Haematopoietic System

HEMATOPOİESİS

Haematopoiesis is the **formation of blood cellular components.**

In the embryonal period: It originates from mesenchymal tissue.

In Fetal period: It is made at liver, spleen, and lymphoid tissue in the end of organogenesis.

End of fetal period and in adulthood: It stops in the liver.

Granulocyte, platelet, erythrocyte in Bone marrow

Monocyte (macrophages) in Bone marrow, partially mononuclear phagocytosis system cells in tissues (old RES)

Lymphocyte: In primary lymphoid tissue (B lymphocyte in B.Fabricius; T lymphocyte in thymus); then the secondary lymphoid tissues

Views in the construction of blood cells

Unitaris: All the same root

Dualist: in separate tissues (as above)

DISORDERS OF STEM CELLS
Congenital Abnormalities in Blood Cell Function

- ***Chediak-Higashi syndrome***
- ***Bovine leukocyte adhesion deficiency***
- ***Canine leukocyte adhesion deficiency***
- ***Pelger-Huet anomaly***
- **Feline mucopolysaccharidosis**
- ***Sphingomyelinos***

Chediak-Higashi Syndrome

- *The Chediak-Higashi syndrome is a composite disorder of granule formation in cells and is of a simple recessive character in cattle of the Hereford, Brangus, Japanese black breeds, cats, mink (Aleutian disease), mice, and humans.*
- *The disease is manifested clinically by partial albinism or color dilution, high susceptibility to infections, and a hemorrhagic tendency.*
- *Enlarged cytoplasmic granules*, which are the result of fusion of preexisting granules of normal size, are found in most types of cells which normally contain granules.

Chediak-Higashi syndrome

- The partial albinism is ascribed to *clumping of melanin granules* in such tissues as eye and skin and their fusion with lysosomes.
- There are fewer, larger granules than normal also in hepatocytes, renal epithelium, neurons, endothelial cells, and the blood leukocytes.
- The prolonged bleeding time and hemorrhagic tendency is, at least in part, due to defects in platelets.
- Giant lysosomes are present in circulating granulocytes, lymphocytes, and monocytes.
- Phagocytosis appears to be normal but bacteriocidal activity is impaired.

Pelger-Huet Anomaly

- The Pelger-Huet anomaly is a benign dominant hereditary condition characterized by hyposegmentation of neutrophil nuclei which have mature aggregation of chromatin despite their immature shape.
- The condition occurs in humans, dogs, and rabbits

ERYTHROPOIESIS

is the process which produces red blood cells.

In postnatal birds and mammals (including humans), this usually occurs within the red bone marrow.

ANEMIA

- Anemia is a sign of disease that results either from an increased rate of destruction or loss of erythrocytes, or from a decreased rate of their production.
- Anemia may be classified on the basis of the bone marrow response (regenerative or nonregenerative) or on the basis of red cell indices (macrocytic/microcytic, normochromic/hypochromic) which indirectly reflect the nature of the anemia itself.
- Anemia is classified an etiologic or pathogenetic basis with reference to various mechanisms for assessing bone marrow production.

ANEMIA

- The appearance of an anemic animal is characterized by
- pallor,
- icterus.
- Pallor is due to a reduction in total levels of hemoglobin, and, if the disease has developed slowly, to a dilution of the red cell mass by a proportionate increase in the plasma compartment in order to maintain normal blood volume.

ANEMIA

- **Grossly,** the pallor is accompanied by edema of the lung, and tracheobronchial foam is typical.
- The heart is dilated and, if the anemia has been chronic, the myocardium tends to be flabby, friable, and pale as a result of fatty degeneration.
- The proportion of white to red blood clot is increased.
- The liver and kidney are pale and may be fatty.

❑**In acute anemia**, there is frequently the "nutmeg" appearance of periacinar hepatic necrosis.

ANEMIA

- **In acute hemolytic anemias**, the gallbladder is distended and the feces are intensely stained with bile pigment.
- **In chronic anemias** of deficient hemoglobin production, the gallbladder is empty and the feces are pale.

• The character of the *spleen* varies with the cause and course of the disease.

- **In the acute posthemorrhagic anemias**, the spleen is contracted;
- **in the acute hemolytic anemias**, it is enlarged and pulpy;
- **in the chronic hemolytic and deficiency anemias**, it is enlarged and meaty.

ANEMIA

- Since the spleen is a site of both production and destruction of red cells, the splenomegaly of hemolytic diseases may be the product of extramedullary hematopoiesis, or sinus hyperplasia of increased blood destruction, or both.
- In chronic anemia, the skeletal muscles tend to be pale in proportion to the loss of myohemoglobin.
- *Edema* is a frequent accompaniment of anemia, and serous fluid is found in the serosal sacs and in the dependent tissues of the limbs, ventral wall of the body, and throat.

Hereditary Hemolytic Disorders

- **Due to red cells and enzymes➔**
- **Hereditary stomatocytosis**
- **Familial anemia in dogs**
- **Due to heme synthesis➔**
- **The porphyrias**

Hereditary Stomatocytosis

- Red cells with a rectangular unstained area across their center are termed **stomatocytes.**
- A hereditary anemia with these membrane changes occurs in chondrodysplastic dwarf Alaskan malamute dogs.
- The anemia in these dogs is mild, and characterized by stomatocytosis, macrocytosis, reduced mean corpuscular hemoglobin, increased osmotic fragility, shortened red cell life span, reticulocytosis with marrow erythroid hyperplasia, and increased iron turnover.

Familial anemia in dogs

- A familial hemolytic anemia found in Basenji and Beagle dogs is due to **pyruvate kinase deficiency.**
- They are less active than normal, and on clinical examination have pale mucous membranes and often splenomegaly.
- Morphologically, Basenjis with pyruvate kinase deficiency develop *progressive myelofibrosis with osteosclerosis as well as splenic and hepatic hemosiderosis.*

The Porphyrias

- Porphyrias are diseases that result from abnormal metabolism of porphyrins which may be excreted to excess in urine and feces or deposited in various tissues.
- The pigments are fluorescent, unless iron is chelated in them.
- Porphyrins are basic components of enzymes that contain heme, including hemoglobin, the cytochromes, catalase and many peroxidases.

- **Bovine protoporphyria** affects *Limousin cattle* and is *caused by a deficiency in the activity of ferrochelatase*.
- The inheritance is recessive and heterozygotes are asymptomatic.
- Bovine protoporphyria differs from bovine congenital porphyria in that there is no excretion of porphyrins in the urine, no anemia and no discoloration of bone or teeth; *photodynamic dermatitis is the only consistent clinical manifestation.*
- Pigment is, however, deposited in the liver and heavy concentrations resembling lipofuscin are found in the cytoplasm of hepatocytes, Kupffer cells, endothelium, and portal stroma.

- **Congenital porphyria** occurs in *humans, cattle, and cats* and results from the production of the *abnormal protoporphyrin isomer 1.*
- It also occurs in swine, but the biochemical defect is not known.
- All cells in the body share this defect but, since the effects on the blood system are most apparent, the disease is usually called *erythropoietic porphyria.*
- Only isomer III can be synthesized into heme, although the enzymatic block is never complete and some normal heme is produced.

Anemia of Deficient Cell Production

- The causes of inadequate cell production include immune phenomena, often
- drug-induced,
- toxins both exogenous and due to hepatorenal failure,
- myelophthisis,
- chronic inflammation,
- endocrine dysfunction and
- nutritional deficiency.

Anemia of Deficient Cell Production

- **Aplastic pancytopenia**
- **Bracken fern poisoning**
- **Pure red cell aplasia**
- **Feline panleukopenia**
- **Stachybotryotoxic**
- **Myelophthisic anemia**
- **Anemia of uremia**
- **Anemia of endocrine dysfunction**

Aplastic pancytopenia

- **Aplastic pancytopenia occurs in all species but is most often seen in cats and dogs.**
- **It may be congenital, but is usually acquired and idiopathic, and may be associated with specific infections or toxic agents.**
- **Marrow aplasia may be absolute and rapidly fatal or, more commonly, hypoplastic and chronic.**
- **Any of the three blood cell lines may become aplastic, but characteristically the disease is either one of generalized aplasia resulting in pancytopenia, or of pure red cell aplasia with a hyperplastic myeloid and megakaryocytic marrow.**

Aplastic pancytopenia

- **Viruses may cause marrow depression. (canine and feline parvoviruses and Feline leukemia virus)**
- **Phenylbutazone causes aplasia in humans**
- **All forms of estrogenic drugs are potentially myelotoxic in dogs.**
- **Chloramphenicol causes irreversible myeloid aplasia in humans**
- **Furazolidone at high dose rates is acutely neurotoxic in calves and pigs.**

Aplastic pancytopenia

- Animals with aplastic pancytopenia have epistaxis, bleeding into joints and dependent areas, and are often febrile due to sepsis.
- Animals with pure red cell aplasia are presented with mucosal pallor, lethargy and reduced activity, and are usually afebrile.
- Pancytopenia may be either moderate and chronic, or severe and acute with an absence of neutrophils. Those granulocytes present show toxic changes and little immaturity.
- Thrombocytopenia is severe and nonregenerative, with all platelets aged, small and with little basophilia.
- Anemia is moderate-to-severe and normochromic normocytic without polychromatic response.

Bracken Fern Poisoning

- Bracken fern (Pteridium aquilinum) is abundant in many humid grassland areas of the world, and poisoning by it is often the factor that limits the utilization of pastures.
- Bracken fern poisoning produces a variety of disease syndromes in grazing animals.
- **The acute disease** occurs in horses and pigs as a *neurologic and cardiac manifestation of thiamine deficiency*, in sheep as *polioencephalomalacia*, and in cattle as *aplastic pancytopenia*.
- ***The*** **chronic syndromes** occur in cattle and sheep *as "enzootic hematuria"and"bright blindness" of alimentary tract.*

Bracken Fern Poisoning

- **Grossly,**
- There is hemorrhage in almost all tissues but without any particular pattern.
- They are particularly numerous, however, in the stomach and intestine, to the mucosal surface of which the blood tends to adhere in clots; in the large intestine, the hemorrhages are more diffuse, and copious free blood may be present in the lumen. Hemorrhages beneath mucous membranes usually lead to overlying ulceration.
- Hemorrhages in the liver may be sufficiently numerous to give it an odd variegated appearance, especially when it also contains many infarcts. The hepatic infarcts are spherical or wedge-shaped areas of white or yellow and similar to the lesions of black disease; they may be absent, few, or numerous. The hepatic infarcts, like those in other tissues, are caused by bacterial emboli which localize in small branches of the portal vein, the sinusoids, and the central veins. The bacteria are ordinary saprophytes in many cases and, if the postmortem interval is prolonged, the focal lesions expand about the colonies because of local postmortem putrefaction.
- The heart has extensive subserosal hemorrhage but, in addition, there are loci of myocardial infarction which are discrete yellow areas up to 1 cm long.

Pure red cell aplasia

- Pure red cell aplasia is seen in *humans and dogs.*
- Pathogenetically, there is *immune suppression of differentiated red cell precursors that is T-cell driven and mediated by interferon, and there may also be antibody against erythroid nuclei.*

Stachybotryotoxicosis

- Stachybotryotoxicosis, as a *pancytopenic disease,* occurs in horses and ruminants in Eastern Europe and Russia.
- The responsible fungus *Stachybotrys alternans (atra)* grows on substrates rich in cellulose, and contaminates hay and cereal grain.

Feline panleukopenia

- Pathogenetically, the disease is radiomimetic and the signs and lesions are referable to destruction of proliferating cells, principally in marrow, intestinal epithelium, spleen, lymph nodes and thymus.
- Histologically, lymph nodes, spleen and Peyer's patches have *both thymus- and marrow-dependent hypocellularity.*
- Follicles are characteristically large and occupied by a background of pale dendritic reticular cells made apparent by lysis of the follicular center cells.

Myelophthisic anemia

- Myelophthisis of leukemia is seen most often in dogs, cats, and cattle.
- The anemia of leukemia has 4 mechanisms: stem cell displacement, panmyelosis, immune depression, and cachexia.
- Marrow failure with consequent loss of all normal cells represents the end stage of acute leukemia.
- These cell deficits occur earlier and with greater diversity in acute myelogenous leukemia than in acute lymphocytic leukemia.
- The basic difference between these two diseases appears to depend on the relative distribution of the leukemic stem cells in the bone marrow.

Anemia of Uremia

- Anemia of uremia occurs in all species but is most often recognized in the dog and cat, which are the domestic species that most commonly survive to old age.
- There are 4 principal mechanisms of anemia in renal failure.
- These are excessive hemolysis of red cells due to retention of creatinine and guanidinosuccinic acid, toxic depression of erythropoiesis, loss of renal erythropoietin, and blood loss from the kidney.
- The major limiting factor in the anemia of uremia in humans and animals appears to be inadequate levels of erythropoietin.

Anemia of endocrine dysfunction

- Pituitary dysfunction
- Hypothyroidism
- Adrenal insufficiency

Anemia of Deficient Hemoglobin Production

- **Iron-deficiency anemia**
- **Copper-deficiency anemia**
- **Cobalt deficiency anemia**
- **Megaloblastic anemia**
- **Anemia of chronic disorders**
- **Anemia of malnutrition**

Iron-deficiency anemia

- Iron is an essential component of hemoglobin, myoglobin, the cytochrome enzymes of mitochondria and hepatic microsomes, and the metalloflavoproteins (NADH), and is required as a cofactor for the function of other enzymes.
- The physiological anemia of the young is a defensive strategy to deny bacteria access to iron during the period of transition from passive to active immunity.
- **Excessive loss** of iron is the result of *chronic loss of blood* and is an important cause of iron deficiency; it is the only cause in adult animals, since normally only very small amounts of iron are excreted and lost.
- Hematologically, *the anemia is classically hypochromic and microcytic in all species,* and accompanied by neutropenia with hypersegmentation.

Copper-deficiency anemia

- Copper is a cofactor in a variety of oxidative enzymes of diverse function.
- Deficiency of the element may affect electron transport (cytochrome oxidase), the absorption of iron and its utilization in hematopoiesis (ceruloplasmin), protection from antioxidants (superoxide dismutase), tyrosine degradation and pigmentation (tyrosinase), neurotransmitter metabolism (dopamine hydroxylase), or cross-linkage of elastin and tropocollagen (lysyl oxidase).
- *Anemia is not invariably present in copper deficiency, but it is probable that anemia will occur if the deficiency is sufficiently severe and prolonged.*
- The morphological characters of the anemia vary with the species, that in rats, pigs, rabbits, and lambs is microcytic, hypochromic; in cattle and adult sheep, it is macrocytic, hypochromic; and in dogs, normocytic and normochromic.

•*Cobalt-deficiency anemia*

- *Cobalt deficiency is a disease of ruminants expressed as ill-thrift.*
- *Cobalt deficiency is a deficiency of vitamin B12.*

•*Megaloblastic anemia*

- *Anemia characterized by reticulocytopenia and marrow erythroid hyperplasia with early asynchrony of rubricytes occurs infrequently in cats and dogs.*
- **Vitamin B12** is stored in the liver in amounts sufficient to maintain animals for many months without further absorption.
- On the other hand, there is very little storage of folic acid, and signs of deficiency may appear after relatively short periods of disease in animals that are anorectic or receive chemotherapy.

Anemia of Malnutrition

- Anemia of malnutrition is most commonly a disease of the young and is seen most frequently in sheep and goats, and less often in kittens and puppies where poor nutrition may be complicated by ecto- and endoparasitism
- Hematologically, the anemia of malnutrition is largely normochromic, normocytic, but may be hypochromic if complicated by parasitism and blood loss.
- *The anemia is primarily due to reduced red cell production with minor hemolysis,* as in anemia of chronic disorders..

Hemolytic Anemias

- Classification by association is based on identification of an underlying cause and includes primary (idiopathic) immune hemolytic anemia and secondary (symptomatic) immune hemolytic anemia.
- These may be isoimmune, drug-induced, associated with infectious disease, associated with other immune disorders (systemic lupus erythematosus), or associated with lymphoid or other malignancy.
- In **symptomatic immune anemias,** the cause is identified, and is usually adherence of **drug or virus** to red cells thereby sensitizing them to the immune system.
- In **idiopathic immune anemias,** which form the bulk of cases, it is not clear whether the error is due to an actual change in red cell antigenicity or to loss of selfrecognition by the immune system.

Hemolytic Anemias

- **Immune-mediated hemolytic anemias**

  Isoimmune hemolytic anemia in the foal, calf and piglet

  Drug-induced hemolytic anemias

  Primary or idiopathic immune hemolytic anemia

- **Infectious hemolytic anemies**
- **Anemia of blood cell parasitism**
- **Anemias of vascularparasitism: trypanosomiasis**
- **Hemolysis due to physical and chemical agents**
- **Hemolytic anemia due to mechanical damage to red cells**
- **Hemolytic anemia due to splenic hyperfunction**

Drug-induced hemolytic anemia

Many drugs have been associated with Coombs-positive hemolytic anemia and these same drugs may cause immune thrombocytopenia.

The most commonly implicated drugs are **quinidine, quinine, para-aminosalicylic acid, phenacetin, penicillin, insecticides, sulfonamides, chlorpromazine, and dipyrone.**

There appear to be two types of immune hemolytic anemia associated with drugs.

One is caused by **an antibody that reacts only with cells exposed to the drug**.

In the other, **the antibody reacts with normal red cells in the absence of the drug.**

Primary or idiopathic immune hemolytic anemia

- This type of anemia is most common in dogs and cats, less common in cows and horses.
- **Clinically**, there is usually depression of sudden onset in an animal in good body condition.
- There is mild-to-marked pallor and often mild icterus.
- When hemolysis and thrombocytopenia are present, there will be mucosal bleeding and often epistaxis, dark stools and hematuria.
- Heart rate and respiratory rate are increased in proportion to the degree of anemia, and a hemic murmur may be present.
- The spleen may be palpably enlarged.

Primary or idiopathic immune hemolytic anemia

- Occasionally, immune hemolytic anemia in the dog may resemble **systemic lupus erythematosus** of humans.
- **The canine form of systemic lupus erythematosus** is characterized by Coombspositive hemolytic anemia with thrombocytopenia, polyarthritis and glomerulonephritis.
- Rarely these lesions are accompanied by symmetrical facial dermatosis, serositis with accumulation of fluid body cavities, and combinations of leukopenia, hepatosplenomegaly and lymphadenopathy.
- Antibodies to double-stranded DNA are relatively common, as are positive lupus erythematosus preparations.
- All breeds of dogs may be affected and the disease, as in humans, is most severe in young females.

Infectious Hemolytic Anemies

Equine infectious anemia

- Equine infectious anemia virus (EIAV) is a member of the Lentivirinae subfamily of retroviruses that infects horses, mules, and donkeys.
- The disease has a worldwide distribution.
- The location of outbreaks in marshy areas led to the common name of "swamp fever".
- Their occurrence during the summer led to the demonstration that the virus is arthropod-borne. The likely vectors are the stable fly (Stomoxys calcitrans), horse flies (Tabanus spp.), and Anopheles mosquitoes.
- **Transmission** is mechanical not biological, and may also occur accidentally by contaminated needles, syringes and tattoo equipment or experimentally by parenteral administration of blood or virus.

Equine infectious anemia

- **Patogenesis:** The virus infects cells of the monocyte- macrophage system but, in acute viremic states.
- It proliferates in the lymphatic tissues (liver, spleen, lymph nodes, bone marrow).
- **C3 appears on erythrocyte membranes, and this probably accounts for macrophage recognition and erythrophagocytosis.**
- **Hemolysis occurs when C3 link with the antibody.**

- The clinical disease is divided into ***acute, subacute*** **and** ***chronic*** forms.

Equine infectious anemia

- **The acute disease** is characterized by pyrexia and marked depression, with anorexia, weight loss and pitting, dependent edema.
- **There are petechial hemorrhages most reliably seen on the ventral surface of the tongue** but also present on ocular and vulvar mucosa. **The tongue is most reliably examined by rotation in situ, since forced extraction tends to cause petechiation.**
- Mild icterus develops after a short febrile period and is accompanied by pallor of mild-to-marked degree.
- The febrile periods may progress to death in less than a week.

Equine infectious anemia

- *Anemia is severe and sufficient to cause death,* with erythrocyte counts as low as 1 × 1012/L, hemoglobin of 25-50 g/L, and hematocrits of 0.08-0.15 L/L.
- There is *consistent thrombocytopenia* during febrile periods with resulting petechiae.
- In the early stages of disease, there is anisocytosis, marked for the horse, with moderate poikilocytosis and, **characteristically for the horse, no polychromatic red cells.**
- Nucleated erythrocytes are not present in peripheral blood. In the early stage of an **acute att**ack, there is macrocytosis.
- **Later t**he anemia is normochromic, normocytic and nonresponsive.

Equine infectious anemia

- Icterus is always present in febrile, anemic horses, and bilirubin is usually between 170 and 250 Ixmol/L; most is unconjugated.
- Lipemia is occasionally seen in the acute disease.
- With chronicity (30 days or more), there is a drop in albumin of around 10 g/L and a corresponding increase in gamma globulin so that the total protein is relatively unchanged but the albumin/globulin ratio is decreased.
- The serum iron rises in the acute disease and drops with chronicity, while the total iron-binding capacity remains normal or mildly elevated.

Equine infectious anemia

- **Grossly;**
- *In horses dead of the acute disease, there is anemia, icterus and widespread foci of hemorrhage.*
- There is edema of the ventral abdominal wall and in the suspensory ligaments of the viscera.
- The spleen is enlarged, turgid and fleshy with capsular hemorrhages, a bulging **but not** oozing cut surface, and inapparent lymphoid follicles.
- The liver is enlarged, dark and turgid with a fine lobular pattern and focal capsular hemorrhages.

- Petechial hemorrhages are present on the renal capsules and in the perirenal tissues. On cut surface, there are multiple fine hemorrhages throughout the cortex and medulla.
- **The most significant gross lesions occur in bone marrow** where the degree of reddening is in direct proportion to the duration of the disease.

- **In acute cases**, the conversion of fat to hematopoiesis in the femoral marrow occurs first in proximal cancellous and then subendosteal diaphyseal and distal cancellous areas.
- The red and yellow areas are initially firm and opaque, often with focal areas of hemorrhagic infarction.
- **In chronic cases,** the red conversion may include all of the medullary marrow and is alternately pink and translucent in areas of serous atrophy of fat, and cyanotic where congested sinuses have dilated as adjacent hematopoietic areas atrophy.

- **Microscopic lesions** occur in most tissues, but are most prominent in the **heart, lungs, liver, spleen, kidney, marrow and lymph.**
- **The myocardium** has fiber atrophy in chronic cases, and interstitial edema in acute cases, with perivascular lymphocytic aggregations that irregularly permeate the surrounding interstitium.
- There is mild pulmonary alveolar thickening and an overall appearance of hypercellularity.
- Occasionally, hemosiderin-bearing macrophages are found in alveolar walls and are likely intravascular.

- **The liver** presents a spectrum of changes which varies from mild periportal lymphocytic infiltrates to atrophic cords with sinusoidal dilation, Kupffer cell hyperplasia, broad loosely arranged periportal lymphoid infiltrates, and increased interstitial connective tissue.
- As the disease progresses, hepatic hemosiderosis increases, largely in Kupffer cells.
- **In subacute cases** there is periacinar fatty vacuolation, and **in acute cases** hemorrhage and necrosis.
- In animals in which the disease has been quiescent for some months, hepatocytes appear normal and lymphoplasmacytic infiltrates subside but sinusoidal hemosiderin-bearing macrophages remain as evidence of previous hemolysis.

- **Splenic follicles** are variably enlarged but hypocellular, often with a **"bull's-eye"** appearance due to a sharp distinction between the cells of the follicular center and the mantle and marginal layers, and a sharp transition to congestion in the surrounding sinusoids.
- In acute cases, the spleen is congested and, being largely composed of unsupported red cells, fractures on sectioning. Later there is sinus hyperplasia with stromal proliferation.
- The tissue is then cellular, fleshy and cohesive.
- Splenic hematopoiesis is never as prominent as in the dog with idiopathic immune hemolytic anemia, but hemosiderosis with macrophages and plasma cell proliferation is prominent.

- **Lymph nodes** are edematous and have medullary hemosiderosis with persistence of follicles and thin moth-eaten paracortical areas.
- In acute disease, the lymphoid tissue is highly reactive and there may be lymphocytic colonization.
- ***Renal lesions*** in acute disease are largely hemorrhagic with some glomeruli obscured by erythrocytes and fibrin.
- Lymphocytic infiltrates may be intense and separate tubules in an irregular manner.
- There is some degree of epithelial atrophy and mild pigmentation that appears to be both bilirubin and hemosiderin.

- **The red *bone marrow*** in acute disease has 40% or less of fatty areas and the hematopoietic cells are densely packed.
- There is an erythroid shift with synchronous maturation, and a reduction in mature granulocytes, although eosinophils are prominent.
- Megakaryocytes are not increased, which may indicate that the thrombocytopenia may be at least partially due to ineffective production.
- Hemosiderin is prominent as is erythrophagocytosis.
- Large macrophages can be found which contain hemosiderin, red cells and rubricytes.

- **The disease is one of acute intracellular hemolysis followed by immunoproliferation and finally by hematopoietic and to a lesser extent immune exhaustion.**

Hemolysis due to physical and chemical agents

- **Heinz-body hemolytic anemia**
- **Copper poisoning**
- **Cold hemoglobinuria**
- **Postparturient hemoglobinuria**

Heinz-body hemolytic anemia

- Heinz bodies appear as small round inclusions within the red cell body.
- Heinz bodies are formed by damage to the hemoglobin component molecules, usually through oxidant damage by administered drugs, or from an inherited mutation (i.e. change of an internal amino acid residue).

Heinz-body hemolytic anemia

- Hemolytic anemia due to denaturation of globin occurs in cattle, horses and dogs fed onions, and in cattle and sheep fed rape or kale.
- The same mechanism is operative in the anemia of horses with hemolysis after receiving phenothiazine, and in cats given methylene blue as a urine acidifier.
- Heinz-body anemia also occurs in horses that eat the leaves of red (swamp) maple (Acer rubrum).
- Heinz-body hemolytic anemia occurs as an inherited deficiency of the glucose-6-phosphate dehydrogenase (G-6-PD) enzyme in humans, and also rarely in sheep and dogs.

Heinz-body hemolytic anemia

- **If the oxidizing attack is mild**, the Heinz bodies are selectively removed by splenic phagocytes, and the red cells return to the circulation with a slightly reduced volume.
- **If the reaction is severe**, the Heinz bodies appear free in plasma, complicate platelet counts, and are removed by the spleen and liver.
- Hemoglobinemia, hemoglobinuria, and icterus occur in severe cases.
- The anemia may be moderate to severe, normochromic and moderately macrocytic, and responsive, with Heinz bodies flee and projecting from the outer edge of red cells.

Cold hemoglobinuria

- Hemoglobinuria after the ingestion of cold water occurs in calves and occasionally older cattle, principally as a disease of winter, and is seen in cattle which are housed in warm barns and given water at nearfreezing temperature.
- *Hemolysis occurs most often in penned animals which are watered at irregular intervals and which therefore tend to drink large volumes when allowed access.*
- *The* disease is common although *rarely fatal.*
- The clinical signs consist of dyspnea with open-mouth breathing, followed by the passage of port-wine colored urine within 1-2 hours of drinking.
- The activity of cold agglutinins has been suggested as a cause of the hemolysis

Postparturient hemoglobinuria

- The syndrome of postparturient hemoglobinuria occurs primarily in dairy cows and typically is seen within 2-6 weeks after parturition.
- The earlier the onset the more severe the disease.
- It is characterized by *intravascular hemolysis, hemoglobinuria, and anemia.*
- **Grossly,** *the principal changes are icterus, pallor, thin watery blood which is dark, and red-to-brown discoloration of the urine.*
- There is fluid accumulation in the serous cavities, and subcutaneous and interfascial edema.
- There are extensive ecchymotic hemorrhages on the cardiac surfaces.
- The liver is slightly enlarged, turgid and pale with an ischemic nutmeg appearance caused by periacinar necrosis.

Postparturient hemoglobinuria

- The gallbladder is distended.
- The spleen is enlarged and congested in peracute cases but, in those that survive several days, it is of normal appearance. In spite of the frequent association of hemoglobinuria and death, it is unusual to find the blue-black pigmentation of kidneys characteristic of chronic copper poisoning in sheep.
- Icterus is often severe with canalicular cholestasis, which indicates extensive intracellular as well as intravascular hemolysis where the pigment is not lost in urine.
- Kidneys may be swollen, pale and soft, without hemoglobin pigmentation.
- The lungs are edematous and there is frequently interstitial and subcutaneous emphysema associated with terminal dyspnea.