DEGENERATIONS AND METABOLISM DISORDERS

Asst. Prof. Dr. Ozan AHLAT

oahlat@ankara.edu.tr

PIGMENT METABOLISM DISORDERS

Pigment (Dye, staining)

- Various exogenous and endogenous substances can alter the color of tissues.
- Some pigments are physiologically found in tissues and organs.
  - **Melanin** in the skin,
  - **Hemoglobin** in erythrocytes,
  - **Bilirubin** in bile

Pathological pigments

- It may be that the (endogenous) pigments normally produced in the body are **more, less or not normal.**
- Discoloration of the skin and hair as a result of the absence of melanin pigment in albinismus
  - Increased bile pigment (bilirubin I and II) in the blood and staining the tissues yellow in the icterus
- Improper production of pigments produced in the body **genetically, enzymatic or for any reason, or the formation of another pigment instead**
  - Porphyria

Pathological pigments

- Exogenous pigments can also **accumulate** in the body and lead to discoloration.
  - Anthracosis
- Some pigments are formed as a result of some diseases. T
- he appearance of this type of pigment in organs and tissues is considered a symptom of that disease.
- In addition, as a result of their accumulation, they disrupt the function of that organ and are themselves the cause of the disease.

Classification

Endogenous pigments

- **Hemoglobinogenic pigments**(Hemoglobin, Hemosiderin, Hematoidin, Hematoporphyrin, Formalin, Sulfosiderin, Bilirubin)
- **Anhemoglobinogenic pigments** (Melanin, Cloisonne kidney, Lipofuscin, Ceroid, Dubin-Johnson pigmenti)

Exogenous pigments

- Antracosis, Siderosis, Silicosis, Asbestosis, Calomel, Argyrosis, Tattoos, Kaolin, Carotenoid pigments

Hemoglobinogenic (Hematogenous) Pigments

Hemoglobin

- It is a complex pigment found in erythrocytes.
- It consists of the ferrous compound "hem", which is colored with "globin" in its protein structure.
- The "hem" part is composed of a porphyrin ring and contains iron ferro (Fe++) shape.
- Porphyrin is formed by connecting 4 pyrols with methan bridges (hydrocarbon radicals) and forming a ring-shaped structure.
- This is called protoporphyrin III or uroporphyrin III, and Pyrrolles are called porfobilinogens.

Hemoglobin

- This pigment, which is released by the breakdown of erythrocytes, occurs pathologically in two ways.
- **HEMOLYSIS:** It occurs when erythrocytes in the blood vessels are broken down by an infectious-non-infectious effect. This is called hemolysis, and the phenomenon of anemia that occurs as a result of such destruction of erythrocytes is called hemolytic anemia.
- Its effects and findings occur in many organs.
- **ERYTHROLYSIS:** Hemoglobin is released as a result of erythrolysis by disrupting and breaking down erythrocytes that go out of the vein in relation to local hemorrhages in tissues.
- However, the effect is local.

Hemolytic anemia

Blood parasites

Viral (equine infectious anemia), bacterial agents, bacterial toxins and their products

Toxicity, intoxications

Auto-immune diseases

Isoimmune or isohemolytic effects (blood incompatibility)

Hemolytic anemia

- As a result of hemolysis, **hemoglobinemia** occurs.
- Part of the hemoglobin comes to the kidneys and is excreted in the urine, and **hemoglobinuria** develops.
- Hemoglobin accumulated in the kidneys, **macroscopically,** it causes the kidney to appear dark red in color and with the accumulation of hemoglobin in the tubules, it causes dark red striping.
- **Microscopically,** red-brownish granules are observed in the tubule lümen.
- **Degenerative changes** due to the accumulation of hemoglobin in the kidneys and ultimately **hemoglobinemic nephrosis** are observed.

Localized hemorrhage

- Trauma can physically disrupt a vessel and cause hemorrhage by rhexis (rhexis = breaking forth, bursting).
- Hemorrhage by rhexis can also occur following vascular erosion by inflammatory reactions or invasive neoplasms.
- Minor defects in otherwise intact blood vessels allow small numbers of erythrocytes to escape by diapedesis (dia = through, pedian = leap).
- Erythrocytes move out of the vessels and break down, erythrolysis occurs.
- Hemoglobin is came out, and the tissues are stained red due to erythrocytes and hemoglobin.

Localized hemorrhage

- Erythrocytes that move out of the vessel do not stay in this way for a long time and they are phagocyted by local tissue macrophages or monocytes from the blood and turn into hemosiderin, hematoidin, hematin, converted to biliverdin and bilirubin (Biliverdin and bilirubin are normally formed in the spleen.)

Hemosiderin

- **In hemolytic anemias,** it is possible to see hemosiderosis in the spleen, liver and many organs.
- **In localized hemorrhages,** it occurs only in that area and mostly follows rhexis ecchymosis or hematomas in the skin and subcutaneous tissue related to trauma.
- In both cases, **hemosiderin** can be seen with **hematoidin, biliverdin, bilirubin,** as well as other **hematogenous pigments.**

Hemosiderin

- Most of the erythrocytes destroyed in hemolytic anemia are phagocyted by the cells of the mononuclear phagocytic system (MPS) and accumulate in their phagolysosomes, and such cells are called siderocytes.
- In such events, the accumulation of hemosiderin occurs most often in the spleen and liver.
- The spleen is swollen and acquires a brownish-yellow color.
- A large number of siderocytes are found on microscopic examination.
- With the progression of the process, biliverdin, bilirubin occur and icterus develops.
- It also happens that in the liver, especially Kupffer cells are laded with hemosiderin.

Hemosiderin

- Hemosiderosis related to hemorrhage is formed in the organ where there are hemorrhage from diapedesis or rhexis.
- It depends on the destruction of erythrocytes that move out from vessel.
- Locally, hemosiderin is taken into the cytoplasm of macrophages.
- Chronically, other blood pigments are also encountered.

Hemosiderin

- It is the pigment formed as a result of the destruction of hemoglobin.
- Ferritin is a granular pigment in the form of iron-protein (containing trivalent iron), originating from hemoglobin, golden yellow or yellow brown.
- It is detected in the tissue with **Turnbull's blue and Prussian blue** and stain blue.
- It is normal to have some hemosiderin in the spleen. (In newborns, sometimes in the elderly.)
- **Hemosiderosis** is the accumulation of hemosiderin (Localized or generalized)

Hemosiderosis

Generalized Hemosiderosis

- Hemolytic anemias
- Equine Infectious Anemia
- Blood parasites (Babesiosis, Theileriosis)
- Toxicosis (Chronic Copper toxicosis)

Localized hemosiderosis

- Hemorrhage due to trauma in the skin, subcutaneous tissues and muscles
- Chronic passive congestion

Heart failure cells in lung

- **As a result of heart failure** (especially valvular stenosis), blood becomes stagnant in the lung vessels, capillary bed.
- Erythrocytes from the vessels with impaired permeability move out from the vein (diapedesis hemorrhage), they are destroyed.
- Hemosiderin is phagocytosed by alveolar macrophages and accumulates in their cytoplasm.
- Siderocytes are seen in the lung. Because these are shaped due to heart failure, they are called **heart failure cells**.
- Chronically, fibrosis also develops in the lung.
- The organ has a firm consistency (indurative) and has a brownish discoloration because of the numerous hemosiderin-laden alveolar macrophages (Brown induration).

Hematoidin

- It is a yellowish-colored, hematogenous pigment that refracts light slightly, in the form of spiny (thornlike), crystallized bundle, angular crystal (rhomboid, prismatic crystal) or amorphous, homogeneous granules.
- It occurs by destruction of erythrocytes that move out from the vessel, releasing hemoglobin and removing iron and opening the porphyrin ring.
- It has a bilirubin I structure and **does not contain iron**.
- In internal bleeding, old ecchymosis and hematoma, hemorrhagic infarction and other necrosis, old scar tissues and hemorrhage.

Hematin

- It occurs with the effect of acids on hemoglobin.
- It is a brownish-black hematogenous pigment.
- It is not stained by Prussian blue, since it is attached to the iron in its structure; in this way, it is differentiated from the hemosiderin
- In the kidney tissue after **severe hemolytic crisis.**
- When hemoglobin, which is released in the bleeding that occurs in the stomach ulcer, is combined with stomach acid (hydrochloric acid, HCL), it is because of this pigment that the blood acquires a brownish-black color.
- Hematemesis is the vomiting of blood (gastric bleeding)

Hematoporphyrin

- It is a non-ferrous pigment.
- The porphyrin ring in the hemoglobin molecule is composed of four pyrrole moieties linked together around the central iron ion.
- **Congenital erythropoietic porphyrias** of calves, cats, and pigs are the result of genetic defects caused by a **deficiency of uroporphyrinogen III synthase.**
- The disease name *pink tooth* comes from the discoloration of dentin and bone.

Cloisonné kidney

- **Cloisonné kidneys,** which occur in goats, are the result of proximal tubular basement membrane thickening as a result of deposits of **ferritin** and **hemosiderin.**
- Renal function is **normal.**
- Grossly, these kidneys have diffuse, intense, black or brown discoloration of the **cortex.**

Formalin pigment (Acid hematin)

- The “acid” hematin that forms in tissues fixed in unbuffered, and therefore acidic (pH < 6), formalin appears as dark brown to nearly black, granular or crystalline material mainly in vessels or other areas of the tissue section where erythrocytes (and hemoglobin) are numerous.
- If the formalin solution was not properly buffered.
- It can be so abundant in congested tissues.

Malaria pigment (Hemozoin)

- *Plasmodium spp*. is transmitted by mosquitoes and locate in mononuclear phagocytic system cells such as the spleen, lymph nodes, bone marrow, and erythrocytes, causing hemolysis.
- Splenomegaly
- Crystalline, brownish-brown pigment appears in the MPS cells, and erythrocytes.
- The pigment is not stained by iron stain.

Pseudomelanin (Sulfosiderin)

- Sulfur-hemoglobin or methemoglobin; is a postmortal change.
- It occurs as a symptom of **putrefaction.**
- After death, erythrocytes are hemolyzed.
- Especially, sulfur proteins that found in the intestines are broken down.
- The released sulfur combines with hemoglobin, which is formed as a result of hemolysis, and acquires a greenish color.
- Especially the inner part of the abdominal wall, the serosal surfaces of the intestine and partly other organs close to the intestines are stained green. This is called **pseudomelanosis.**

Bile pigments

- After hemoglobin is destroyed, **iron** and **globin** are used by the body.
- Firstly, **porphyrin** is converted to **biliverdin** by macrophages.
- **Biliverdin** is converted to **bilirubin** via **biliverdin reductase**.
- **Bilirubin**, which enters the blood, comes to the liver in a form dependent on albumin.
- It enters the hepatocyte in the liver, where it is conjugated, combining with **glucuronic acid.**
- **Conjugated bilirubin** is secreted into the bile ducts.

Bile pigments

- When bile reaches the duodenum, **bilirubin** is converted by bacteria to **urobilinogen.**
- Most of the urobilinogen is reabsorbed through the distal parts of the small intestine, transporting it to the liver via portal circulation. **(Entero-hepatic circulation)**
- Part of the urobilinogen participates in the general circulation and is excreted in the urine from the kidney.
- Urobilinogen, which cannot be absorbed from the intestine, is oxidized in the intestine to **urobilin** and **stercobilin** and excreted with feces.
- **Cholemia:** The presence of excess bile in the blood.

Icterus (jaundice)

- Icterus (jaundice) is characterized by the accumulation of bile-colored substances (bile pigment) in the blood and staining the organs yellow.
- Sclera and conjunctiva, mucous membrane of the vagina, omentum, mesenterium, intima layer of the aorta and adipose tissue.
- The icterus consists of three pathways.
  - **Hemolytic**
  - **Hepatotoxic**
  - **Obstruction**

Hemolytic (prehepatic, superfunctional) icterus

- It occurs in various diseases that lead to hemolysis of erythrocytes.
- Excess bilirubin I cannot be processed, accumulates in the blood and hyperbilirubinemia I occurs.

Hemolytic (prehepatic, superfunctional) icterus

- **Blood protozoan diseases** such as Babesia, Theleria, Anaplasma
- **Some bacterial infections** such as hemolytic streptococcus, *Cl. hemolyticum*, leptospira
- **Some viral diseases** such as viral anemia of horses
- **Organic and inorganic toxic substances** that cause hemolysis such as rhizine, saponin, nitrobenzene, chlorate, nitrate, copper, arsenic compounds, lead, snake venom
- **Hemoperitoneum and hemothorax** that develop in cases of diffuse internal bleeding
- Affecting erythrocytes in **some autoimmune diseases and immunological conditions**
- Isoimmune hemolytic anemia (neonatal icterus) in foals

Hepatotoxic (intrahepatic, retention) icterus

- It is based on liver disorder.
- When **hepatosis or hepatitis** is formed in the liver by **toxic, infectious effects** and **cirrhosis** occurs, bilirubin I coming to the liver cannot be processed and sufficiently converted into bilirubin II.
- Both the binding (conjugation) of bilirubin stops partially or completely (conjugation icterus) and the transport stops partially or completely (transport icterus).
- Some toxic infectious effects, such as leptospirosis, are the cause of both hemolytic and hepatotoxic icterus.

Obstruction (posthepatic, resorption) icterus

- Bilirubin I is converted to bilirubin II.
- There is no abnormality in the liver and bile production is normal.
- However, the transfer of bile to the intestine is prevented.
- Inflammation of the bile ducts,
- Parasite infestation (Fasciola hepatica, F. gigantica) or obstruction by gallstones,
- Obstruction of the ductus choledochus for a reason such as enteritis,
- As a result of external pressure on the bile ducts (such as tumor, abscess, cyst or cirrhosis),

Findings in icterus

Grossly;

- Organs, tissues, mucous membranes appear yellow in varying degrees depending on the degree and type of jaundice.
- Since there is no bile in the feces in obstructive jaundice, the color of the stool is light and clay-colored.
- In other cases, it is yellow-brown in color.
- When the bile is excreted in the urine, the color of the urine is brownish green

Microscopically;

- Yellow-brown masses, are seen especially in the biliary capillaries of the liver, in the disse spaces, in the cytoplasm of the liver and kidney epithelium.

The results of icterus

- Digestive system disorders,
- Nervous findings when it accumulates in the nerves
- Symptoms of autointoxication in the mixing of bile into the blood (cholemia)
- When it accumulates in the liver, changes such as necrosis, atrophy, cirrhosis develop in liver cells, except hepatotoxic ones.

Anhemoglobinogenic (Nonhematogenous) pigments

Melanin

- It is an **endogenous and autogenously** synthesized brown-black pigment.
- It is found between germinativum cells in the skin, in the iris and retina, in hair follicles, in the meninges, in the oral mucosa of dogs.
- Melanin is produced in **melanocytes** of neural and neuroectodermal origin.
- Melanin production is under the influence of melanin stimulating hormone **(MSH)** released from the pituitary gland.
- First, **DOPA** (dihydroxyphenylalanine) is formed by the action of the copper-containing **tyrosinase** (phenyloxidase) enzyme on **tyrosine**. Dopaquinone is converted to melanin by the action of the enzyme DOPA oxidase over dopachrome.

Hyperpigmentation (Melanosis)

- It is the accumulation of melanin more than normal and its formation in places where melanin is not seen.
- It can be congenital or acquired.
- It is seen as black-brown, irregular patches in various organs, especially in the lungs and aorta.
- Melanosis maculosa
  - **Congenital**
    - It is found in calves and rarely in lambs.
    - Oral mucosa, in the lung, liver and heart as patches with irregular edges; Diffuse melanin pigmentation is observed in the M. spinalis canal and meninges.
  - **Adults**
    - Often localized in cattle and sheep in Australia, especially liver

Acquired hyperpigmentation of melanin

- Benign-Malignant melanoma
- Acanthosis nigricans in dogs (due to endocrine disorder)
- Freckles (Ephelides) and moles (Nevus pigmentosus) in humans
- Skin and oral mucosa in Addison's disease (due to adrenal cortex insufficiency)
- In inflammatory skin infections
- In vitamin C deficiency
- As a result of the effect of estrogen or similar drugs

Melanin hypopigmentation

- In case of decrease in ACTH as well as decrease in MSH in **pituitary gland insufficiency**
- In **tyrosinase deficiency** and related copper deficiency (eg enzootic ataxia in lambs) in hair
- General depigmentation (loss of pigment, reduction) in the **deficiency of melanocytes**
- In the form of non-pigmented patches on the skin **after wound healings**
- Melanin deficiency occurs **congenitally or later.**
- It is seen in many parts of the body **(generalized)** or limited **(localized)** in some parts of the body.
- Generalized ones are usually related to congenital gene defect.

Melanin hypopigmentation

- The general congenital absence of melanin is called **albinism.**
- It develops in two ways due to tyrosinpermenase and phenoloxidase deficiency as a result of tyrosinase-forming gene defect.
- It is seen in horse, cattle, buffalo, rabbit and laboratory animals (rat, mouse).
- Skin and hairs are colorless.

Melanin hypopigmentation

- It is the appearance of local, non-pigmented or less pigmented areas and spots that occur later on the skin. These are called **"leucoderma".**
- If discolored areas are also seen in the hairs of older animals, this form is called **"leukotrichi".**
- Traumatic, toxic, infectious or actinic (effect of rays) effects
- **Chronic inflammations** (eg: Depigmented areas around the vulva, scrotum and anus after **Dourine disease of horses**)
- On parts of rope and saddle hit and scar tissue in pack animals
- **Copper deficiency** (in lambs, the wool cover becomes grizzled, in calves the hair around the eyes becomes white.)

Lipofuscin (wear and tear pigment)

- It is a yellowish-brown-golden pigment in the form of fine granules, formed in lysosomes as a result of **peroxidation and polymerization of unsaturated fatty acids** originating from the membranes of cell organelles taken into lysosomes by autophagocytosis.
- It is localized in the perikaryon part of nerve cells, hepatocytes close to the biliary capillaries, myocardial cells close to the apex of the heart and adrenal cortex cells.
- Regarding the antioxidation mechanism disorder in aged animals, it is also called the **"aging (senile) pigment"** because it is formed in the destroyed cells, especially in the brain, liver and heart muscle.

Lipofuscin

- Affected tissues, such as the liver, are atrophic, firm in consistency, and brownish-yellow in color. (Brown atrophy)

Microscopically;

- Lipofuscin pigment is found in the cell cytoplasm.
- Atrophy and lipofuscin pigment in all muscle can be seen in aged dairy cows with cachexia.

Ceroid

- It is an oxidized, polymerized unsaturated fatty acid product.
- It is the pigment that gives the oil its yellow color.
- **Vitamin E deficiency** and **impaired fat metabolism** develop due to **choline deficiency** in the liver.
- The difference from lipofuscin is that there are changes in cells, intra- and extracellular.
- **Yellow Fat Disease** in Cats: Continuous intake of fish products containing unsaturated fatty acids and in Vit. E deficiency, it accumulates in liver, adipocyte, cardiac and intestinal smooth muscle and neurons.
- It causes panniculitis.
- The texture turns orange, lemon yellow.

Exogenous Pigments

Anthracosis

- The major dust inhaled by coal mine workers is carbon, so this form of pneumoconiosis is called anthracosis.
- **Carbon particles** in the lung account for the black discoloration in anthracosis.
- Especially with the lower exposure in urban-dwelling people or animals that breathe polluted air,
- Fine gray-black stippling to the lung ,visible through the visceral pleura, plus a dark gray discoloration of tracheobronchial lymph nodes.

Anthracosis

Microscopically;

- Black-brown pigmentation, free and/or phagocytized by macrophages, is characteristic around the lung alveoli, especially around the bronchi, bronchioles, and vessels.
- In addition, similar changes are seen in the lymph nodes of the region as they are carried by the macrophages via the lymphatic route.

Cloisonné böbrek

- Keçilerde meydana gelir.
- Böbrek fonksiyonu **normaldir.**
- Proksimal tubul bazal membranlarında **ferritin ve hemosiderin** birikiminden dolayı kalınlaşma görülür.
- Makroskobik olarak; böbreklerde **kortekste** diffuz, yoğun siyah veya kahverengi renk değişiklikleri dikkati çeker.

Siderosis

- It is formed by taking iron powders as aerogen.
- The deposition is due to iron oxide appearing as red crystals.
- Inflammatory reaction and fibrosis are rarely seen.

Silicosis

- It is formed by the ingestion of silicon dioxide salts in workers working in quarries and mines.
- Granulomas consisting of necrosis and foreign body giant cells are seen in the lungs.

Asbestosis

- It is seen in asbestos workers.
- In the lungs, granulomas with yellow-colored asbestos bodies in the middle, including giant cells, fibrosis, and also mesothelioma are seen in the pleura.

Calomel

- When used for therapeutic purposes, lead sulfide (PbS) is formed as a result of the combination of lead with sulphurous hydrogen.
- Pigmentation in the form of black lines (lead line) occurs in the intestines and especially in the gingiva.

Argyrose

- With the therapeutic administration of silver nitrate, dark gray pigmentation occurs in the skin, kidneys and vascular endothelium.
- There is no inflammatory reaction.

Tattoo

- It is the pigmentation created by injecting dyes such as Indian ink and carmine under the skin.

Kaolin

- It is seen in those working in the porcelain industry.
- It is formed by the action of aluminum silicate (kaolinite).
- It is observed as homogeneous slightly pink crystals in macrophages in the lung.
- It is the cause of pneumoconiosis in humans and monkeys.

Carotenoid pigments

- They are oil soluble pigments of vegetable origin.
- The main ones are α-carotene, β-carotene (vitamin A precursor) and xanthophyl.
- It is seen as a slight yellow staining of the tissues.
- Especially in horses and cattle (Jersey, Guernsey), adipose tissues are intermingled with icterus as they turn yellowish.
- Organs and mucous membranes are normal.
- Such yellow discoloration seen in adipose tissue is defined as **pseudoicterus.**
- It occurs in tumor-like structures called xanthomas.
- Hepatic carotenosis in cattle

CALCIUM METABOLISM DISORDERS

- Decrease in blood calcium “**hypocalcemia”** or increase in **“hypercalcemia”**
- Inability to accumulate calcium in the bones, insufficient accumulation or decrease of the normally accumulated calcium by mobilization from the bone afterwards
- It is the deposition of calcium in soft tissues.
- Calcified areas in tissues are seen diffuse, chalky-white or as hard granules.
- The consistency of calcified tissues is hard, a crackling sound is obtained when cutting with a knife.

- **In tissue sections stained with hematoxylin-eosin**; The calcified areas are either finely granulated as if sprinkled with dust, larger coarse granules, or dark blue to violet to form large, irregular masses.
- The presence of calcium in the tissue can also be demonstrated by special staining methods such as **Von Kossa**, **Alizarin Red S.**

Calcification

- The accumulation of calcium in tissues other than bones and teeth is called **“heterotopic calcification”**, **“pathological calcification”** or simply **“calcification”**.
- Calcium does not accumulate as an ion.
- Similar to **hydroxyapatite in bones**, **calcium carbonate** precipitates in the form of salts such as **calcium phosphate,** and **other ions** (such as iron) may also be present in its structure.
- For this reason, the term **"calcium mineralization"** or simply **"mineralization"** can be used instead of calcification.
- Pathological calcification is seen as either **dystrophic** or **metastatic calcification.**

Dystrophic calcification

- It is characterized by the subsequent precipitation of calcium salts in degenerated and necrotic tissues.
- Unlike metastatic calcification, **there is no change in calcium metabolism.**
- **It is localized and limited** only to the damaged, deteriorated area.
- There is no hypercalcemia, any change in the parathyroid gland, or a disorder in the kidneys.

Dystrophic calcification-Pathogenesis

- In degenerated and necrotic tissue areas, firstly **acidosis** occurs and **calcium ion increases** due to cell destruction. **Calcium salts** are formed and precipitated by the subsequent shifting of the necrotic region to **alkaline and alkalizing.**
- In enzymatic fat necrosis related to the pancreas or other fat necrosis outside the abdominal cavity, the formation mechanism of calcification is slightly different, and alkaline phosphatase saponified with fatty acids plays an important role.

Dystrophic calcification-Etiology

Granulomatous inflammation

Old parasitary granulomas

Various disorders that lead to degeneration and necrosis of cells in the organism

Metastatic calcification

- It is related to the **disorder of calcium metabolism.**
- Although **localized** in a specific tissue, it often occurs in a **generalized, systemic** form in various tissues.
- There is no previous disorder in the tissue where calcium accumulates.
- The main disorder is related to factors that play a role in calcium metabolism (such as parathyroid hormone (PTH), vitamin D, kidneys, phosphorus).
- After the accumulation of calcium in the tissue, related disorders occur.

Metastatic calcification-Pathogenesis

- With the deterioration of the factors that play a role in calcium metabolism, **“hypercalcemia”** occurs.
- Calcium then precipitates as salt in various soft tissue cells or intercellular (extracellular) ground substances.
- It accumulates into the cell in mitochondria and sometimes in lysosomes.
- Extracellular, it accumulates between elastic collagen fibers in the ground substance.
- Mostly; It precipitates into the media of aorta and other vessels, subendocardial and epicardial regions of the heart, gastrointestinal tract mucosa, joints, basement membranes of lungs and kidneys, gland lumens.

Etiology of hypercalcemia

- Hyperparathyroidism
- Renal failure
- Hypervitaminosis D
- Bone diseases, (Neoplasia, osteomalacia etc.)
- Excessive Ca intake

Hyperparathyroidism

- It is characterized by excessive release of parathyroid hormone from the parathyroid.
- In parallel with the increase in osteoclast activity and calcium mobilization in bones, calcium increases in the blood.
- Reabsorption of the phosphorus is reduced while renal Ca excretion decreases.
- Vitamin D helps the absorption of more calcium from the intestines. The result is **HYPERCALCEMIA.**

Hypervitaminosis D

Trisetum flavescens, sarı yulaf

- Excess calcium absorption from the intestines

occurs.

Etiology;

- Excess vitamin D intake with food
- Long-term administration of vitamin D as a drug,
- Plants containing substances with similar effects to vitamin D (causes **enzootic calcinosis** in cattle and sheep).
- Calcium is deposited in various soft tissues, in particular, kidneys, endocardium, great veins, stomach wall, lungs, joints, ligaments.

Other causes of metastatic calcification

- **Hyperadrenocorticism** in dogs
- **Calciphylaxis**
  - When the same substance or the substance producing its effect is reintroduced to the sensitized organism for the second time; It is characterized by local or general calcification depending on the application method.
- **Calcergia**
  - It is formed by the action of a calcifying calcergen such as lead acetate, dextran without prior sensitization.
  - Local or systemic
  - Nephrocalcinosis

Nephrocalcinosis

- **Primary:** It develops due to excess Ca excretion from the kidneys.
- **Secondary**: It develops as a result of kidney disorder (chronic nephritis and nephrosis).

Calcinosis circumscripta

- Calcinosis circumscripta is a localized deposit of calcium salts in the dermis or subcutis, and less often in other soft tissues or in the tongue.
- Unknown etiology

Calcium Metabolism Disorders in Bones

Causes of decreased calcium in bones

- Excessive Parathyroid Hormone
- Hypovitaminosis D
- Chronic Kidney Diseases
- Malabsorption (Chronic enteritis)
- Genetic disorders
- Gestation, lactation
- Bone diseases

Hypovitaminosis D

- Malnutrition, insufficient calcium intake, insufficient absorption of calcium from the intestines, chronic gastrointestinal disorders (malabsorption, maldigestion), insufficient sunlight, chronic nephritis, etc.
- Especially the kidneys play an important role.

- **Primary (congenital)** and **secondary** vitamin D deficiency occurs due to the inability of the kidneys to make vitamin D enzymatically or the lack of vitamin D formation due to kidney dysfunction.

Skeletal Disorders of Calcium Metabolism

- **O/X type leg:** Legs are short and thick
- **Lordosis** is the inward curve of the lumbar spine
- **Kyphosis** is a curving of the spine that causes a bowing or rounding of the back
- **Scoliosis** is an abnormal lateral curvature of the spine

Miller, A. D., & Zachary, J. F. (2017). Nervous System. *Pathologic Basis of Veterinary Disease*, 805–907.e1.

Osteomalacia

- It is the demineralization and melting of the bones that have completed their development in adults.
- It is formed by the mobilization of calcium.
- It results from the deterioration of mechanisms that play a role in calcium metabolism, such as vitamin D, Ca, phosphorus, parathyroid hormone, kidneys.
- It mainly occurs in the elderly.
- In the case, the bones soften, become suitable for fractures and multiple calluses are formed.

Osteoporosis

- It is a disorder characterized by a decrease in the substance of the bones that have completed their normal development, the disappearance of bone trabeculae, and the formation of cavities in their places and the bone taking on a spongy appearance.
- It is frequently seen in the elderly, as well as in cats and dogs.
- It occurs due to phosphorus deficiency especially in cows due to pregnancy and high lactation.

Fibrous osteodystrophy

- It is a disorder characterized by an increase in osteoclasts in bones, insufficient mineralization, and an increase in connective tissue and collagen, as well as deterioration of osteoid tissue due to the mobilization of calcium from the bone.

Hypophosphatemia

- Phosphorus deficiency results in hypercalcemia.
- In this case, the secretion of calcitonin from the C cells of the thyroid increases and the function of osteoclasts is inhibited.
- As a result, the bones acquire a rubbery, rubber-like consistency.

Rachitism

- It is basically similar to osteomalacia and lack of osteoid tissue calcification in adults.
- However, it is formed in the developing bones in the youngs.
- Insufficiency of endochondral ossification, especially in the epiphyseal regions; There is a lack of calcium accumulation.
- As a result, rosary-like bone (osteoid) nodules in the costochondral regions of the above-mentioned ribs; Skeletal deformations such as short and thick legs occur.

DISORDERS OF PURINE METABOLISM

Gout (Uricosis)

- Accumulation of uric acid or urate crystals in tissues.
- Human (especially in joints), poultry (articular-visceral), reptiles, primates
- It is based on a disorder of purine metabolism.
- Purine bodies are formed by becoming basic purines from nucleic acids that are produced by the degradation of proteins.
- These are adenine and guanine.
- With these changes, uric acid is formed and excreted in the urine.

Gout (Uricosis)

- If excess protein is taken from the outside or nucleic acids are degraded excessively in the body, the excessive formed uric acid accumulates in the blood of animals and passes into the tissues, forming the uricosis.
- In other animals, the situation is different.
- In these, uric acid is converted to allantoin with the help of the uricase enzyme in the liver, and therefore, it does not occur in other animals.

Gout (Uricosis)-Etiology

- **Uricase enzyme deficiency**
- Impaired renal excretion of uric acid
- **Vitamin A deficiency** in poultry
- Dehydration
- Nutrition with a **diet rich in calcium and protein**
- **Nephrotoxic effects** (lead poisoning)
- In humans; diseases such as protein-rich diet, chronic alcoholism, leukemia, pernicious anemia, lymphoma

Gout (Uricosis)-Pathogenesis

- **Na-urate crystals** located in tissues are phagocytosed by macrophages and taken into the phagolysosomes, but cannot be digested.
- As a result, **crystals and lysosomal enzymes come out with the destruction of macrophages.**
- With the effect of these enzymes, **tissue necrosis** develops and urate crystals precipitate into necrotic tissue.
- Following this, the tissue reaction begins.
- Necrotic tissue containing crystals is surrounded by macrophages, lymphocytes, inflammatory zone containing **foreign body giant cells** and **connective tissue** from the outside.
- Thus, the **gout nodule**, or **tophi**, is formed.
- Macroscopically, **the cut-section of these nodules is chalky white.**

Visceral gout

- It is seen in **serosae.**
- White or slightly grayish-white foci, **as if sprinkled with chalk powder,** are observed in the air sacs in the body cavity, in the serosa surfaces of the organs.
- **In particular, seeing the pericardium in such a metallic sparkling is very important in terms of diagnosis.**

Articular gout

- Although it is not very common in poultry, it is seen in the extremities joints, joint capsule or periarticular region.
- It resembles visceral gout when it is located in the joint synovium, a **"tophi"** shaped nodule develops when it is located in the periarticular.

Gout (Uricosis)-Microscopical findings

- Serous membranes contain granular urate salts, uric acid crystals, amorphous material and fibrin precipitates.
- Granulocytes, macrophages and lymphocytes are found.
- Nodules called **“Tophi”** are in the form of **foreign body granuloma.**
- There are urate and uric acid crystals in the center, foreign body giant cells, macrophages, lymphocytes and connective tissue cells peripherally.
- Similar changes are seen in the kidneys as a result of uric acid accumulation, especially in the medulla. (Renal tubules and ureters)

Oxalosis

- Accumulation of calcium oxalate crystals in tissues
- Toxications
  - Various plants (Halogeton, rhubarb, greasewood)-Sheep
  - Ethylene glycol (antifreeze)-Dogs

CONCREMENTS
BEZOARS

Concrements

- They are hard masses of different sizes and shapes, formed by the binding of organic and mostly inorganic materials and collecting them in colloid or crystal form in the cavities of the secretory organs and the digestive system.
- These are called **"stone", "calculus".**
- The structure of the organism and the nutrients taken, metabolic disorders, precipitation of dissolved substances in the secretions; It plays a role in the formation of mixing of inflammatory substances.
- Diseases caused by these are called **lithiasis.**
- **Urolith, cholelith, sialolith, enterolith**
- **The result:** hydronephrosis, icterus, etc.

Pseudoconcrements

- They differ from true ones in terms of their origin, structure, type, formation.
- They are characterized by the condensation and drying of exudate, such as fibrin and pus, and formation of a crust by precipitation of inorganic salts on them.

Bezoars

- **Trichobezoars** (Mass of hair in the stomach, hairballs)**:** They are formed by the collection of ingested hairs in the rumen and abomasum in the form of balls in ruminants (usually calves) and the precipitation of salts on them.
- It is mostly seen in cases of **phosphorus deficiency**
- **Phytobezoars**(Plant mass in stomach, plant balls)**:** They are formed by the precipitation of salts on plant such as oats and rye.
- It results in indigestion and obstruction.
- In addition, lump-shaped formations made by feces are called **“conglobate”.**