LECTURE 9
Diseases of Blood System

•1. Anaemias. Thrombocytopenias and Thrombocytopathies. Coagulopathies.

•2. Hemoblastosises. Diseases of Organs of Lymphoreticular System.

Diagnostic *Diseases of Blood System*

-To define the peculiarities of anaemia morphogenesis and other blood diseases the sternal puncture of marrow biopsy is widely used.

•- In breast bone (sternum) punctate it is possible to diagnose leucaemia and the marrow regeneration level under the anaemia as well as the type of erythropoiesis (erythroblastic, normoblastic, megaloblastic).

Anaemia

•- is a blood disease of erythrocytes quantity or their hemoglobin saturation

•- in the peripheral blood can appear erythrocytes of different size (poikilocytosis, poikilocythemia), different shape (anisocytosis),

•- different level of colouring (hyperchromatism and hypochromatism),

•- erythrocytes with inclusions (Jolli's corpuscles, Kabo's rings),

•-nuclear erythrocytes (erythroblasts, normoblasts, megaloblasts).

Classification of Anemia According to Underlying Mechanism

•***Blood Loss***

•***Increased Rate of Destruction (Hemolytic Anemias)***

•***Impaired Red Cell Production***

Classification of Anemia According to Underlying Mechanism

•***Blood Loss***

•Acute: trauma

•Chronic: lesions of gastrointestinal tract, gynecologic disturbances

Classification of Anemia According to Underlying Mechanism

•***Increased Rate of Destruction (Hemolytic Anemias)***

•Intrinsic (intracorpuscular) abnormalities of red cells

••*Hereditary*

•••Red cell membrane disorders

•••••Disorders of membrane cytoskeleton: spherocytosis, elliptocytosis

•••••Disorders of lipid synthesis: selective increase in membrane lecithin

•••Red cell enzyme deficiencies

•••••Glycolytic enzymes: pyruvate kinase deficiency, hexokinase deficiency

Classification of Anemia According to Underlying Mechanism

•***Increased Rate of Destruction (Hemolytic Anemias)***

••••Enzymes of hexose monophosphate shunt: G6PD, glutathione synthetase

•••Disorders of hemoglobin synthesis

•••••Deficient globin synthesis: thalassemia syndromes

•••••Structurally abnormal globin synthesis (hemoglobinopathies): sickle cell anemia, unstable hemoglobins

••*Acquired*

•••Membrane defect: paroxysmal nocturnal hemoglobinuria

Increased Rate of Destruction (Hemolytic Anemias)

•••Antibody mediated

•Extrinsic (extracorpuscular) abnormalities

•••••Isohemagglutinins: transfusion reactions, erythroblastosis fetalis

•••••Autoantibodies: idiopathic (primary), drug-associated, systemic lupus erythematosus, malignant neoplasms, mycoplasmal infection

•••Mechanical trauma to red cells

•••••Microangiopathic hemolytic anemias: thrombotic thrombocytopenic purpura, disseminated intravascular coagulation
•••••Cardiac traumatic hemolytic anemia
•••Infections: malaria, hookworm
•••Chemical injury: lead poisoning
•••Sequestration in mononuclear phagocyte system: hypersplenism

Classification of Anemia According to Underlying Mechanism
•***Impaired Red Cell Production***
•A Disturbance of proliferation and differentiation of stem cells: aplastic anemia, pure red cell aplasia, anemia of renal failure, anemia of endocrine disorders
•B Disturbance of proliferation and maturation of erythroblasts
•1 Defective DNA synthesis: deficiency or impaired use of vitamin B12 and folic acid (megaloblastic anemias)
•2 Defective hemoglobin synthesis
•••••Deficient heme synthesis: iron deficiency
•••••Deficient globin synthesis: thalassemias
•3 Unknown or multiple mechanisms:
• sideroblastic anemia,
•anemia of chronic infections,
•myelophthisic anemias due to marrow infiltrations

•(normocytic, microcytic, or macrocytic);
• degree of hemoglobinization, reflected in the color of red cells (normochromic or hypochromic); and other special features, such as shape.
•These red cell indices are often judged qualitatively by physicians, but precise quantitation is done in clinical laboratories using special instrumentation.

•The most useful red cell indices are as
•follows:
•• *Mean cell volume:* the average volume of a red blood cell, expressed in femtoliters (cubic micrometers)
•• *Mean cell hemoglobin:* the average content (mass) of hemoglobin per red blood cell, expressed in picograms
•• *Mean cell hemoglobin concentration:* the average concentration of hemoglobin in a given volume of packed red blood cells, expressed in grams per deciliter

Howell-Jolly bodies

•There is also a nucleated RBC just beneath this RBC. Abnormal and aged RBC's are typically removed by the spleen. The appearance of increased poikilocytosis, anisocytosis,

•The size of many of these RBC's is quite small, with lack of the central zone of pallor. These RBC's are spherocytes. In hereditary spherocytosis, there is a lack of spectrin, a key RBC cytoskeletal membrane protein. This produces membrane instability that forces the cell to the smallest volume--a sphere. In the laboratory, this is shown by increased osmotic fragility. The spherocytes do not survive as long as normal RBC's.
Classification of anaemias
According to the aetiology and pathogenesis there are three groups of anaemias:

• - posthemorrhagic anemia (as a result of blood loss),

•- anaemia as a result of hematosis disturbance, and

•- hemolytic anaemia (as a result of increased erythrocytes destruction).
According to the clinical course anaemias can be

•acute and

•chronic.
<u>Posthemorrhagic anaemia</u>

Classification of Posthemorrhagic anaemia

•*acute posthemorrhagic anaemia*

•*chronic posthemorrhagic anaemia*

<u>Posthemorrhagic anaemia</u>

•develops as a result of hemorrhage

•-of the stomach or bowels vessels under the ulcer or tumouric affection,

•-of uterine tube rupture under the extrauterine pregnancy,

•-of aortic rupture,

•-of lung vessels fret under tuberculosis, and others.

ANEMIAS OF BLOOD LOSS
Acute Blood Loss

•The clinical and morphologic reactions to blood loss depend on the rate of hemorrhage and whether the bleedingis external or internal. The effects of acute blood loss are mainly due to the loss of intravascular volume, which can lead to cardiovascular collapse, shock, and death. If the patient survives,
•the blood volume is rapidly restored by shift of water from the interstitial fluid compartment. The resulting hemodilution lowers the hematocrit. Reduction in the oxygenation of renal juxtaglomerular cells triggers increased production of erythropoietin, which stimulates the proliferation of committed erythroid stem cells (CFU-E) in the marrow. It takes about 5 days for
•the progeny of these CFU-Es to fully differentiate, an event marked by the appearance of increased numbers of newly released red cells (reticulocytes) in the peripheral blood.
•The iron in hemoglobin is recaptured if red cells are lost internally, as into the peritoneal cavity, but external bleeding leads to iron loss and possible iron deficiency, which can hamper restoration of normal red cell counts.

ANEMIAS OF BLOOD LOSS
Acute Blood Loss

•The earliest change in the peripheral blood immediately after acute blood loss is *leukocytosis,* due to the mobilization of granulocytes from marginal pools. Initially, red cells appear normal

•in size and color (normocytic, normochromic). However, as marrow production increases, *there is a striking increase in the reticulocyte count, reaching 10% to 15% after 7 days*.

•Reticulocytes are recognizable as polychromatophilic macrocytes in the usual blood smear. Early recovery from blood loss is often accompanied by *thrombocytosis,* which is caused by

•increased platelet production.

ANEMIAS OF BLOOD LOSS
Chronic Blood Loss

•Chronic blood loss induces anemia only when the rate of loss exceeds the regenerative capacity of the marrow or when iron reserves are depleted. Iron deficiency anemia, which has

•identical features regardless of underlying cause (e.g., bleeding, malnutrition, malabsorption states), will be discussed later.
Chronic stomach ulcer
•. Ulcer edges are gasketed due to connective tissue spread in the shape of a roll. Ulcer bottom partially or in the whole area has dark brown painting. Pathologic process corrodes vessels wall and hemorrhage appears (haemorrhagia per diabrosion). Haemoglobin under hydrochloric acid affection turns to muriatic haematin of dark brown painting which paints the ulcer bottom and walls. Prolonged stomach hemorrhages under the ulcerous disease are complicated with **chronic posthemorrhagic anaemia.**

Cardiac (pericardial) tamponade
• In the cavity the blood is seen. On the heart top there is a spread subepicardial myocardial infarction This is the recurrent myocardial infarction with myomalacia. The myomalacia area is filled with blood, via this area the blood from the left ventricle cavity arrived to the cardial cavity and the tamponade appeared. The death came as a result of abrupt pressure change in the cardial ventricle hole, and it stops in the systole phase.
hemorrhage in abdominal cavity
Postoperative hemorrhage in abdominal cavity
Posthemorrhagic anaemia

•the *acute posthemorrhagic anaemia* comes

•of the big vessels bleeding and the death occurs faster than morphologic manifestations of anaemia appear.

•the *chronic posthemorrhagic anaemia* develops

• of the prolonged bleeding of small vessels
Morphology of Posthemorrhagic anaemia

• -the *bleach* skin, mucous tunics, and internal.

•- Red marrow of flat bones, epiphysial plates hyperplasies and turns to intence, succulent.

•- Yellow marrow *metaplasies* to red,

•- there appear the centres of *extramedullary hematosis* in the spleen, thymus, lymph nodes and other tissues.

•- As a result of hypoxia (oxygen starvation) in the internal there can develop *dystrophic* changes, small *hemorrhages* in mucous and serous tunics.

Subepicordial hemorrhages

•. On the front heart surface by the course of the terminal branch of coronary vessels the subepicardial diapedetic hemorrhages are seen – the dark brown macules of vague outlines. Increased vessels penetrability is caused by hypoxia, thrombocytopenia which break as a result of compensatory high spread of myeloid or lymphoid hematopoietic shoots with the corresponding oppression of other (erythrocytic, thrombocytic, megakaryocytic). The brown painting is explained by the local hemosiderosis.

Fatty hepatosis

In the cut the liver has yellow painting while the whole stretch, little increased, the capsule is smooth. Fatty dystrophic liver appears under chronic anaemias as a result of hypoxia. Under hypoxia there appears the hyperlipemia because of the nutrients which not completely realized as a plastic and energetic material thus more blood arrives to liver with arterial blood. Also under the oxygen deficiency hepatocytes are not able to split completely the fat which arrives to liver from intestine via portal vein. Liver function lowers on this.

chronic posthemorrhagic anaemia

•*Ordinary (simple, general) adiposity.* In the macropreparation there is represented subcutaneous fat of the front abdominal wall of 10-12 cm (3,93-4,72 inches) thickness. This adiposity is probable under chronic anaemias as a result of nutrients which not completely used as plastic and energetic material with saving of fats in depot.

<u>Anaemia as a result of hematosis disturbance</u>

•develops under

•- the deficiency of iron,

•- the deficiency of B-12 vitamin, folic acid.

•To this type hypo- and aplastic anaemias are numbered.

Asiderotic (iron-deficiency) anaemia

•is always hypochromic and

•develops under the poor arrival of iron into the organism with food.

•Such anaemias are common among children,

•and also under intense need of iron while pregnancy, female juvenile or climacteric chlorosis.

•This anaemia can appear under the stomach, bowels diseases, especially after their resection.

iron-deficiency) anaemia

•The most common cause for a hypochromic microcytic anemia is iron deficiency. The most common nutritional deficiency is lack of dietary iron. Thus, iron deficiency anemia is common. Persons most at risk are children and women in reproductive years (from menstrual blood loss and from pregnancy).

iron-deficiency anaemia

•Hypochromic microcytic anemia of iron deficiency (peripheral blood smear). Note the small red cells containing a narrow rim of peripheral hemoglobin. Scattered fully

•hemoglobinized cells, present due to recent blood transfusion, stand in contrast.

•Diagrammatic representation of iron absorption. Mucosal uptake of heme and nonheme iron is depicted. When the storage sites of the body are replete with iron and erythropoietic activity is normal, most of the absorbed iron is lost into the gut by shedding of the epithelial cells. Conversely, when body iron needs increase or when erythropoiesis is stimulated, a greater fraction of the absorbed iron is transferred into plasma transferrin, with a concomitant decrease in iron loss through mucosal ferritin.

B-12 and folicdeficient anaemias

•*Synonyms of B-12 and folicdeficient anaemias:*

•megaloblastic anemia

•hyperchromatism anemia,

•pernicious (Biermer's, Biermer-Ehrlich) anemia
Megaloblastic anemia

• A peripheral blood smear shows a hypersegmented neutrophil with a six-lobed nucleus
Causes of Megaloblastic Anemia

•***Vitamin B12 Deficiency***

•Decreased intake

••Inadequate diet, vegetarianism

•Impaired absorption

••Intrinsic factor deficiency

••••Pernicious anemia

••••Gastrectomy

••Malabsorption states

••Diffuse intestinal disease, e.g., lymphoma, systemic sclerosis

••Ileal resection, ileitis
Causes of Megaloblastic Anemia
••Competitive parasitic uptake
••••Fish tapeworm infestation
••Bacterial overgrowth in blind loops and diverticula of bowel
•Increased requirement
••••Pregnancy, hyperthyroidism, disseminated cancer
•***Folic Acid Deficiency***
•Decreased intake
••Inadequate diet—alcoholism, infancy
•Impaired absorption
••Malabsorption states
••Intrinsic intestinal disease
••Anticonvulsants, oral contraceptives
•Increased loss
••Hemodialysis
•Increased requirement
••Pregnancy, infancy, disseminated cancer, markedly increased hematopoiesis
•Impaired use
••Folic acid antagonists
•***Unresponsive to Vitamin B12 or Folic Acid Therapy***
•Metabolic inhibitors of DNA synthesis and/or folate metabolism, e.g., methotrexate
Megaloblastic anemia
•(bone marrow aspirate). *A* to *C*, Megaloblasts in various stages of differentiation. Note that the orthochromatic megaloblast *(B)* is hemoglobinized (as
•revealed by cytoplasmic color), but in contrast to normal orthochromatic normoblasts, the nucleus is not pyknotic. The granulocytic precursors are also large and have abnormally
•"immature" chromatin.

B-12 and folicdeficient anaemias

•Here is a hypersegmented neutrophil that is present with megaloblastic anemias. There are 8 lobes instead of the usual 3 or 4. The size of the RBC's is also increased (macrocytosis, which is hard to appreciate in a blood smear).

B-12 and folicdeficient anaemias

•*Pathogenesis of B-12 and folicdeficient anaemias*

• are characterized by erythrogenesis destruction and

• appear under food B-12 vitamin disturbance in the stomach, which is observed under its diseases, when gastromucoprotein secretion prolapse is met.

•Such changes can be of hereditary origin or autoimmune genesis.

B-12 and folicdeficient anaemias

•*Aetiology*

•Under the lymphogranulomatosis,

•polyposis,

• syphilis,

•corrosive (necrotic, (toxico) chemical) gastritis,

• malignant growths of stomach,

• after the stomach, bowels resections there can appear perniciouslike anaemias. The cause of such anaemia can be exogenous deficiency of B-12 vitamin or folic acid of children fed on goat's milk.

B-12 and folicdeficient anaemias

•Pathogenesis

•- the hemopoesis is realized by the megaloblastic type and

•- the blood destruction exceeds the hematosis.

B-12 and folicdeficient anaemias

•Morphology
•The pathomorphologic manifestations of this anaemia are as next: liver, spleen, kidney *hemosiderosis*,
• *fatty degeneration* of parenchymatous organs,
•general obesity,
• bleach lemon-tinged skin,
•small *hemorrhages* in mucous, serous tunics and skin.
•In gastrointestinal tract there are *atrophic and sclerotic* changes,
• the marrow turns to raspberry-red with the predominance of erythroblasts, normoblasts, and megacaryoblasts.
•In lateral and posterior (dorsal) columns of spinal cord there is *funicular myelosis*, in the brain there are the centres of encephalomalacia and ischemia.

Hypoplastic and aplastic anaemias
can be:

•*endogenous or inherited* (familial aplastic anaemia of Fankoni and Erlich's hypoplastic anaemia), and

•- *exogenous or acquired* (radiation, toxic, medicamentosis anaemias).

The case of aplastic anemia.

•Hematopoietic elements in this bone marrow biopsy are markedly reduced. Of course, besides, RBC's the platelets and granulocytes will often be diminished. Sometimes a drug or toxin is the cause and sometimes infection. When no known cause can be found, it is termed idiopathic aplastic anemia.

•In contrast to aplastic anemia, leukemia results in a highly cellular marrow. The marrow between the pink bone trabeculae seen here is nearly 100% cellular, and it consists of leukemic cells of acute lymphocytic leukemia (ALL) that have virtually replaced or suppressed normal hematopoiesis. Thus, though the marrow is quite cellular, there can be peripheral cytopenias. This explains the complications of infection (lack of normal leukocytes), hemorrhage (lack of platelets), and anemia (lack of red blood cells) that often appear with leukemia.

Acquired
Causes of Aplastic Anemia
•Idiopathic
•••Primary stem cell defect
•••Immune mediated
•Chemical agents
•••Dose related
•••••Alkylating agents
•••••Antimetabolites
•••••Benzene
•••••Chloramphenicol
•••••Inorganic arsenicals
•••Idiosyncratic
•••••Chloramphenicol
•••••Phenylbutazone
•••••Organic arsenicals
•••••Methylphenylethylhydantoin
•••••Streptomycin
•••••Chlorpromazine
•••••Insecticides (e.g., DDT, parathion)
•Physical agents (e.g., whole-body irradiation)
•Viral infections
•••Hepatitis (unknown virus)
•••Cytomegalovirus infections
•••Epstein-Barr virus infections
•••Herpes varicella-zoster
•Miscellaneous

•••Infrequently, many other drugs and chemicals

Hemolytic anaemia

is characterized by increased erythrocytes destruction which can be :
•intravascular and
•extravascular
•The physiologic destruction of senescent red cells takes place within the mononuclear phagocytic cells of the spleen. In the great majority of hemolytic anemias, the premature destruction
•of red cells also occurs within the mononuclear phagocyte system (extravascular hemolysis), which undergoes a form of work-related hyperplasia marked by splenomegaly. Much less
•commonly, lysis of red cells within the vascular compartment (intravascular hemolysis) predominates.
HEMOLYTIC ANEMIAS

•Hemolytic anemias share the following features:

•• A shortened red cell life span (normal = 120 days); that is, premature destruction of red cells

•• Elevated erythropoietin levels and increased erythropoiesis in the marrow and other sites, to compensate for the loss of red cells

•• Accumulation of the products of hemoglobin catabolism, due to an increased rate of red cell destruction

Hemolytic anaemia
•*Intravascular anaemia* appears when hemolytic poisons get into the organism, under the
•**Aetiology**
•badly burns (toxic anaemia),
•under malaria,
•sepsis and other infections (infectious anaemia),
•under blood transfusion of incompatible blood group or Rhesus factor (posttransfusion anaemia),
•under immune pathologic processes (immune, isoimmune and autoimmune anaemias (hemolytic disease of newborns, chronic lympholeucosis, marrow carcinomatosis, systemic lupus erythematosus, medicamentosis immune hemolysis, thermal hemoglobinuria and other).
HEMOLYTIC ANEMIAS
Intravascular hemolysis

•of red cells is caused by mechanical injury, complement fixation, infection by intracellular parasites such as falciparum malaria, or exogenous toxic

•factors. Mechanical injury caused by defective cardiac valves, thrombi within the microcirculation, or repetitive physical trauma (marathon running, bongo drum beating) can physically

•lyse red cells. Complement fixation can occur on antibody-coated cells during transfusion of mismatched blood. Toxic injury is exemplified by clostridial sepsis, which releases toxins that

•attack the red cell membrane.
HEMOLYTIC ANEMIAS
Intravascular hemolysis
•Whatever the mechanism, intravascular hemolysis is manifested by (1) hemoglobinemia, (2) hemoglobinuria, (3) jaundice, and (4) hemosiderinuria. Free hemoglobin in plasma is promptly
•bound by an a2 -globulin (haptoglobin), producing a complex that is rapidly cleared by the mononuclear phagocyte system, thus preventing excretion into the urine. Decreased serum
•haptoglobin is characteristic of intravascular hemolysis. When the haptoglobin is depleted, free hemoglobin is prone to oxidation to methemoglobin, which is brown in color. The renal
•proximal tubular cells reabsorb and catabolize much of the filtered hemoglobin and methemoglobin, but some passes out with the urine, imparting a red-brown color. Iron released from
•hemoglobin can accumulate within tubular cells, giving rise to renal hemosiderosis. Concomitantly, heme groups derived from the complexes are catabolized to bilirubin within the
•mononuclear phagocyte system, leading to jaundice. In hemolytic anemias, the serum bilirubin is unconjugated and the level of hyperbilirubinemia depends on the functional capacity of
•the liver and the rate of hemolysis. When the liver is normal, jaundice is rarely severe. Excessive bilirubin excreted by the liver into the gastrointestinal tract leads to increased formation
•and fecal excretion of urobilin

•Malaria is a parasitic disease caused by the genus Plasmodium, of which there are four species that affect man. Shown here are "ring forms" of Plasmodium vivax in red blood cells. This disorder can produce hemolysis and anemia.

Hemolytic anaemia
Extravascular hemolysis

•takes place whenever red cells are rendered "foreign" or become less deformable. Since extreme alterations in shape are required for red cells to navigate the splenic sinusoids successfully, reduced deformability makes the passage difficult and leads to sequestration within the cords, followed by phagocytosis This is an important pathogenetic mechanism of extravascular hemolysis in a variety of hemolytic anemias. With extravascular hemolysis the following discussions of thalassemia major and minor
Hemolytic anaemia

•Marrow smear from a patient with hemolytic anemia. The marrow reveals greatly increased numbers of maturing erythroid progenitors (normoblasts).
Hemolytic anaemia

•*Extravascular (intracellular) anaemia* is mostly of inherited origin and divides into

•--erythrocytopathy,

•--erythrocytoenzymopathy and

•--hemoglobinopathy
Hemolytic anaemia

•*erythrocytopathy anaemia*

•To the hemolytic anaemias of such origin as erythrocytes membrane structural defect are ranked such diseases as

•microspherocytosis,

•inherited ovalocytosis and other.
Hemolytic anaemia

•Hereditary spherocytosis (peripheral smear). Note the anisocytosis and several dark-appearing spherocytes with no central pallor. Howell-Jolly bodies (small dark nuclear

•remnants) are also present in red cells of this asplenic patient
Hemolytic anaemia
Sickle cell anemia
Hemolytic anaemia
Sickle cell anemia

•*A*, Spleen in sickle cell anemia (low power). Red pulp cords and sinusoids are markedly congested; between the congested areas, pale areas of fibrosis resulting from

•ischemic damage are evident.

•*B*, Under high power, splenic sinusoids are dilated and filled with sickled red cell
Hemolytic anaemia
Sickle cell anemia

•Splenic remnant in sickle cell anemia.
Hemolytic anaemia
Erythrocytoenzymopathic hemolytic anaemia

• appears because of enzyme deficiency of pentose-phosphate cycle - glucose 6-phosphate dehydrogenase and pyruvate kinase. This anaemia grows progressively worse under viral infections, usage of some medicaments.
Hemolytic anaemia Erythrocytoenzymopathic hemolytic anaemia

•G6PD deficiency: effects of oxidant drug exposure (peripheral blood smear). *Inset*, Red cells with precipitates of denatured globin (Heinz bodies) revealed by supravital

•staining. As the splenic macrophages pluck out these inclusions, "bite cells" like the one in this smear are produced
Classification of Immunohemolytic Anemias

•***Warm Antibody Type***

•The antibody is of the IgG type, does not usually fix complement, and is active at 37°C.

•*Primary* (idiopathic)

•*Secondary*

•••Lymphomas and leukemias

•••Other neoplastic diseases

•••Autoimmune disorder (particularly systemic lupus erythematosus)

•••Drugs

Classification of Immunohemolytic Anemias

•***Cold Agglutinin Type***
•The antibodies are IgM and most active in vitro at 0° to 4°C.
•••Antibodies dissociate at 30°C or above; agglutination of cells by IgM and complement fixation occurs only in peripheral cool parts of the body (e.g., fingers, ears, and toes).
•*Acute* (mycoplasmal infection, infectious mononucleosis)
•*Chronic*
•••Idiopathic
•••Associated with lymphoma
•***Cold Hemolysins (Paroxysmal Cold Hemoglobinuria)***
•IgG antibodies bind red cells at low temperature, fix complement, and cause hemolysis when the temperature is raised above 30°C.
Hemolytic anaemia
Warm Antibody Immunohemolytic Anemia.

•This is the most common form (48% to 70%) of immune hemolytic anemia. About 50% of cases are idiopathic (primary); the remainder arise secondarily in the setting of a predisposing condition or drug exposure.
•Most causative antibodies are of the immunoglobulin G (IgG) class; only sometimes are IgA antibodies culpable. Most red cell destruction in this form of hemolytic disease is extravascular. IgG-coated red cells bind Fc receptors on monocytes and splenic macrophages, which results in loss of red cell membrane during "partial"
•phagocytosis. As in hereditary spherocytosis, the loss of cell membrane converts the red cells to spherocytes, which are sequestered and removed in the spleen, the major site of red cell
•destruction in this disorder. Thus, moderate splenomegaly is characteristic of this form of anemia.
•As with other forms of autoimmunity, the cause of autoantibody formation is largely unknown. In many cases, the antibodies are directed against the Rh blood group antigens. The mechanisms of drug-induced hemolysis are better understood. Two predominant immunologic mechanisms have been implicated.
Hemolytic anaemia
Warm Antibody Immunohemolytic Anemia.

•• Hapten model. The drugs—exemplified by penicillin and cephalosporins—act as haptens by binding to the red cell membrane. Antibodies directed against the cell-bound drug
•result in the destructive sequence cited before. This form of hemolytic anemia is usually caused by large intravenous doses of the antibiotic and occurs 1 to 2 weeks after onset of
•therapy. Sometimes the antibodies bind only to the offending drug, as in penicillin-induced hemolytic anemia. In other cases, such as quinidine-induced hemolysis, the antibodies
•recognize a complex of the drug and a membrane protein. In drug-induced hemolytic anemias, the destruction of red cells can occur intravascularly after fixation of complement or
•extravascularly in the mononuclear phagocyte system.
•• Autoantibody model. These drugs, of which the antihypertensive agent a-methyldopa is the prototype, in some manner initiate the production of antibodies directed against
•intrinsic red cell antigens, in particular the Rh blood group antigens. Approximately 10% of patients taking a-methyldopa develop autoantibodies, as assessed by the direct
•Coombs test. However, only 1% develops clinically significant hemolysis.

Hemolytic anaemia
Cold Hemolysin Hemolytic Anemia.

•Cold hemolysins are autoantibodies responsible for an unusual entity known as *paroxysmal cold hemoglobinuria*, characterized by acute intermittent massive intravascular hemolysis,
•frequently with hemoglobinuria, after exposure to cold temperatures. This is the least common form of immunohemolytic anemia. Lysis is clearly complement dependent. The
•autoantibodies are IgGs that bind to the P blood group antigen on the red cell surface at low temperatures. Complement-mediated intravascular lysis does not occur until the cells
•recirculate to warm central regions, as the enzymes of the complement cascade function more efficiently at 37°C. The antibody, also known as the Donath-Landsteiner antibody, was first
•recognized in association with syphilis. Today, most cases of paroxysmal cold hemoglobinuria follow infections such as mycoplasma pneumonia,
•measles, mumps, and ill-defined viral and "flu" syndromes. The mechanisms responsible for production of such autoantibodies in these settings are unknown.
Hemolytic anaemia
Resulting from Trauma to Red Cells

•Red blood cells can be disrupted by physical trauma in a variety of circumstances. Of these, hemolytic anemias caused by cardiac valve prostheses, or narrowing or obstruction of the
•microvasculature, are most important clinically. Severe traumatic hemolytic anemia is more frequently associated with artificial mechanical valves than bioprosthetic porcine valves.
•Hemolysis in both instances stems from shear stresses produced by turbulent blood flow and abnormal pressure gradients. Microangiopathic hemolytic anemia, on the other hand, occurs
•when red cells are forced to squeeze through abnormally narrowed small vessels. Narrowing is most often caused by fibrin deposition in association with disseminated intravascular
•coagulation (discussed later in this chapter). Other causes of microangiopathic hemolytic anemia include malignant hypertension, systemic lupus erythematosus, thrombotic
•thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS), and disseminated cancer, most of which are discussed elsewhere in this book. The common feature among all these
•disorders is a microvascular lesion that causes mechanical injury to circulating red cells. This damage is evident in peripheral blood smears in the form of red cell fragments (schistocytes),
•"burr cells," "helmet cells," and "triangle cells" . Except for TTP and HUS, hemolysis is not a major clinical problem in most instances.

Hemolytic Anemia

Microangiopathic hemolytic anemia

•A peripheral blood smear from a patient with hemolytic-uremic syndrome shows several fragmented red cells.

Hemolytic anaemia

•*Hemoglobinopathic hemolytic anaemia* develops under disturbance of haemoglobin synthesis – a and b-thalassemia or under appearance of anomalous haemoglobin – S,C,D,E. Falcated cellular anaemia can combine hemoglobinopathies.

Hemolytic anaemia

•***Morphologic manifestations*** *of hemolytic anaemias* are mainly very specific:

•general hemosiderosis,

•hemolytic jaundice in serious cases with hemoglobinuric nephrosis,

•splenomegaly under inherited hemolytic anaemias,

• presence of centres of extramedullar hemopoesis.

thanks