TOXICOPATHOLOGY

Topic covered-

- Bracken fern toxicity
- Copper toxicity
- Molybdenum toxicity
- Nitrate and nitrite poisoning
- Fluoride toxicity

BRACKEN FERN

- Bracken Fern (*Pteridium aquilinum*)
- Different syndromes in horses and cattle
- In horses, thiamine deficiency and a neurologic syndrome
- Cattle less sensitive owing to the thiamine production by the ruminal microflora

Source

- Thiaminase in bracken fern greater concentrations in the rhizome than the leaves or stem .
- Contains other substances, such ptaquiloside, that cause disease in cattle.
- *Equisetum arvense* (horsetail)
- *Marsilea drummondii* (nardoo fern)

Species

- Horses more commonly affected with the neurologic syndrome.
- Cattle more commonly affected with bone marrow depression and enzootic hematuria (tumors of the urinary bladder).
- Pigs and sheep reluctant to consume bracken fern.

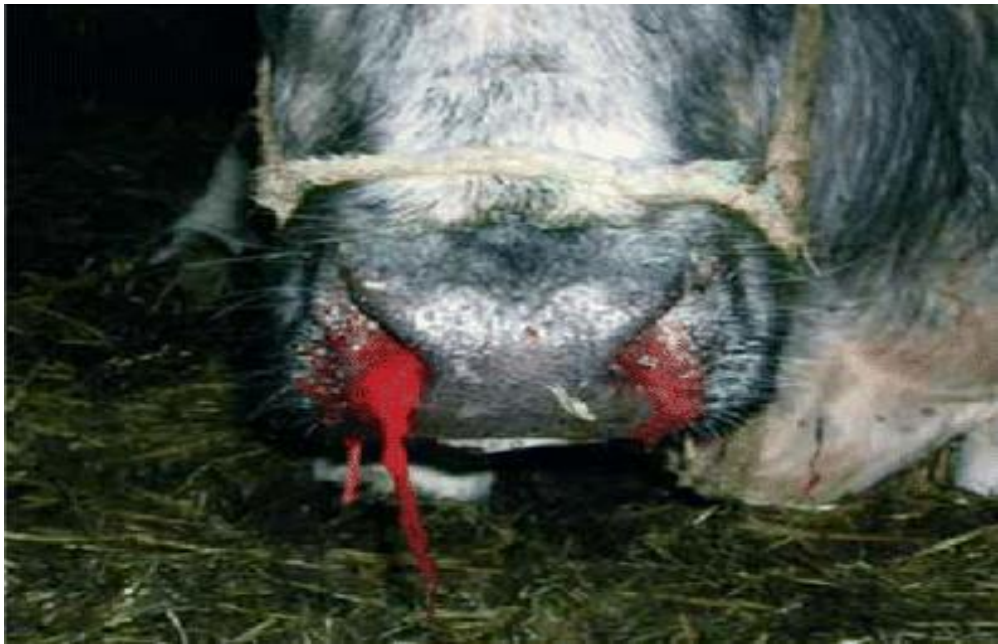
Clinical Signs

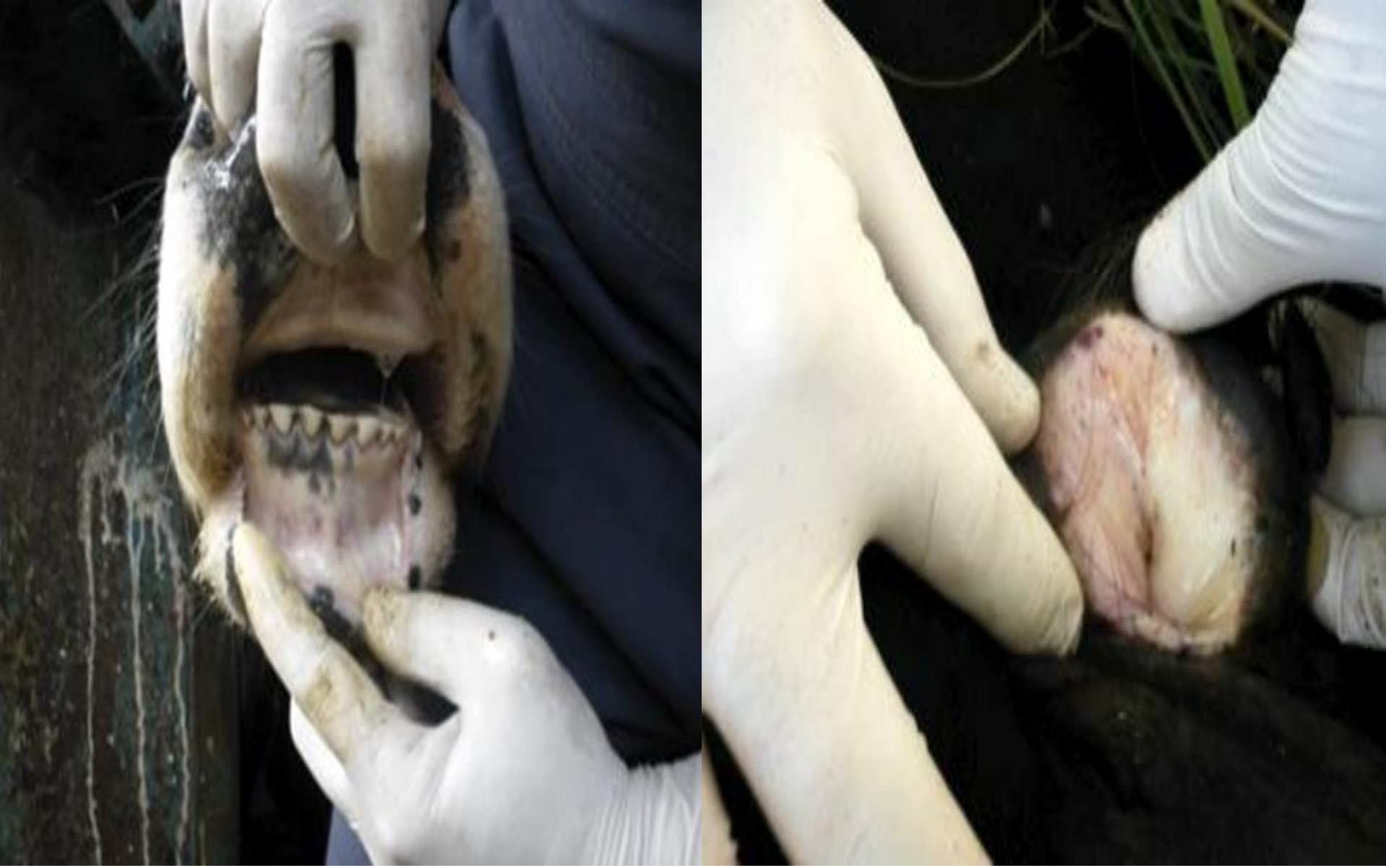
HORSES

- Thiamine deficiency
- Weight loss with normal appetite
- Clonic spasm and opisthotonos
- Incoordination
- Ataxia
- Recumbency

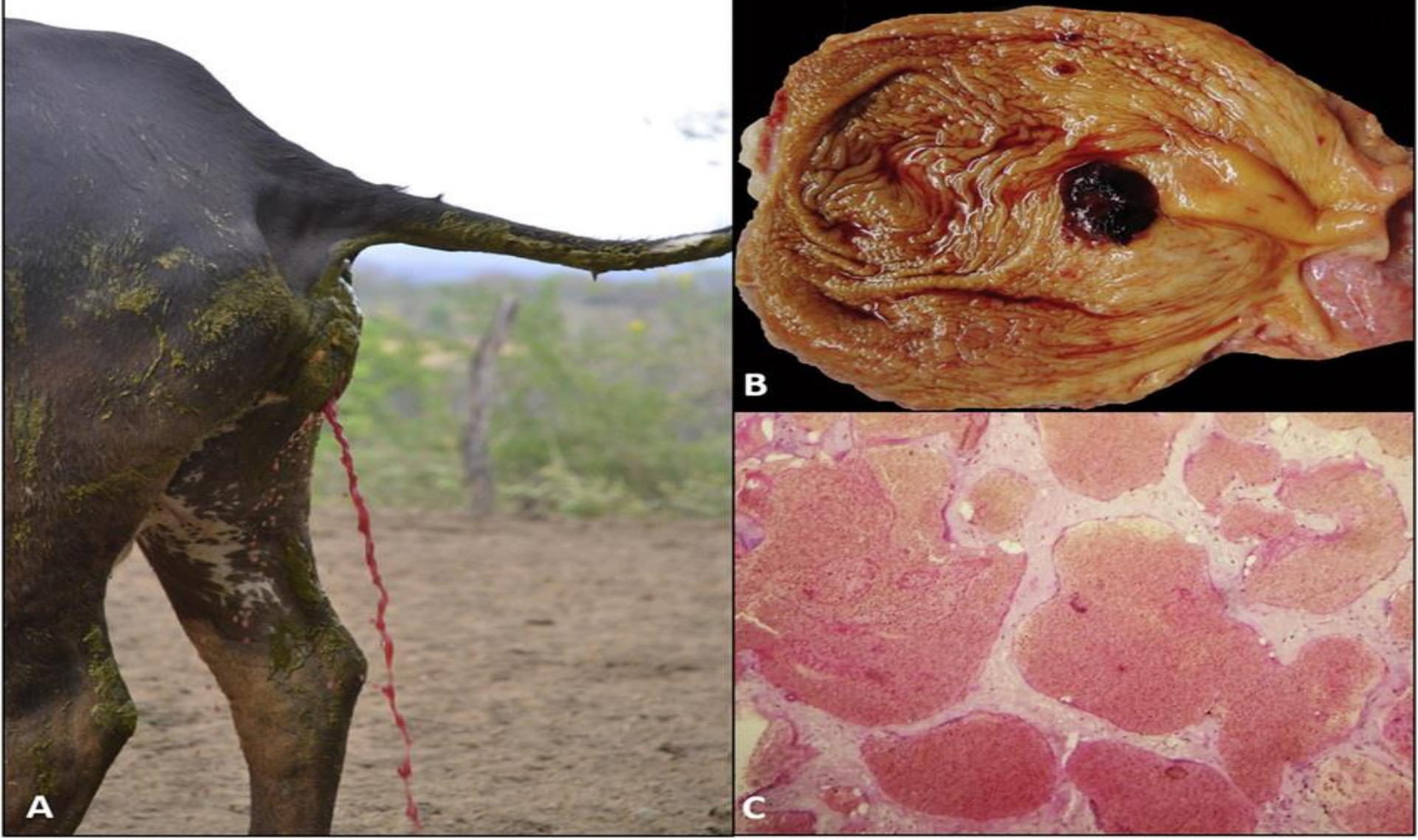
CATTLE

- Generally after long-term consumption of the plant
- Elevated body temperature
- Weight loss
- Anemia
- Bloody discharges from orifices
- Hematuria





Petechial hemorrhage and pale mucus membrane



(A) Affected animal with severe clinical hematuria .
(B) Neoplasia in the urinary bladder .
(C) Histological lesions Cavernous hemangioma .

Toxic principles-

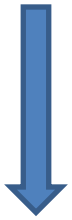
I. Thiaminase
II. Aplastic anemia factor (ptaquiloside)
III. Hematuria factor
IV. Quercetin

Mechanism of Action

- Two or more principal toxins: thiaminase and ptaquiloside more commonly associated with poisoning.

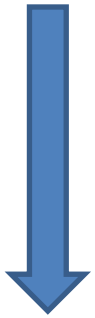
A) THIAMINASE

➢ Thiamine (vitamin B1) is an essential cofactor in decarboxylation reactions.

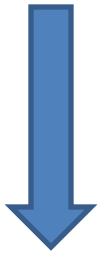


➢ Thiaminase cleaves thiamine into a pyrimidine and a thiazole group.

- Conversion of pyruvate to acetyl coenzyme A and oxidation of ketoglutarate to succinyl coenzyme A are inhibited.



- Aerobic metabolism is decreased, and less adenosine triphosphate is produced.



- Elevation of pyruvate concentration can alter neuronal function.

PTAQUILOSIDE

- In alkaline conditions, the ptaquiloside is converted to the active carcinogen dienone that alkylates DNA leading to tumor formation.

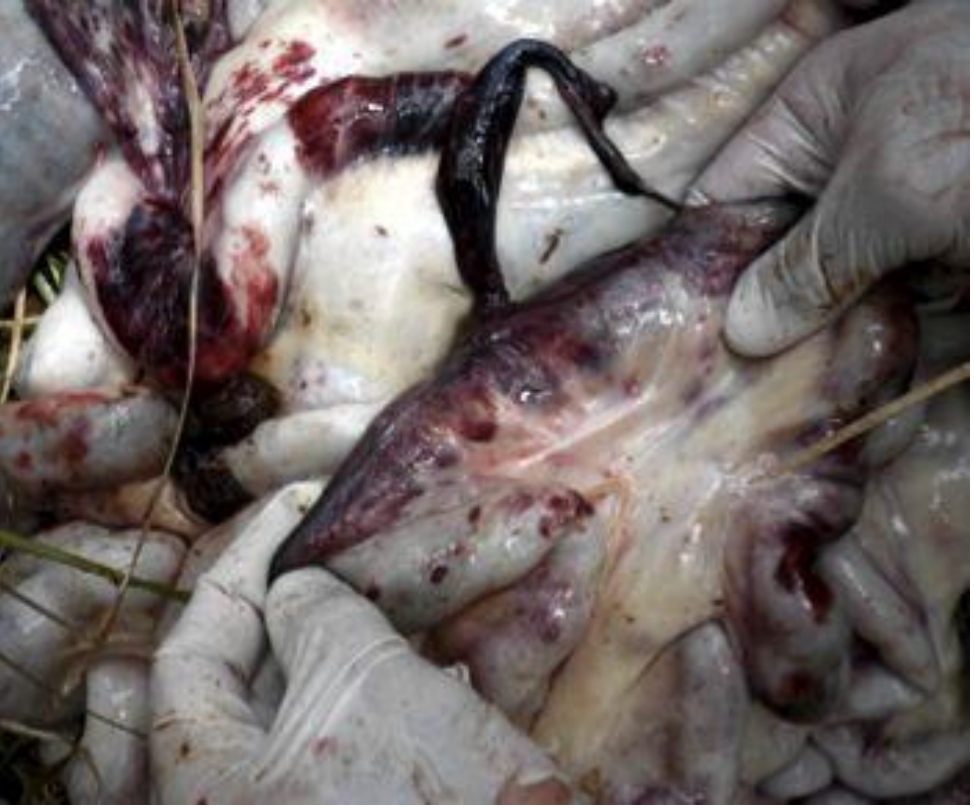
- Formation of small polyp like tumors in the bladder often leads to multiple bleeding that causes formation of red urine (enzootic hematuria/ red water disease).

Diagnosis

- History of exposure
- Clinical signs
- Decreased serum thiamine concentration
- Decreased erythrocyte transketolase activity
- Elevated serum pyruvate concentration
- Elevated serum lactate concentration

Post-mortem finding

- Acute bracken poisoning in cattle- multiple hemorrhages throughout the carcass.
- Necrotic ulcers present in the GI tract.
- In chronic enzootic hematuria in cattle.



1. Hemorrhage in intestine

2. Hemorrhage over serosal surface of the omasum

Treatment and Prevention

- Thiamine (vitamin B1) 0.5–5 mg/kg IV, subcutaneously.
- CATTLE
- Blood transfusion up to 4 L
- Broad-spectrum antibiotics

Copper

- Copper and molybdenum are intimately related.
- Chronic copper toxicities has a component of molybdenum deficiency.
- Molybdenum intoxication manifests as a copper deficiency.
- There is an interaction between sulfur, copper and molybdenum.

Source

- Copper-containing fungicides and algaecides (copper sulfate)
- Anthelmintic
- Dietary supplementation calculation errors
- Contamination from mining operation

Species

- Sheep most sensitive, goats more resistant, cattle, swine.
- Copper intoxication in dogs usually related to breed disposition to copper storage disease (Bedlington terriers)

Clinical Signs

I. CHRONIC TOXICOSIS

- Hemolytic crisis
- Weakness
- Pale mucous membranes
- Anorexia
- Hemoglobinuria
- Hemoglobinemia
- Icterus

Figure 1. Severe icterus in ocular mucosae in sheep.

ACUTE TOXICOSIS

- Gastrointestinal pain
- Nausea, vomiting
- Colic
- Diarrhea
- Shock

Mechanism of action

- NORMAL COPPER MOVEMENT IN MAMMALIAN CELLS-

➢ Copper is absorbed from the gastrointestinal tract.

➢ Most mammals absorb copper from the small intestine.

➢ Sheep also absorb copper from the large intestine

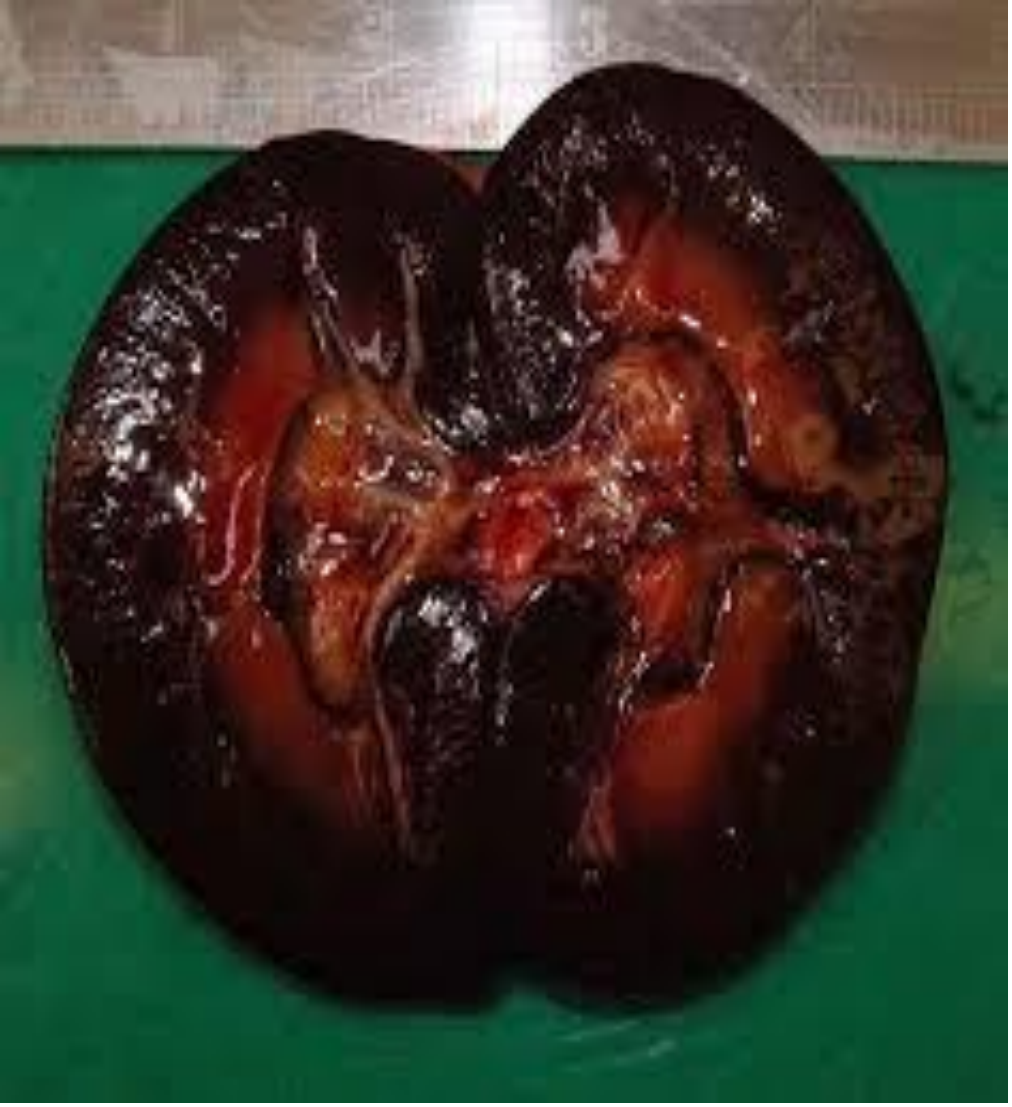
➢ Copper is bound to a serum protein—albumin or transcuprin.

➢ Most absorbed copper is initially transported to the liver and kidney.

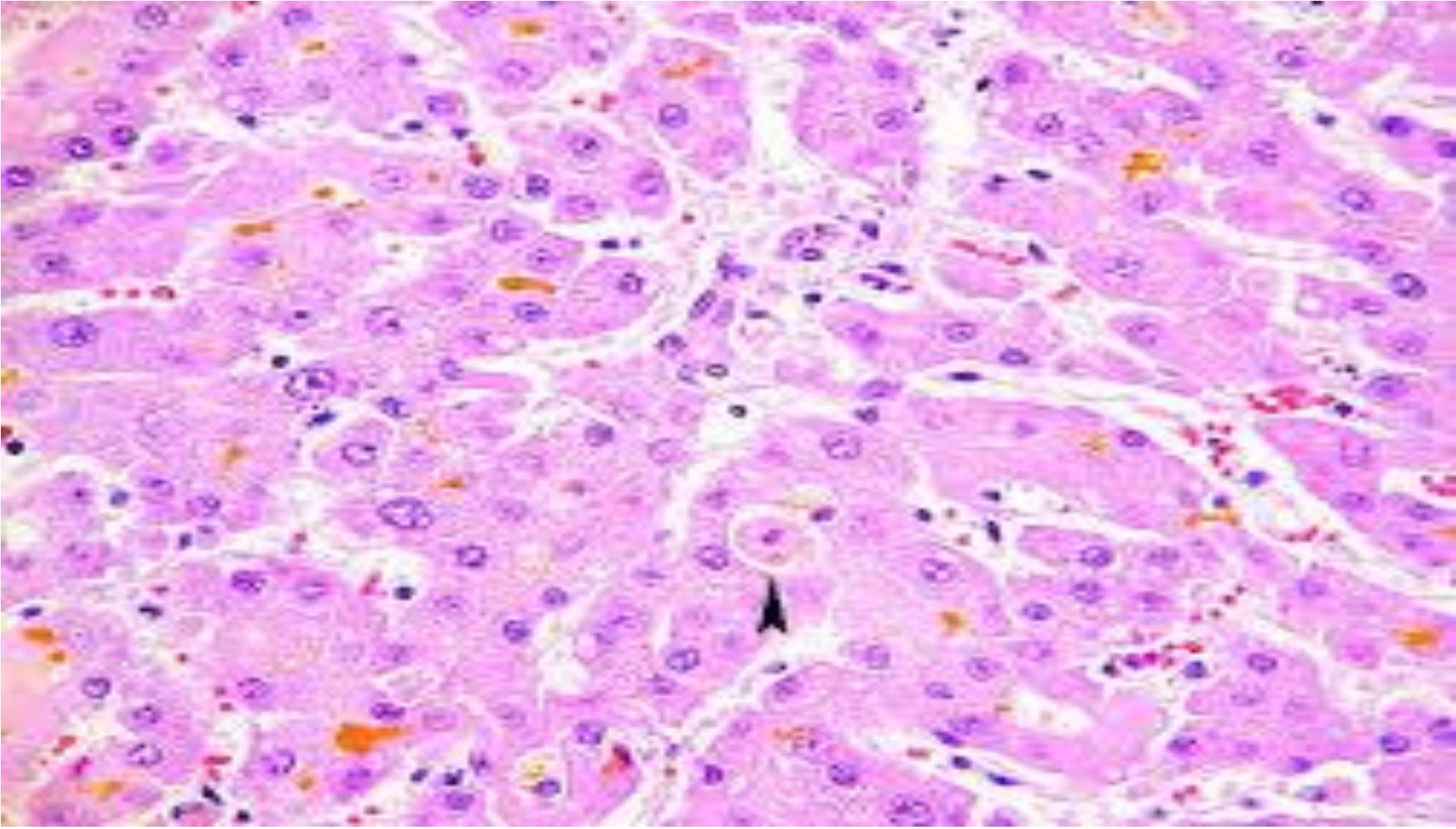
- In chronic poisoning- copper accumulates in the liver where it cause hepatic necrosis, and then copper is released into the bloodstream.
- This results in the lysis of red blood cells.

GROSS AND HISTOPATHOLOGIC FINDINGS

- Enlarged, gun metal–colored (bluish-black) kidneys
- Red-colored urine (from hemoglobin)
- Cytoplasmic vacuolation of hepatocytes
- Renal tubular necrosis
- Hemoglobin within renal tubules
- Hepatic necrosis
- Icterus



Characteristic gun metal kidney of sheep with chronic Cu toxicity



Liver from a 4-year-old Suffolk ewe that died with lesions of a hemolytic crisis. Note the bile stasis and individual hepatocyte necrosis (arrow)

Diagnosis

- Clinical signs,
- Clinical pathology increased serum bilirubin concentration
- Hemoglobinemia
- Hemoglobinuria
- Increased serum concentration of liver enzymes (lactate dehydrogenase, aspartate aminotransferase, sorbitol dehydrogenase)

Treatment

- SYMPTOMATIC THERAPY
  - Fluids

- CHELATION THERAPY
  - D-penicillamine
  - Ascorbic acid increases copper excretion
  - Chelation too expensive for treating a flock of sheep

- PREVENTION
  - Administer ammonium or sodium molybdate 50 to 500 mg/kg per day in feed.
  - Maintain 6:1 copper to molybdenum ratio in sheep rations..

Molybdenum (Teart Scours, Peat Scours)

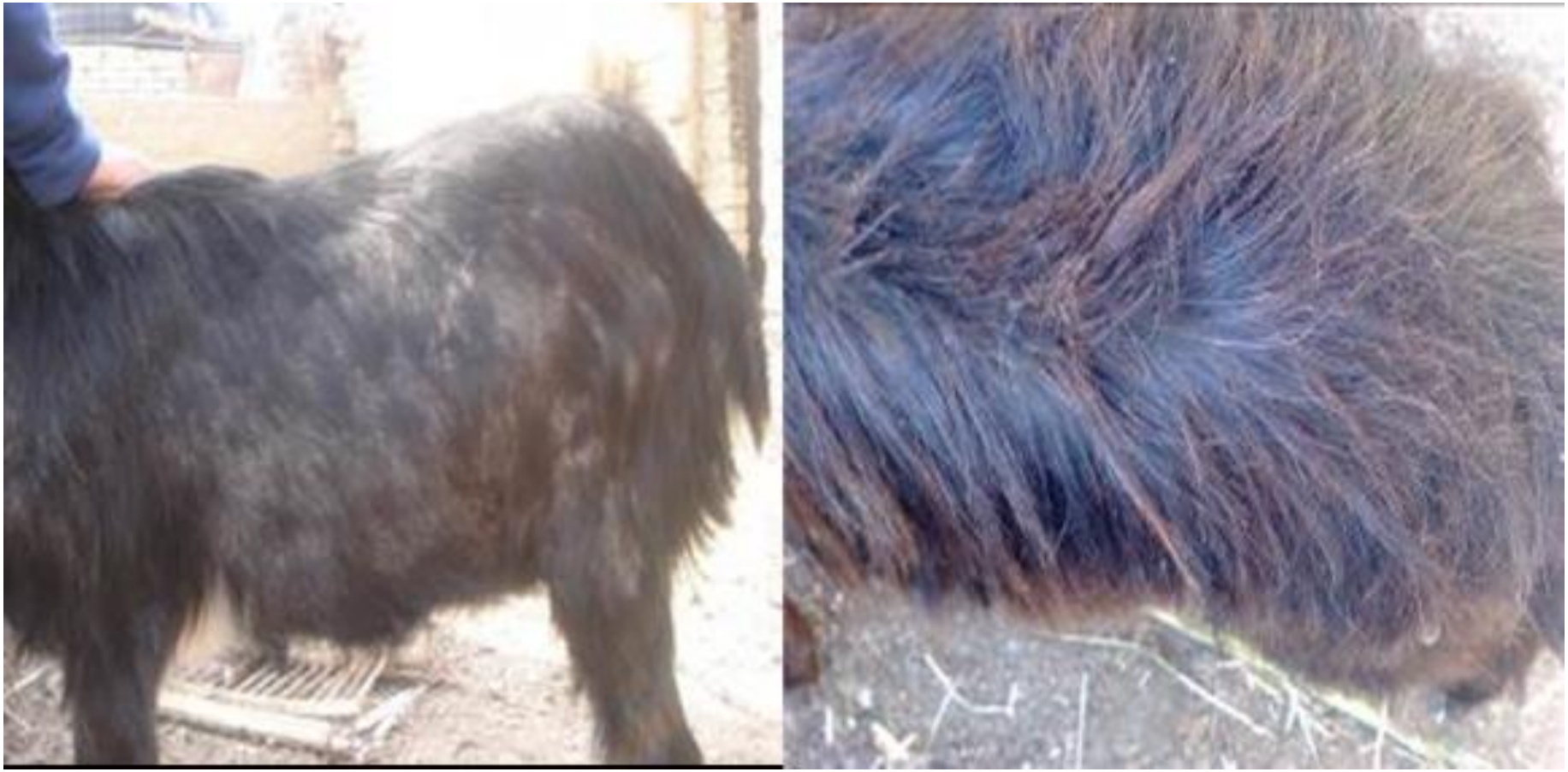
- Toxicities manifests as copper deficiency.
- A complex interaction occurs between molybdenum, copper, and sulfur.

Species

- Cattle (young more susceptible than old) most commonly, sheep.
- Horse and pig usually not affected.

Clinical Signs

- Diarrhea (teart scours)
- Fluid feces, gas bubbles in the feces
- Depigmentation of hair coat, periocular distribution more noticeable on black animals
- Lameness
- Decreased growth rate



Hypocupremic goat show hair depigmentation and steely appearance

➢ Clinical pathology

- Decreased packed cell volumes
- Microcytic, hypochromic anemia

Toxicity

- Interaction with other minerals
- Elevated sulfur concentration in diet decreases copper and molybdenum uptake.
- Molybdenum toxicosis can be potentiated by high sulfur content or low copper content.
- In ruminants (cattle) >10 ppm in the diet induces toxicosis.
- A copper to molybdenum ratio less than 2:1 precipitates toxicosis.

Mechanism of Action

- Molybdenum toxicosis induces copper deficiency.
- Copper is bound by molybdenum to form a soluble complex.
- The complex is excreted in urine.
- Body stores of copper decrease.
- Activity of copper-sensitive enzymes (e.g., superoxide dismutase) decreases.
- Molybdenum may have direct effects on the liver and kidney.

Diagnosis

- Clinical signs
- History of exposure to sources of molybdenum
- Chemical analysis
- Molybdenum concentration in liver >5 ppm
- Copper concentration in liver <10 ppm

Treatment and Prevention

- Remove animal from source of molybdenum (pasture or feedstuff).
- Administer copper replacement therapy.
- Copper glycinate injection
- Short duration of action copper in the form of sulfate or oxide provide 1 g copper per head per day.

Nitrate Intoxication

- A common intoxication of ruminants that can cause sudden death.
- Nitrate (NO3) is absorbed by the roots of plants and converted to nitrite (NO2).

Source

- Many plants, especially from the genus Sorghum-
- Sudan grass
- Sorghum
- Johnson grass (Sorghum vulgaris)
- Corn (Zea mays)
- Alfalfa
- Barley
- Nitrogen fertilizers, drainage from fertilized fields, water sources.

Species

- Cattle, sheep, and goats are most commonly poisoned by nitrate.
- Neonatal animals are at greater risk.
- All species are susceptible to nitrite intoxication.

Mechanism of Action

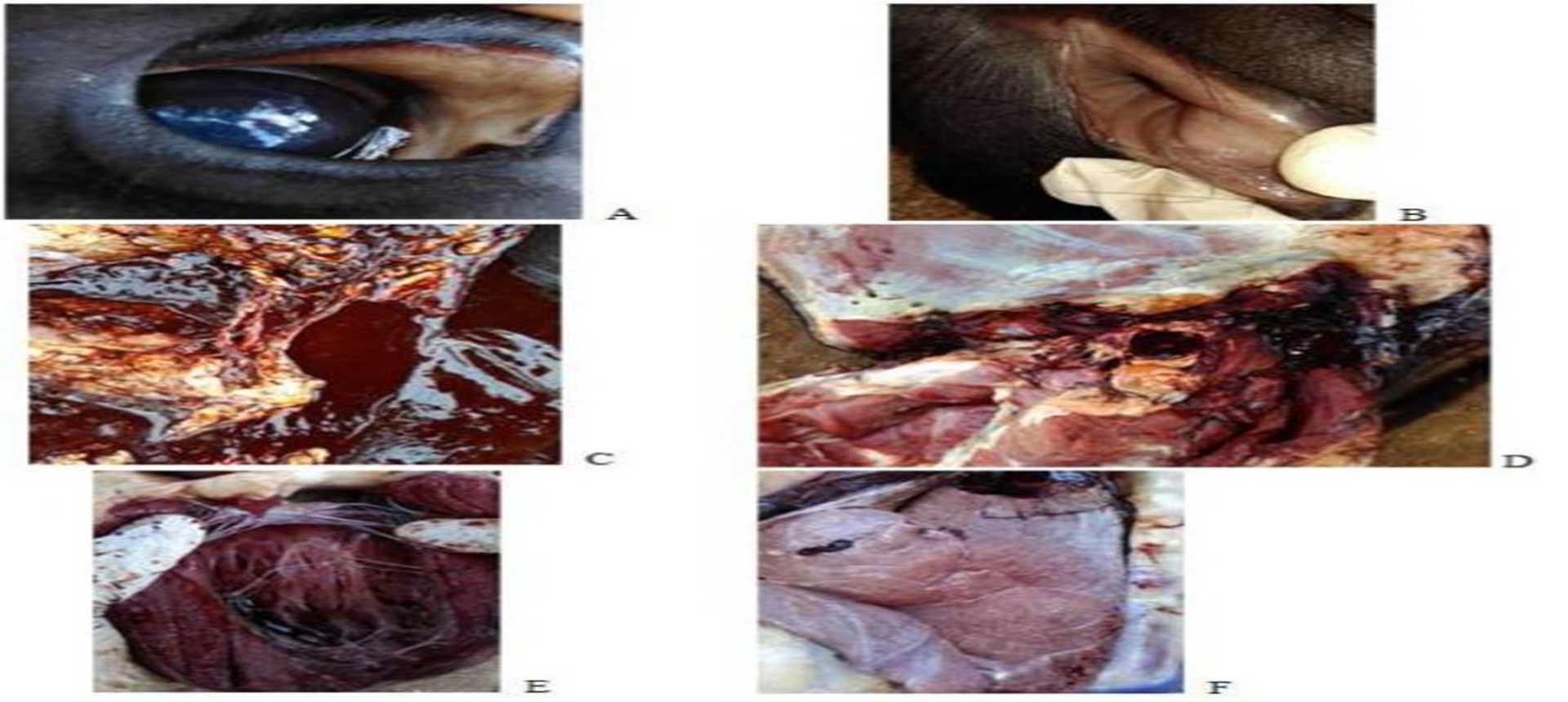
- NO_3 is reduced by ruminal bacteria to NO_2
- NO_2 is absorbed from the rumen into the bloodstream.
- NO_2 oxidizes the iron in hemoglobin from ferrous (Fe^{2+}) to ferric (Fe^{3+}) state.
- This form of hemoglobin is called met hemoglobin (MetHb).
- MetHb is not capable of transporting oxygen to tissues.

Clinical Signs

- Rapid clinical course
- Signs to death generally less than 3 hours
- Sudden death with no signs
- Tachypnea, , tachycardia
- Restlessness
- Dyspnea
- Ataxia
- Cyanosis
- Terminal convulsions

Post-mortem findings

- In acute poisoning hemorrhagic gastroenteritis, congestion of internal organ.
- Inflammation of kidney and urinary bladder.
- Blood become chocolate color due to met hemoglobin formation.
- Tissue may also be stain brown and mucus membranes are cyanotic.

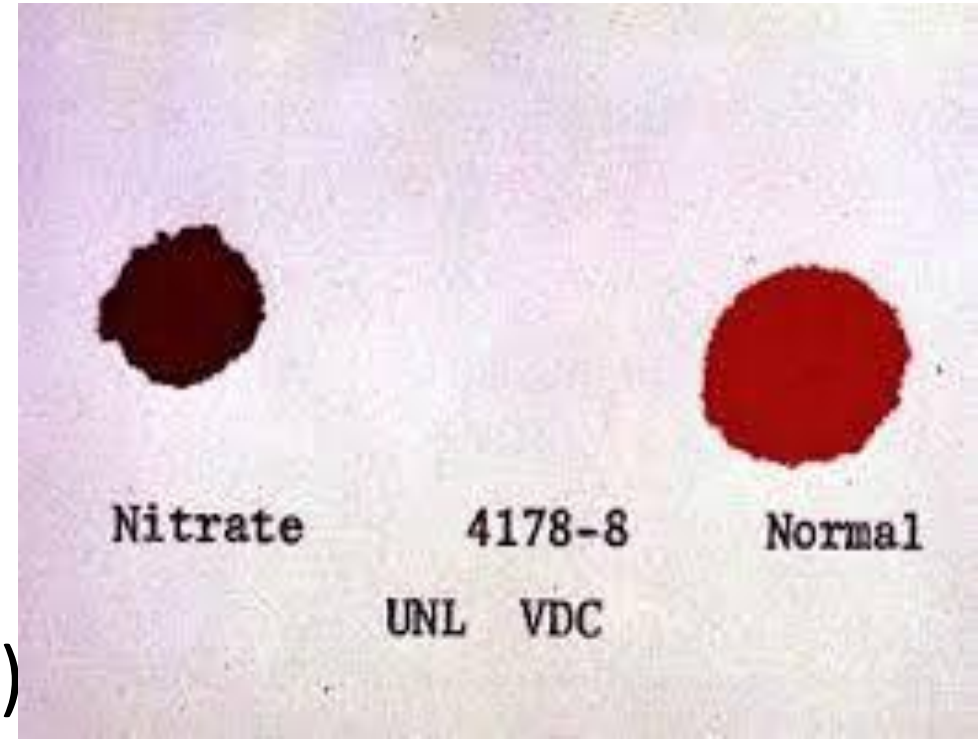


A) Brownish mucosa of conjunctiva; B)brownish mucosa of vaginal vestibule; C) chocolate color blood; D) cherry colored skeletal musculature; E) cherry colored myocardium; F) brownish lung; G)

Diagnosis

- History of feed-related intoxication or death
- Clinical signs
- Chocolate-brown–colored blood
- Chemical analysis of suspect feed and water

- Chemical analysis
- Serum
- Urine
- Ruminal contents
- Aqueous humor (eyeball)



Treatment

- Goal is to reduce met hemoglobin to normal hemoglobin.
- Administer methylene blue 4–30 mg/kg IV of 1% solution.
- Rapidly reduced by NADPH MetHb reductase in erythrocytes
- Reduced methylene blue reverts MetHb back to Hb
- Remove the source (feed or water).

Fluoride Intoxication

- Fluorosis is most common in herbivores as chronic intoxication.
- Fluorosis occurs in older animals (breeding beef cows and dairy cattle) more commonly than in younger animals.

Source

- Consumption of plants or soil contaminated with fluoride from industrial operations (smelter plants, fertilizer manufacturing)
- Rock phosphate contaminated with fluoride
- Water containing fluoride

Species

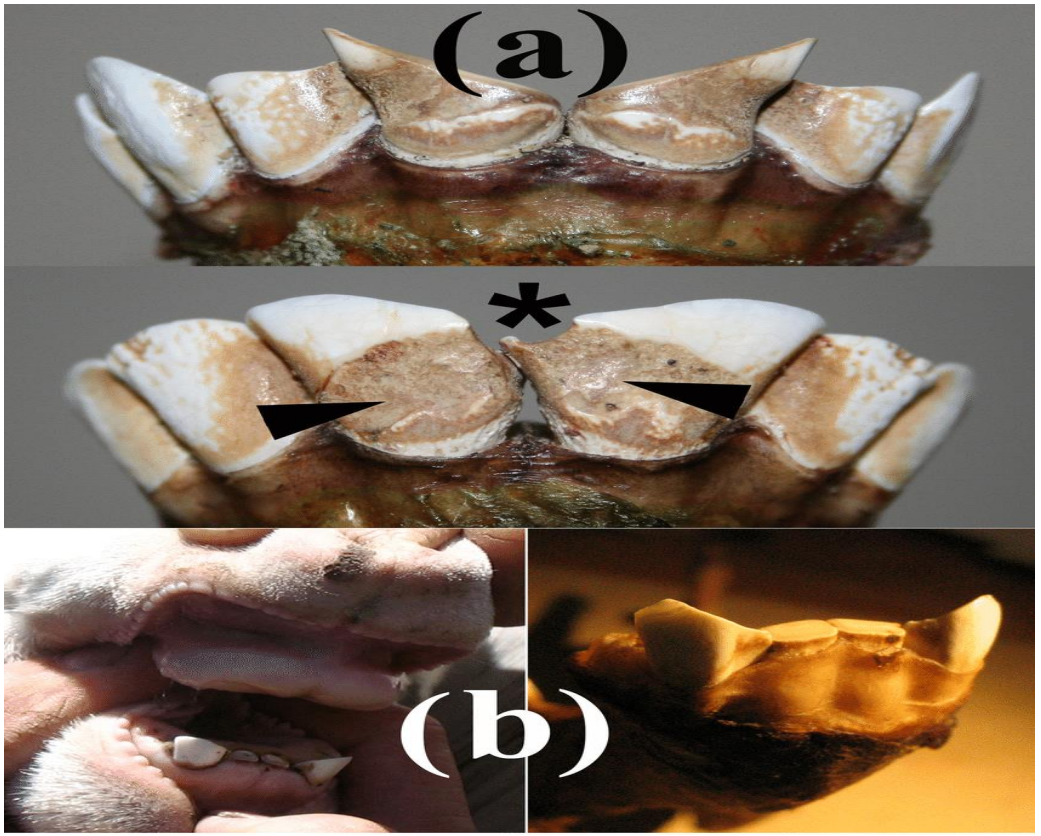
- All species susceptible
- Herbivores at greatest risk of chronic fluorosis
- Cattle and sheep affected more often than horses

Mechanism of Action

- Fluoride is absorbed and alters production of the bony matrix.
- Fluoride has an affinity for calcium.
- Fluoride can replace the hydroxyl groups in the hydroxyapatite of bone.
- Low concentration increases bone density and strength.
- Higher concentration causes formation of weaker bones and teeth.

Clinical Signs

- Enamel hypoplasia
- Mottled or stained teeth
- Excessive dental wear
- Lameness



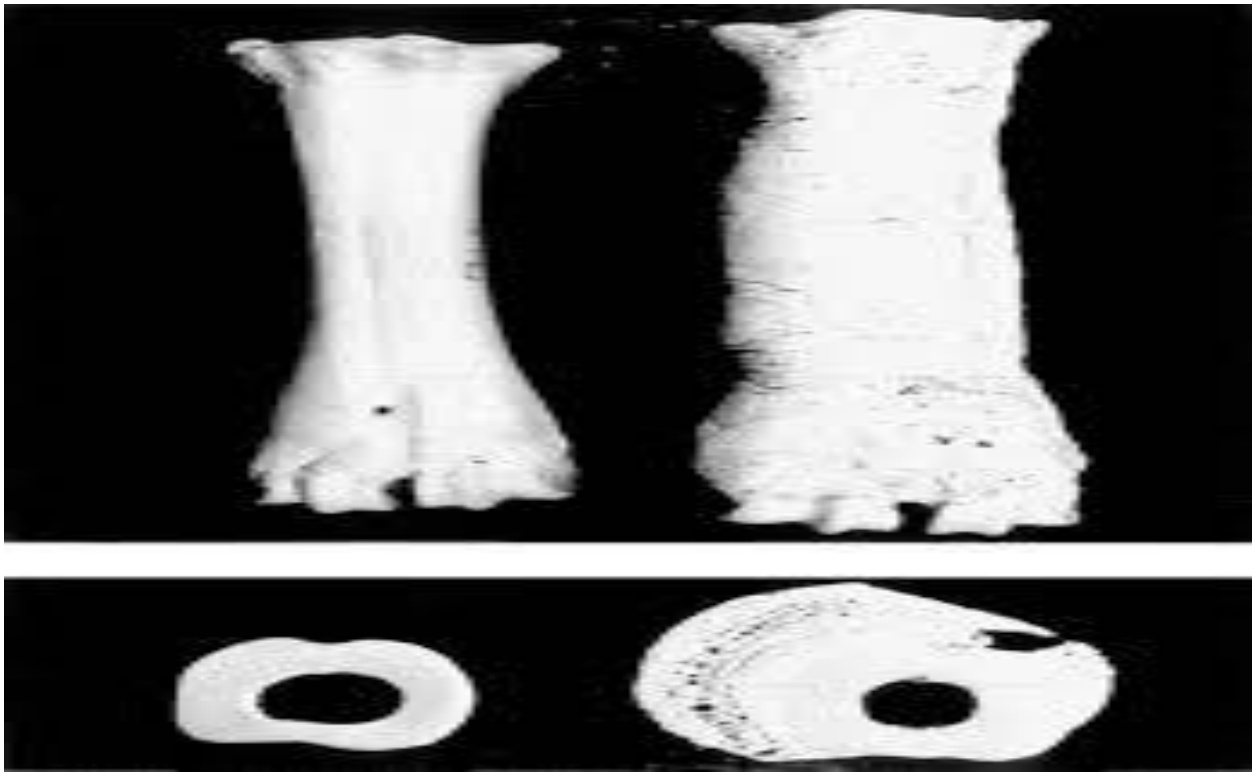
- Exostosis of the diaphysis or metaphysis of weight-bearing bones

Post mortem findings

- Acute toxicity-
- Cyanosis and early rigor mortis
- Hemorrhagic gastroenteritis, congestion and edema of the organ.

- Chronic toxicity-
- Mottling, staining and excessive wearing is seen in the teeth.
- Bones become chalky white, soft and thickened in diameter

- There is atrophy of spongia, defective and irregular calcification of newly formed osseous tissue, hypoplasia of enamel and dentin.



Comparison of normal bovine metatarsal bone (left) with a bone from an animal with severe osteofluorosis. Marked periosteal hyperostosis with encroachment upon articular structures is apparent.

Diagnosis

- Clinical sign
- History of exposure
- Chemical analysis for fluoride
- water should contain <5 ppm fluoride

Treatment

- No specific therapy for chronic fluorosis.
- In areas with elevated fluoride water content, diet should be low in fluoride.
- Supplementation with sources of aluminum, calcium carbonate and defluorinated phosphate may decrease fluoride absorption and enhance excretion.


Thank
you!!