COBALT DEFICIENCY
SALT SICKNESS; PINE OF SHEEP; WHITE LIVER DISEASE IN SHEEP

Cobalt deficiency is a disease of ruminants, due to primary or secondary cobalt deficiency, which is essential for synthesis of vitamin B_{12} (cyanocobalamin). The disease characterized clinically by disturbances in appetite (such as inappetence and pica), loss of bodyweight, loss of production, and defect in reproduction performance in sheep.

EPIDEMIOLOGY:

- The disease occurs in ruminants; sheep and cattle.
- Cattle less susceptible than sheep.
- Young ruminants (lambs and calves) are more affected than adults.
- Bulls, rams and calves are more commonly affected, although dairy cows kept under the same condition may develop a high incidence of ketosis.
- The disease does not occur in omnivores or carnivores because vitamin B_{12} is present in their feed (animal source protein such as meat). Horses appear to be unaffected.

ETIOLOGY:

1. Primary cobalt deficiency: occurs only on soil which are deficient in cobalt such as sandy, pumice and granite soils, volcanic ash soil (as in Japanese soil), acidic soil, high rainfall soil, and heavily liming of soil (calcium carbonate) will reduce the availability of cobalt in soil, and manganese appears to have a similar action.
    - Pastures containing less than 0.04 - 0.07 mg/kg DM result in disease in cattle and sheep (minimal daily requirement is 0.04 – 0.07 mg/kg DM of cobalt in sheep and cattle)
2. Secondary cobalt deficiency:

PATHOGENESIS:

Cobalt is unique as an essential trace element in ruminant nutrition because it stored in the body in limited amounts only and not in all tissues.

The function of cobalt in ruminants:

1. Cobalt in rumen is participating in the production of vitamin $B_{12.}$ In ruminants, the requirement for vitamin B_{12} is very higher than other species.
2. (via the rumen flora, Cyan-globulin + Cobalt ------→ Vitamin B_{12}). Vitamin B_{12} is important for normal erythropoiesis.
3. Cobalt is an important for metabolism of propionic acid (mobilization of the propionic acid via rumen).
4. Cobalt and vitamin B_{12} are important in carbohydrate metabolism.
5. Cobalt may play a role in the synthesis of thiamin (vitamin B_1)

The function of the B_{12} in ruminants:

- It is Important for metabolism of nucleic acid, and protein.
- It has function in carbohydrate and fat metabolism.
- It plays role in purine and pyrimidine synthesis.
- It is important for transfer methyl group.
- It has a role in formation of protein from amino acids.
- It maintains the nervous system integrity.
- It promotes red cells synthesis.
- It is an essential cofactor (vitamin B_{12}-dependent enzymes) for methionine synthase and methyl malonyl-CoA mutase enzymes. Methionine synthase transfers the methyl group from folic acid to homocysteine forming methionine. So, vitamin B_{12} is important for folic acid metabolism and in case of vitamin B_{12} deficiency leads to secondary folic acid characterized by anemia.

Ruminants depend on gluconeogenesis for energy supply because very little glucose is being absorbed. Rate of gluconeogenesis increases with increase feed intake. The major substrate for gluconeogenesis is propionate. Metabolic utilization of propionate after its absorption from the rumen is dependent on the transformation of propionate into succinyl CoA, that requiring 2 enzymes (biotin- and vitamin B_{12}- dependent enzymes), as: -

Propionate ----------*{ATP + CoA}* ——→ **Propionyl CoA** ---------*{propionyl CoA carboxylase, biotin dependent enzyme; carboxylation}* ———→ **Methyl malonyl-CoA** --------*{methyl malonyl-CoA mutase, vitamin B_{12}-dependent enzyme}* ———→ **Succinyl-CoA.**

Succinyl-CoA enters Krebs cycle for producing energy.

<u>In case of cobalt deficiency, there are: -</u>

Reduction in the synthesis of vitamin B12. Consequently, impairment of propionate metabolism and inability to produce energy (impairment of gluconeogenesis) with accumulation of methyl malonyl-CoA in the blood.

Inability to mobilize propionate from the rumen. Consequently, with failure in appetite.

From 1 & 2, resulting in negative energy status with loss of production and reproduction performances and anemia.

<u>In case of white liver disease in sheep:</u>

The disease is unknown if the disease is a simple cobalt deficiency, or a hepatotoxic disease in cobalt/vitamin B_{12} deficiency because: -

A. Marginal to deficient-cobalt grass is essential for the development of the disease.
B. Hepatic dysfunction occurs in affected sheep.

CLINICAL FINDINGS:

No specific signs are characteristic of cobalt deficiency.

1. Gradual decrease in appetite.
2. Loss of bodyweight., emaciation, and weakness (wasting).
3. Pica is likely to occur, especially in cattle.

4. Signs of anemia as pale mucous membranes, easily fatigued, increase in heart and respiration rates.
5. Losses in reproduction performance (wool and lactation).
6. In sheep, one of the most important signs is the severe lacrimation with profuse outpouring of fluid sufficient to mat the wool of the face.
7. Animal may die within 3 – 12 months after the first appearance of illness.
8. In pregnant ewes, stillbirth, increase neonatal mortality, production of weak lambs unable to stand or sucking.

White liver disease of sheep:

- A specific toxic-hepatic dysfunction of sheep.
- The disease is recorded in New Zealand, Australia, and UK, and Norway.
- The disease characterized clinically by:
  - Acute form: photosensitization.
  - Chronic form: anemia and emaciation

CLINICAL PATHOLOGY:

1- Plasma or serum cobalt and vitamin b12 levels:

VALUES	ruminants
SERUM COBALT	Normal: 1 – 3 µg/dl
SERUM B_{12}	Normal: >0.2 µg/L

2- Liver cobalt content:

	Cattle	Sheep
Normal	>0.3 mg/kg DM	>0.2 mg/kg DM
Deficiency	<0.1 mg/kg DM	<0.05mg/kg DM

3- Methylmalonic acid (MMA) and formiminoglutamic acid (FIGLU) levels in plasma and urine:

- Because the difficulties in interpretations of serum vitamin B_{12}, the level of plasma or urine MMA is used as diagnostic and prognostic indicators, as well as it can differentiate between subclinical and clinical cobalt deficiency. An elevated plasma concentration of MMA is early indicator of functional vitamin B_{12} deficiency:
- Neither MMA nor FIGLU is a normal constituent of urine and their presence in urine without the need for quantitative measurement is probably a positive indication of cobalt deficiency.

VALUES	Plasma MMA
Normal in barley-fed animals:	upper limit is 10 µmol/L
Normal in grass-fed animals:	Upper limit is 5 µmol/L

4- Hematology:
   - Affected animals are anemic (***a normocytic, normochromic, non-regenerative anemia***), but their hemoglobin and erythrocyte counts are within normal range because of associated hemoconcentration.
   - The anemia is normocytic and normochromic.
5- Serum biochemistry:
   - Hypoglycemia: < 60 mg/dl.
   - Alkaline phosphatase activity: low < 20 U/L.

NECROPSY FINDINGS:

Gross lesions:

- Extreme emaciation carcass.
- Severe anemic mucous membranes.
- Spleen is dark due to hemosiderin accumulation.
- Liver in sheep is pale and fatty.

Microscopic lesions:

- Fatty infiltration in hepatocytes of sheep.

TREATMENT:

- By either oral cobalt administration or injection of vitamin B12, as:

	Cattle	Sheep
Oral cobalt sulfate	3 – 5 mg/daily/adult cow for 2 weeks	1 – 2 mg/day/ adult sheep for 2 weeks
IM vitamin B_{12}	4 – 7 ug/Kg BW/ week for 3 weeks. or 100 -300 ug/ sheep or lamb/week for 3 weeks. 1 mg/lamb give protection for 14 weeks.	

CONTROL:

1- Recommended daily requirement is 0.11 mg cobalt /Kg DM. Supplementation the diet with cobalt at rate: 0.1 mg/day for sheep, and 0.3 – 1.0 mg/day for cattle.
2- Top-dressing is applied effectively in deficient soils, by using cobalt sulfate 400 – 600 g/ hectare annually.
3- Cobalt heavy-heavy pellets: used in deficient areas, containing 90 % cobalt oxide in the form of boluses (5 g/sheep and 20 g/ cattle).
4- Controlled-release glass boluses of cobalt: also used.
5- Combine cobalt with administration of anthelmintics: anthelmintics are suitable and effective vehicles for supplementing the diet with selenium and cobalt on a regular basis. As, the periods of highest incidence of selenium and cobalt deficiency are coinciding with helminthiasis.

IRON DEFICIENCY

Iron deficiency is usually primary and most likely to occur in newborn animals whose sole source of iron is the milk of the dam, as the milk is being a poor source of iron and the storages of iron in the liver of the newborn are insufficient to maintain normal hemopoiesis for more than 2 – 3 weeks, particularly in piglets. Secondary iron deficiency may occur under certain circumstances such as hemorrhage or excess of calcium in ration. The disease is characterized by iron deficiency anemia.

N.B.: *Iron is not actively excreted from the body in urine or in the intestines. Iron is only lost with cells from the skin and the interior surfaces of the body, intestines, urinary tract, and airways.*

ETIOLOGY & EPIDEMIOLOGY:

I-Primary Iron deficiency in newborn animals fed entirely milk:

1. The iron deficiency is not common in farm animals except in the very young (newborn) whose sole diet is milk of dam, because the milk is a poor source of iron.
2. The iron deficiency anemia in newborns occurs because of: -
    a. They have insufficient iron storages in their livers to maintain normal hemopoiesis.
    b. The milk is the poor source of iron.
    c. They do not have access to the soil, which is the main source of iron in young animals.
    d. They grow rapidly and their requirement for iron is high.
3. The disease usually occurs in piglets at 3 – 6 weeks old, and in lambs at 7 – 10 days. In such animals, the iron deficiency could be prevented when iron dextran is injected after birth (24 hours after birth in lambs, and within 1 weeks after birth in piglets).
4. The disease occurs in claves (*particularly, veal calves*) when fed on milk replacers or milk containing only ≤ 10 mg iron/kg DM (that will cause marked anemia and reduction in growth rate in such calves). The daily intake of iron from milk is 2 – 4 mg in calves, and their daily requirement during the first 4 months of life is of 50 mg/kg BW, so that iron supplementation of the diet is advisable when the diet is entirely milk.
5. The dietary iron requirement for rapidly growing lambs is between 40 – 70 mg/kg BW, and growth rate is suboptimal on diets of < 25 mg/kg BW

N.B.:

- *Good quality veal is traditionally pale (white) in color and is produced by feeding calves milk replacers or milk diet low in iron concentration, because the pallor of veal is due to low concentration of myoglobin and other iron containing compounds in muscles. Feeding milk replacers with 50 mg/kg DM is considered, physiologically, the optimum amount of iron for veal calves but may be too high for acceptable carcass yield in some countries while iron deficient-milk diet is associated with reduction growth rate and a high incidence of infection diseases because of impaired immune system. The objective in the veal calf management is*

to find the narrow line between the maximum production of white (pale, highly acceptable veal) and degree of anemia insufficient to interfere with maximum production.

- *Even when hay and grain are fed to calves and lambs in addition to milk, administration of iron-dextran preparations at dose rate of 5.5 mg/kg BW, leads to marked growth response.*

II- Secondary iron deficiency, due to continued blood loss by hemorrhage: this occurs in any animal and may cause subclinical anemia, and iron deficiency such in case of:

1. Heavy infestation with blood sucking parasites as in lice infestation in cattle and sheep (may lead to fatal anemia in severe infestation, while in chronic infestation may cause no-regenerative anemia and subnormal serum iron levels), in horses infested with strongloids.
2. Addition of calcium carbonate or manganese to the diet of weaned and finishing pigs may cause a conditioned iron deficiency and a moderate anemia but this effect is not apparent in adult pigs.

PATHOGENESIS:

Function of iron:

1. More than half of the iron in the animal body is found as a constituent of hemoglobin.
2. A relatively small amount is found in myoglobin.
3. The iron is important for synthesis certain enzymes (which play a part in oxygen utilization) such as cytochrome oxidase 450, catalase and peroxidase.
4. Iron is necessary for immune cells proliferation and maturation, particularly lymphocytes as well as the phagocytic-killing activity (phagocytosis by lysosomal enzyme; peroxidase) via peroxidase, so iron is important for immune system.
5. Iron play a role in energy production.

So, in case of iron deficiency:

1. Reduction in hemoglobin content and hemopoiesis (Anemia).
2. Reduction in growth rate in young rowing animals (*in calf, the reduction in growth may be due to the reduction of half-life of growth hormone in such animal, while in piglets, the reduction of growth is due to marked impairment of gastric secretion of acid and chloride due to atrophic gastritis, as well as villous atrophy of the small intestine and changes in gastrointestinal flora that lead to diarrhea and reduction in growth)*
3. Increase incidence for infections.

CLINICAL FINDINGS:

The clinical signs usually appear in the young growing animals in the form of:

1. Significant reduction in the growth rate.
2. Reduction in the feed intake. The best indicator for anemia in veal calves is loss of appetite.
3. Signs of anemia (weakness or lethargy, dyspnea with increase in respiration rate and pulse rate, pale skin and mucosa, and poor performances).

4. Rough coat and lusterless hair.
5. Edema of the head and forequarters, giving the animal a fat, puffed-up appearance in piglets.
6. Mild diarrhea may occur in piglets but the feces are usually normal in color.
7. Increase incidence to infections, especially enteritis.
8. Atrophy of the lingual papillae.
9. Death usually occurs suddenly, or the affected animal may survive in emaciated, unthrifty condition.

CLINICAL PATHOLOGY:

1. CBC: in primary iron deficiency, the anemia is (***a microcytic, hypochromic anemia, non-regenerative***), while in secondary iron deficiency (due to chronic blood loss in heavy lice infestation in cattle) the anemia is non-regenerative anemia. Reduction in RBCs counts, PCV and hemoglobin concentration. Borderline of iron-deficiency anemia in veal calves at 4 – 5 months age occurs when hemoglobin concentration of 9 g/L and a saturation of total iron binding capacity of 10%.

N.B.:

- ***Anemia*** *is classified as* ***regenerative*** *or* ***nonregenerative****. In a* ***regenerative anemia****, the bone marrow responds appropriately to the decreased number of red blood cells by increasing production of new blood cells. In a* ***nonregenerative anemia****, the bone marrow responds inadequately to the increased need for red blood cells.*

2. Serum iron level:

	Serum iron level
Sheep & cattle	100 – 200 µg/dL
Newborn calves	170 µg/dL at birth, and 65 µg/dL at 2 months old

3. Serum ferritin concentration: ***Ferritin*** *is a universal intracellular protein that* stores *iron (about 23% iron) and releases it in a controlled fashion. keeping iron in a soluble and non-toxic form. Ferritin that is not combined with iron is called* ***apoferritin****. In case iron deficiency, the ferritin concentration decreases.*

NECROPSY FINDINGS:

Gross examination reveals: -

1. The carcass is emaciated, with characteristic pale, watery blood, and moderate anasarca.
2. The heart is dilated, and enlarged.
3. Liver is enlarged and has mottled tan-yellow appearance.

Microscopic examination: -

1. The bone marrow examination reveals: maturation asynchrony of the erythroid line and lack of hemosiderin stores.
2. Peri-acinar hepatocellular changes (typical of hypoxia).
3. Decreased number of parietal cells in the gastric mucosa and atrophy of the villi of small intestine. (mainly in piglets).

TREATMENT: -

Parenteral iron treatment:

1. Treatment is usually parenteral and consists of organic-iron such as iron-dextran, iron saccharate or gluconate, iron-sorbitol-citric acid complex. These compounds are irritant and may cause large slough when injected IM, so you must give them exactly as prescribed by the manufacturing. ***The dose is 0.5 – 1 g elemental iron in one injection per week***. *The parenteral administration in horse may cause death within a few minutes after administration*.
2. Vitamin B12 is often used in the same injection at dose rate of 5000 µg/week in a single dose.
3. Other additives may be used as folic acid, and choline.

Oral iron treatment:

1. Using iron sulfate or gluconate at a dose rate of 2 – 4 g/day for 2 weeks (in horse and cattle), is effective, safer, and much cheaper, but being unpalatable, so it dispensed in liquid form to be mixed with molasses (as iron dextran IM injection in horse may lead to death within a few minutes after injection).
2. Daily dosing of ferrous sulfate 4 mL of 1.8% solution.
3. Iron pyrophosphate 300 mg/day for 7 days

CONTROL: -

The preventive measures must be directed at newborn animals (piglets, lambs and veal calves), as: -

1. ***Giving iron requirements:***
    a. Piglets: feeding sows a diet containing 2 g iron/ kg DM of diet will prevent iron deficiency anemia in piglets as the piglets will ingest about 20 g of sow's feces/day, which will contain sufficient iron for them.
    b. Veal calves: milk replacer of veal calves may contain up to 40 mg/kg DM of iron for the first 2 months of life, and only 10 – 15 mg/kg DM for finishing period.
    c. In heifer calf *(that used for herd replacement)*: the milk replacer contains 100 – 1000 mg/kg DM. (*note that the requirement of iron for heifer calf is more than that for veal calf, why?*)
2. ***Iron deficiency or Iron deficiency anemia in newborn animals can be prevented by oral treatment directly after birth either orally or injection.***
    a. ***Oral supplement:*** *the iron be given within 12 hours of birth*, especially in piglets and lambs), because *the absorption of iron occurs through the perforate neonatal intestinal mucosa, later administration is not followed by absorption.*
    b. Parenteral injection (IM):

Iron dextran IM injection after birth		
Veal calf	**Housed lamb**	**piglet**
In the first week after birth 300 -600 mg/calf	At 24 hours after birth IM injection of 300 mg/lamb	Between 3rd – 7th day after birth 100-200 mg/piglet

MANGANESE DEFICIENCY

Manganese deficiency in the animal may be primary or secondary, and characterized clinically by infertility (in both male and female) and skeletal deformities both congenital and after birth.

ETIOLOGY:

1. Primary manganese deficiency: occurs in certain areas or localities where the manganese is geological deficient in the soil. Most pastures contain 50 – 100 mg/kg DM, and that considered insufficient in ruminants and causing manganese-responsive infertility, poor quality semen, and skeletal deformities in calves. The level of manganese in diet > 200 mg/kg DM, is considered sufficient to prevent such conditions.
    a. Soil contains < 3 mg/kg of manganese is likely to cause manganese-responsive infertility in cattle.
    b. High Alkalinity of the soil will reduce manganese availability in plants, that will reduce the manganese content of the pastures causing primary manganese deficiency in animals fed on these pastures.
    c. Heavy liming of the soils will reduce the manganese availability in the plants.
    d. Maize (corn & corn silage), and barley have the lowest manganese content, wheat or oats have 3 – 5 times more than maize, and bran is the richest natural source of manganese (10 – 20 times more than maize).
    e. Cow's milk is exceptionally low in manganese.
2. Secondary manganese deficiency: due to presence of some factors that reduce the availability of ingested manganese, such as: -
    a. An excess of calcium and/or phosphorus in the diet will reduce the availability of the ingested manganese to cattle, particularly in young animals.

Only 1 % of ingested manganese is absorbed from the diet and the liver removes most of it, leaving very low blood levels of it.

PATHOGENESIS:

Functions of manganese: -

1. Manganese plays an active role in bone matrix formation.
2. Manganese important for synthesis of chondroitin sulfate, responsible for the rigidity of the connective tissue.
3. Important for normal fertility in male (poor quality semen) and female (increase complications with ovulation and failure of the ovary to release ova).

In case of manganese deficiency, there are defects in bone matrix formation and chondroitin sulfate synthesis, resulting in skeletal abnormalities, as well as infertility.

CLINICAL FINDINGS:

I. In adult cattle:

1. Manganese deficiency causing infertility in both male and female, as: -

A. ***In male,*** lead to poor quality semen.
B. ***In female,*** causing manganese-responsive disease in cattle and ewes, in the form of failure or slow to exhibit estrus, failure to conceive, subnormal size of both ovaries, sub-estrus or weak estrus.

II. In calves and lambs (also in other young animals): congenital chondrodystrophy:

1. Small birth weight (< 15 kg BW), poor growth rate and reduction in performance.
2. Congenital limb or skeletal abnormalities including:
3. Limb bone abnormalities including Knuckling over or at the fetlocks, enlarged painful joints, the bones of the affected legs are shorter and weaker than normal giving the animal dwarflike appearance.
4. Bone of the head abnormalities including doming of the foreheads, and superior brachygnathia.
5. Most of the calves are dyspneic at birth, and with snorting and grunting respiration.

CLINICAL PATHOLOGY:

- Manganese levels in blood, hair and liver and tissue:

Manganese	Blood level	Hair level	Liver level	Tissue livel
Normal range	18-19 µg/dL	12 mg/kg	12 mg/kg	2 – 4 mg/kg
Deficiency	< 18 µg/dL	8 mg/kg	< 4 mg/kg	Not affected

NECROPSY FINDINGS:

In congenital chondrodystrophy in calves, there are:

A. Gross abnormalities:
   a. Shortness, weakness limb bone, enlarged joints, doming of the forehead, and superior brachygnathia.
B. Microscopic abnormalities (histopathology):
   a. There is poor cartilage maturation with excessive amounts of rarefied cartilage matrix.
   b. Degenerative changes in the chondrocytes.
   c. Severe reduction in mucopolysaccharide content of all body hyaline cartilage.

TREATMENT AND CONTROL:

A. The congenital chondrodystrophy in newborns are not treated.
B. Manganese-responsive infertility in cattle:
   a. Respond to manganese sulfate ($MnSO_4$) at dose rate of 2 – 4 g/day (providing animal with 980 mg elemental manganese).
   b. Daily diet supplementation with 75 – 150 mg/kg DM, for 9 weeks, begins 3 weeks before the first service to control infertility in adult and congenital chondrodystrophy in newborns.