoamine oxidase, deltaaminolevalenic acid dehydratase, dopamine-beta-hydroxylase, and cytochrome oxidase. Deficiency of copper may reduce certain enzyme activities. The diminished activity of cytochrome oxidase is a sensitive indicator of copper deficiency.
• Progressive atrophy of the myocardium with replacement by fibrous tissue and resultant sudden deaths, usually after excitement or exercise, has been associated with copper deficiency (falling disease) of cattle. This condition, however, is poorly documented and it remains to be experimentally reproduced. A similar condition is reported in pigs and chickens but not in sheep or horses.
• In copper deficiency of some species, there is a reduction in the activity of a copper containing enzyme, amine oxidase, in the aorta. It is hypothesized that this may result in reduced deamination of lysine in elastin, which may result in less conversion of lysine to desmosine, a cross-linkage group of lysine. In turn, this may result in lessened elasticity of the aorta and other major blood vessels. The tensile strength of the aorta is apparently markedly reduced, and there are spontaneous ruptures of the major blood vessels. The myocardium becomes friable.
• In ruminants, osteoporosis and spontaneous fractures have been documented with excess dietary molybdenum and thus a relative copper deficiency. Bone abnormalities associated with copper deficiency have been reported in rabbits, mice, chicks, dogs, pigs, foals, sheep, and cattle. It has been shown that bone cytochrome oxidase activity was reduced in copper deficient chicks.
• Copper is important in the maintenance and function of myelin, and nerve damage and demyelination are key aspects of "enzootic ataxia" and "sway-back" (usually in lambs).

**Signs**

• Most Species:
  • Anemia characteristic of an iron deficiency (microcytic, hypochromic). Osteoporosis, spontaneous fractures, beaded ribs.
• Many Species:
  • Anemia.
  • Depressed growth.
  • Bone disorders.
  • Depigmentation of hair.
  • Neonatal ataxia.
  • Impaired reproductive performance.
  • Heart failure.
  • Vascular damage.
  • Gastrointestinal disturbances.
• Cattle:
  • Emaciation.
  • Liquid diarrhea (full of gas bubbles) which may begin 8 - 10 days after being placed on a high molybdenum diet.
  • Swollen genitalia.
  • Anemia.
  • Achromotrichia.
  • Prolonged purgation may result in poor weight gains and even death.
  • Sudden deaths.
  • Rough hair coat.
  • Drop in milk production.
  • Loss of libido and general unthriftiness.
Sheep:
- Depigmentation of wool.
- Abnormal wool growth, loss of crimp and quality of wool, stringy wool and anemia in ewes with "enzootic ataxia" (in Australia).
- In the United Kingdom, "sway-back" occurs in lambs, whereas ewes are usually normal.
- Enzootic ataxia and swayback are noted in lambs less than 1 month old. The lambs are severely uncoordinated, ataxic, and usually blind.
- Death results from starvation, exposure, or pneumonia.

Lesions
- Coarse, stringy, poorly pigmented hair or wool.
- Emaciation.
- Hemosiderosis.
- In prolonged cases, osteoporosis and bone fractures have been reported.
- In lambs with "enzootic ataxia" or "swayback", there is lysis of the white matter of the cerebrum and degeneration of the motor tracts of the spinal cord. The damage in the white matter varies from microscopic foci to massive subcortical destruction. There is often neuronal degeneration and demyelination.

Diagnosis
- Clinical signs and lesions.
- Copper and molybdenum concentrations in feeds and forages.
- Good response to the administration of copper.
- Copper and molybdenum concentrations in tissues.
  - Liver-copper concentrations of less than 10 - 30 ppm on a wet weight basis and molybdenum concentrations of greater than 5 ppm are significant. Normal liver-copper concentrations range from 30 - 140 ppm on a wet-weight basis, and liver molybdenum is normally below 3 - 4 ppm.
- Blood.
  - Whole blood copper concentrations of less than 0.6 ppm and molybdenum concentrations above 0.1 ppm are usually present in molybdenum toxicosis-copper deficiency. Normal blood copper concentrations range from 0.7 - 1.3 ppm, while a normal molybdenum level is around 0.05 ppm.

Treatment
- Providing copper orally or parenterally; good response usually. Use caution with sheep.
- Methods:
  - Copper sulfate added to salt-mineral mixture at 1 - 5% depending on molybdenum levels in the feed.
  - Provide 1 gram of copper sulfate/adult cow. Alternative methods include:
    - 1 oz CuSO4/250 gal of water.
    - 1/2-1 lb of CuSO4 to 100 lb of salt.
    - 100 lb of protein concentrate, 100 lb of salt, and 2.5 lb of CuSO4 (feed at rate of 1/6 lb/hd/day.
  - Copper glycinate SQ at 60 mg for calves and 120 mg for mature cattle. May need to be repeated during a season.
## Additional Toxicants

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsine (arsenic hydride) gas which may come from charging storage batteries</td>
<td>All species</td>
<td>Minutes to hours</td>
<td>Days often lethal; poisoning is rare</td>
</tr>
<tr>
<td>Stibine (antimony hydride) gas</td>
<td>All species</td>
<td>Minutes to hours</td>
<td>Days often lethal; poisoning is rare</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>(See Toxicants that Cause Primary Photosensitization)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propylene glycol (especially when given IV)</td>
<td>All species</td>
<td>Hours</td>
<td>Days potentially lethal; particularly after a high intravenous dose</td>
</tr>
<tr>
<td>Rattlesnakes and other pit vipers (phospholipase A)</td>
<td>All species</td>
<td>Minutes to hours</td>
<td>Days potentially lethal</td>
</tr>
<tr>
<td>Saponin-containing plants</td>
<td>(Hemolysis is theoretically possible, but not well documented, see Poisonous Plants that Affect Gastrointestinal Tract)</td>
<td></td>
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</tr>
<tr>
<td>Brassica spp. (kale, brussels sprouts, rapeseed and forage)</td>
<td>(See Toxicants that Cause Goiter)</td>
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<td></td>
</tr>
<tr>
<td>Zinc</td>
<td>(See Toxicants that Affect the Kidneys)</td>
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</tr>
</tbody>
</table>

- Other Oxidant Drugs (Acetanilid and Others)
- Saponin-Containing Plants (See Poisonous Plants that Affect Gastrointestinal Tract)
- Brassica spp. (See Goitrogenic Toxicants)
- Kale, Brussels Sprouts, Rapeseed, and Forage (Brassica)
- Rattlesnakes and Other Pit Vipers (Phospholipase A)

### References

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