

Anemia

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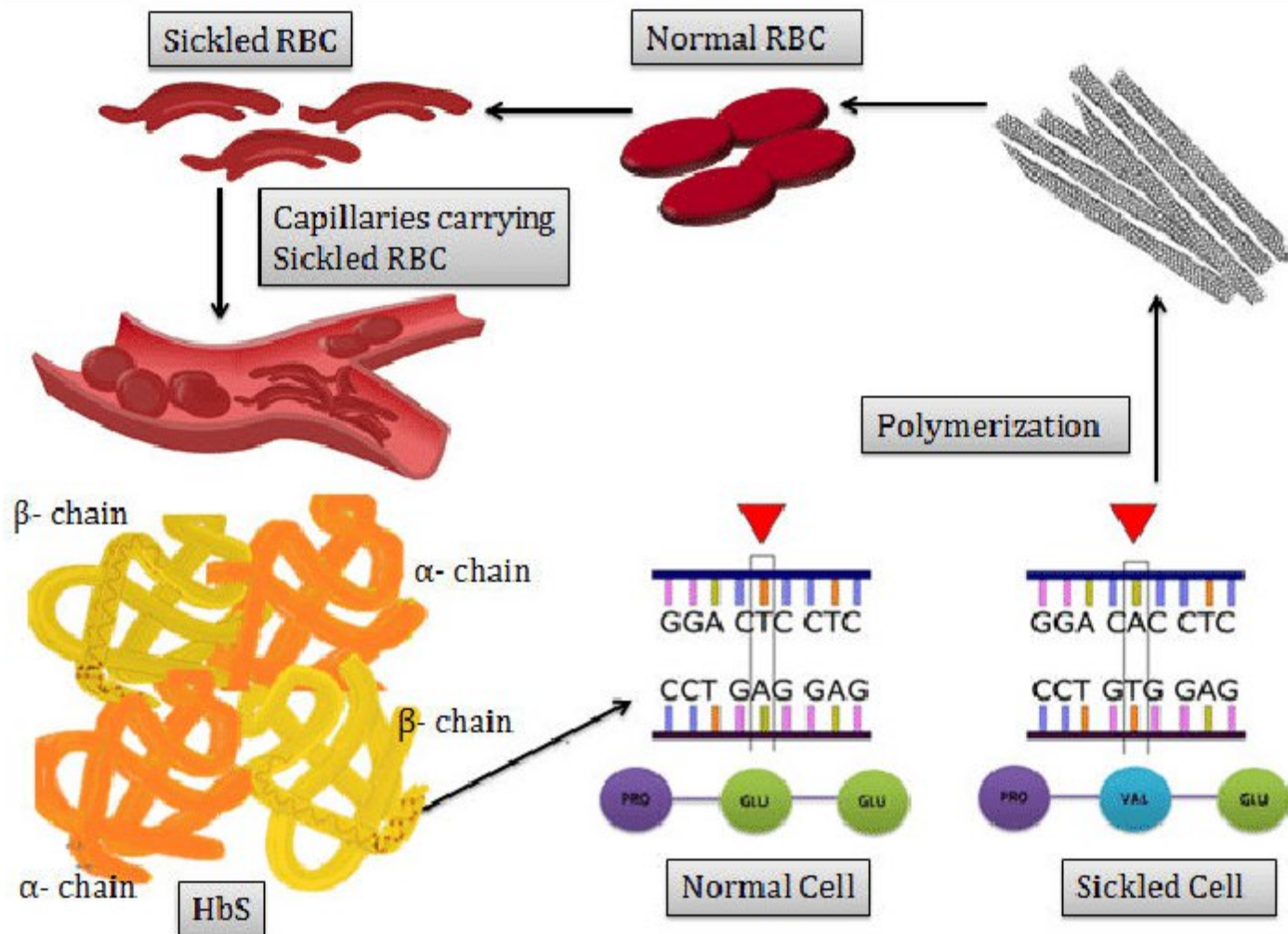
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Sickle Cell Disease

Sickle cell disease is caused by a point mutation in the sixth codon of β -globin gene that leads to the replacement of a glutamate amino acid with a valine amino acid.

Happens in patients who are homozygous (has 2 mutated allele) for HbS, a condition called **HbSS** disease, one mutated allele leads to a carrier state called **HbAS**

Resultant hemoglobin undergoes polymerization, leading to red cell distortion, hemolytic anemia, microvascular obstruction, and ischemic tissue damage.



Sickle Cell Disease

Pathogenesis

The RBCs is sickle or holly-leaf in shape, non deformable.

The major pathologic manifestations are **chronic hemolysis, microvascular occlusions, and tissue damage**

Sickled red cells are also mechanically fragile, leading to **some** intravascular hemolysis as well.

Variables affecting the degree of sickling

Interaction of HbS with the other types of hemoglobin in the cell:

- Greatest sickling in HbSS
- In Sick cell trait (HbAS), HbA interferes with HbS polymerization,
- HbF inhibits the polymerization of HbS, infants do not become symptomatic until they reach 5 or 6 months

Mean cell hemoglobin concentration (MCHC).

- Higher HbS concentrations increase the probability of sickling
- Lower MCHC e.g. α thalassemia decrease sickling

variables affecting the degree of sickling

A decrease in Intracellular pH. augments the tendency for sickling.

High Transit time of red cells through microvascular beds e.g. inflamed tissues

Sickle Cell Disease

Pathogenesis

Microvascular occlusions, are responsible for the most serious clinical features, these are dependent on

- Subtle red cell membrane damage
- Local factors, such as inflammation or vasoconstriction
- Increased adhesion molecules on sickle red cells

Stagnation of RBCs lead to prolonged exposure to low oxygen that augments sickling that in turn worsens occlusion and generate a vicious circle of occlusion and further sickling

Sickle Cell Disease

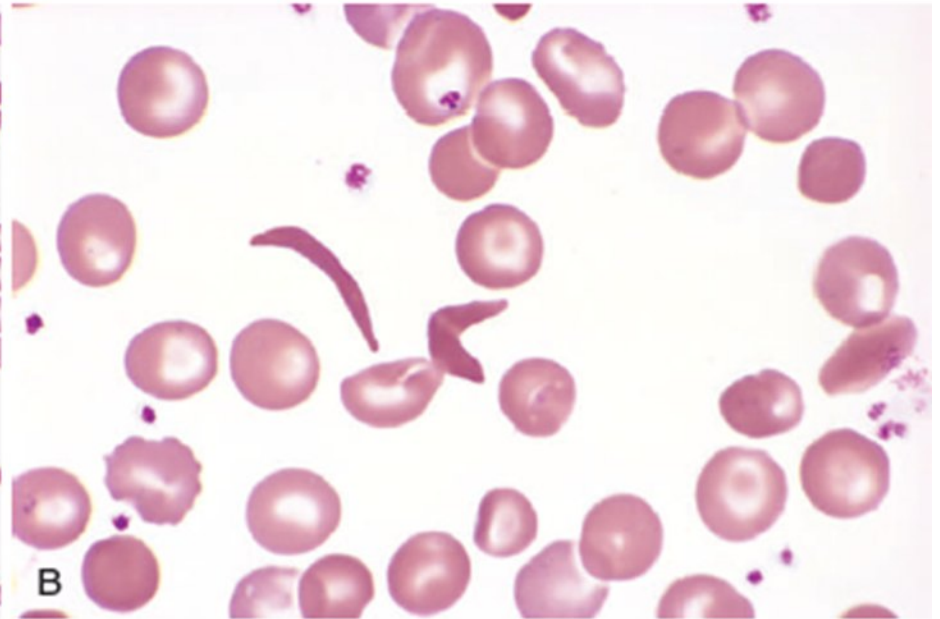
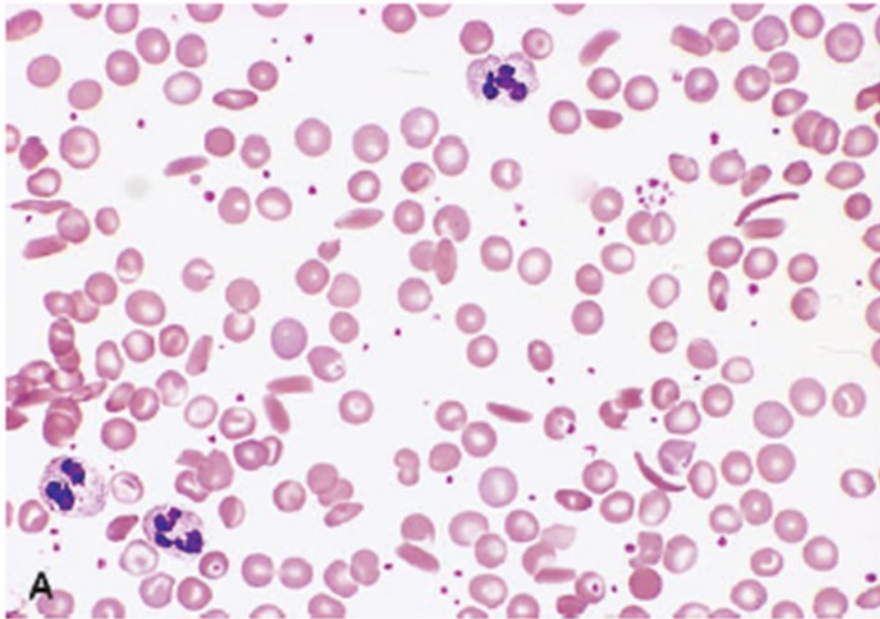
Pathogenesis

In early childhood, trapping of sickled red cells occurs in the spleen leading to its enlargement

With time, splenic infarction, fibrosis, and progressive shrinkage, so that by adolescence or early adulthood only a fibrous splenic tissue is left; this process is called **autosplenectomy**, leading to significant risk of infection by encapsulated organisms in these patients

Sickle Cell Disease

Morphology



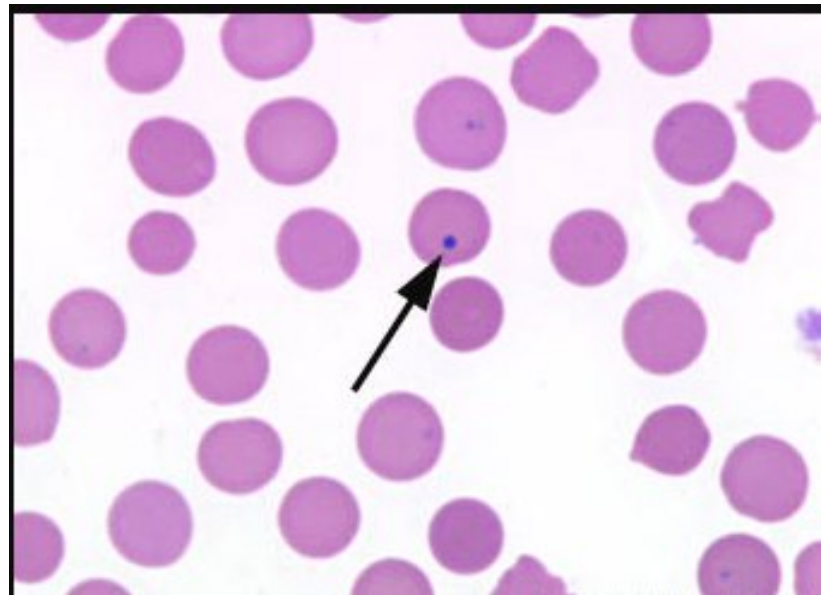
Sickle Cell Disease

Morphology

The peripheral blood demonstrates variable numbers of **sickled cells** and target cells and polychromasia from reticulocytosis

Howell-Jolly bodies (small nuclear remnants) are present in some red cells due to the asplenia

The bone marrow is hyperplastic as a result of a compensatory erythroid hyperplasia.



Sickle Cell Disease

Clinical Features

Manifestations of anemia and jaundice from hyperbilirubinemia

Course is characterized by a variety of acute complications called “crises”

Vaso-occlusive crises or pain crises

- hypoxic injury and infarction that cause severe pain
- Most commonly involved sites are the bones, lungs, and splanchnic vessels

Sequestration crises

- Entrapment of sickle red cells leads to rapid splenic enlargement, hypovolemia, and sometimes shock
- In children

Sickle Cell Disease

Clinical Features

Aplastic crises, infection of red cell progenitors by parvovirus B19

Acute chest syndrome

- Vaso-occlusive crisis involving the lungs
- Fever, cough, chest pain, and pulmonary infiltrates

Priapism, stroke and retinopathy

Sickle Cell Disease

Clinical Features

Chronic complications

- Impairment of growth and development,
- organ damage affecting the spleen, heart, kidneys, and lungs and loss of concentrating ability of the kidney

Increased susceptibility to **infection** with encapsulated organisms, **Pneumococcus pneumoniae** and **Haemophilus influenza** **septicemia and meningitis**

Diagnosis based on Hb electrophoresis and DNA analysis

Thalassemia Syndromes

Inherited mutations that decrease the synthesis of either the **α -globin (α -thalassemia)** or **β -globin chains (β -thalassemia)** leading to anemia, tissue hypoxia, and red cell hemolysis.

The two α chains in HbA are encoded by 4 α -globin genes on **chromosome 16**, while the two β chains are encoded by a 2 β -globin genes on chromosome 11.

Anemia occurs through two mechanisms: decreased red cell production, and decreased red cell lifespan

β -Thalassemia

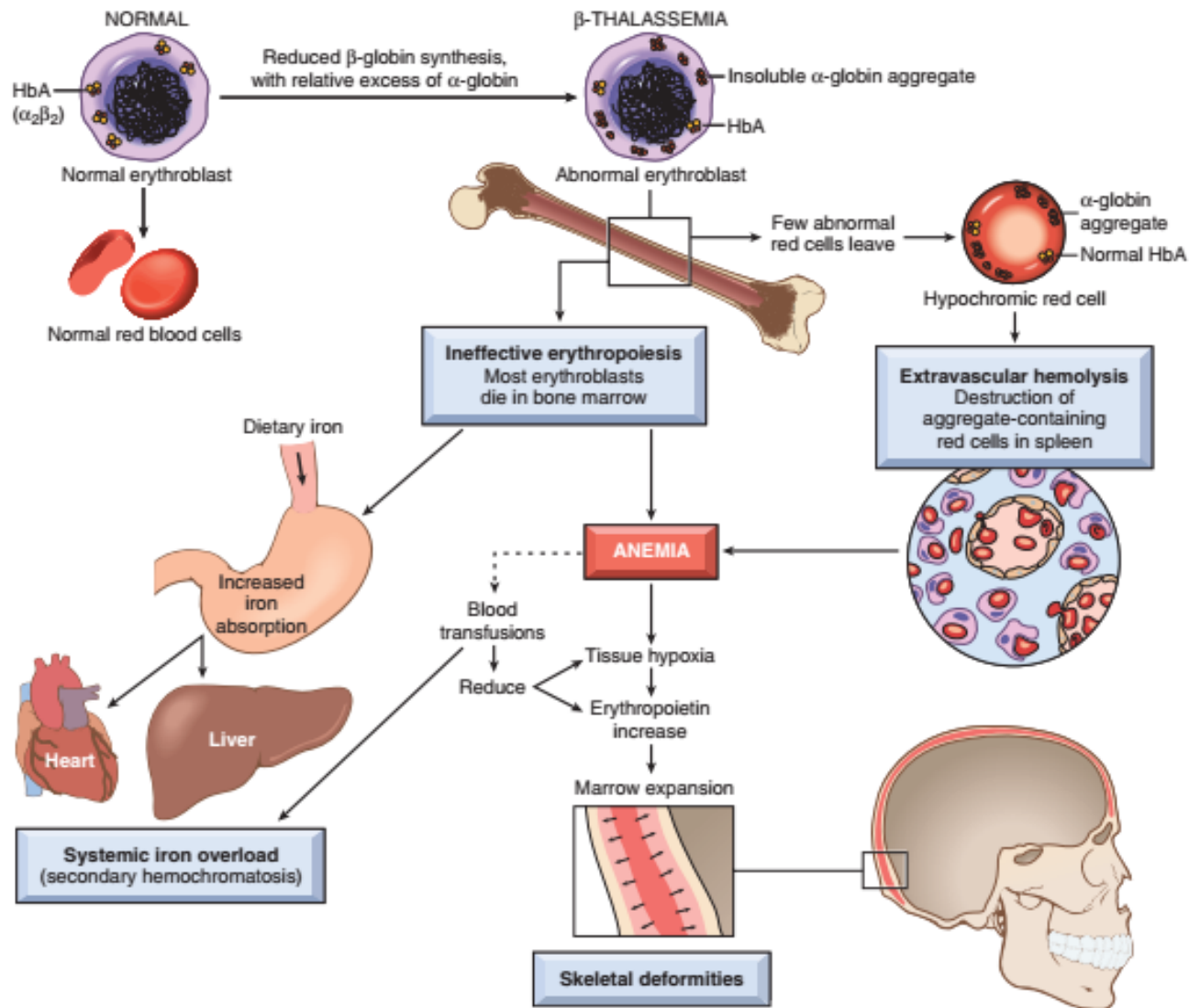
The β -thalassemias are caused by mutations that diminish the synthesis of β -globin chains.

The causative mutations fall into two categories:

- β^0 mutations, associated with absent β -globin synthesis
- β^+ mutations, characterized by reduced (but detectable) β -globin synthesis.

β -Thalassemias

Pathogenesis



β -Thalassemias

Pathological Consequences

Anemia, produced by different mechanisms

- **Ineffective erythropoiesis**, Unpaired α chains precipitate within red cell precursors, forming insoluble inclusions that lead to damage of its membrane, 70% to 85% of red cell precursors undergo apoptosis.
- **Extravascular hemolysis** red cells that are released from the marrow also contain inclusions and have membrane damage, leaving them prone to splenic sequestration and destruction

β -Thalassemia

Pathological Consequences

Massive erythroid hyperplasia

- The expanding mass of red cell precursors erodes the bony cortex, impairs bone growth, and produces skeletal abnormalities

Extramedullary hematopoiesis

- Erythropoiesis will involve liver spleen, and lymph nodes
- The metabolically active erythroid progenitors steal nutrients from other tissues that are already oxygen-starved, causing severe cachexia in untreated patients.

Secondary hemochromatosis

β -Thalassemia

Clinical Syndromes

β -thalassemia major

- Two β thalassemia alleles (Homozygous i.e. β^+/β^+ , β^+/β^0 , or β^0/β^0)
- Severe, transfusion-dependent anemia, Common in **Mediterranean countries** , parts of Africa, and Southeast Asia.
- Anemia manifests at 6 to 9 months age (Hb F $\rightarrow$ HbA)
- Hemoglobin is very low, composed mainly of Hb F, HbA is either absent or very low, HbA2 may be high

β -Thalassemia

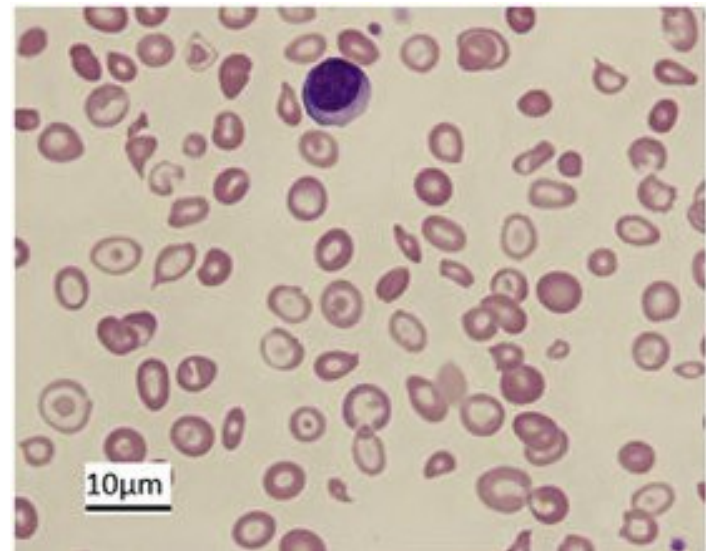
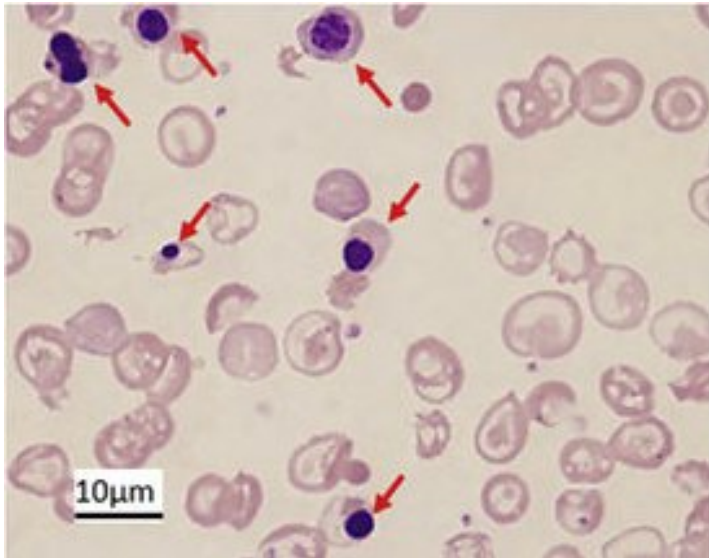
Clinical Syndromes

β -thalassemia major

- Severe anemia, growth retardation and death if untreated
- Pallor, jaundice, cheekbones and other bony prominences are enlarged and distorted.
- Hepatosplenomegaly due to extramedullary hematopoiesis
- Hemochromatosis leads to Cardiac disease, most important cause of death, affects liver, endocrine glands and gonads too

β -Thalassemia

MORPHOLOGY



β -Thalassemia

MORPHOLOGY

Marked anisocytosis: variation in size

Poikilocytosis: variation in shape

Microcytosis and **hypochromia**

Target cells: hemoglobin collects in the center of the cell

The reticulocyte count is elevated, but it is lower than expected for the severity of anemia because of the ineffective erythropoiesis.

Variable numbers of normoblasts seen in the peripheral blood as a result of “stress” erythropoiesis

β -Thalassemia

Clinical Syndromes

β -thalassemia minor or β -thalassemia trait

- Heterozygotes (one allele i.e. β^+/β or β^0/β)
- Affected patients are usually asymptomatic, anemia is mild and mild abnormalities on blood smear.
- Hemoglobin electrophoresis usually reveals an increase in HbA₂ ($\alpha_2\delta_2$) to 4% to 8% of the total hemoglobin
- HbF levels are generally normal or occasionally slightly increased.

β -Thalassemia

Clinical Syndromes

β -thalassemia intermedia.

- Milder variants of β^+/β^+ or β^+/β^0 -thalassemia and unusual forms of heterozygous β -thalassemia
- The clinical and morphologic features as well as transfusion dependence of β -thalassemia intermedia are milder than β -thalassemia major

α -Thalassemia

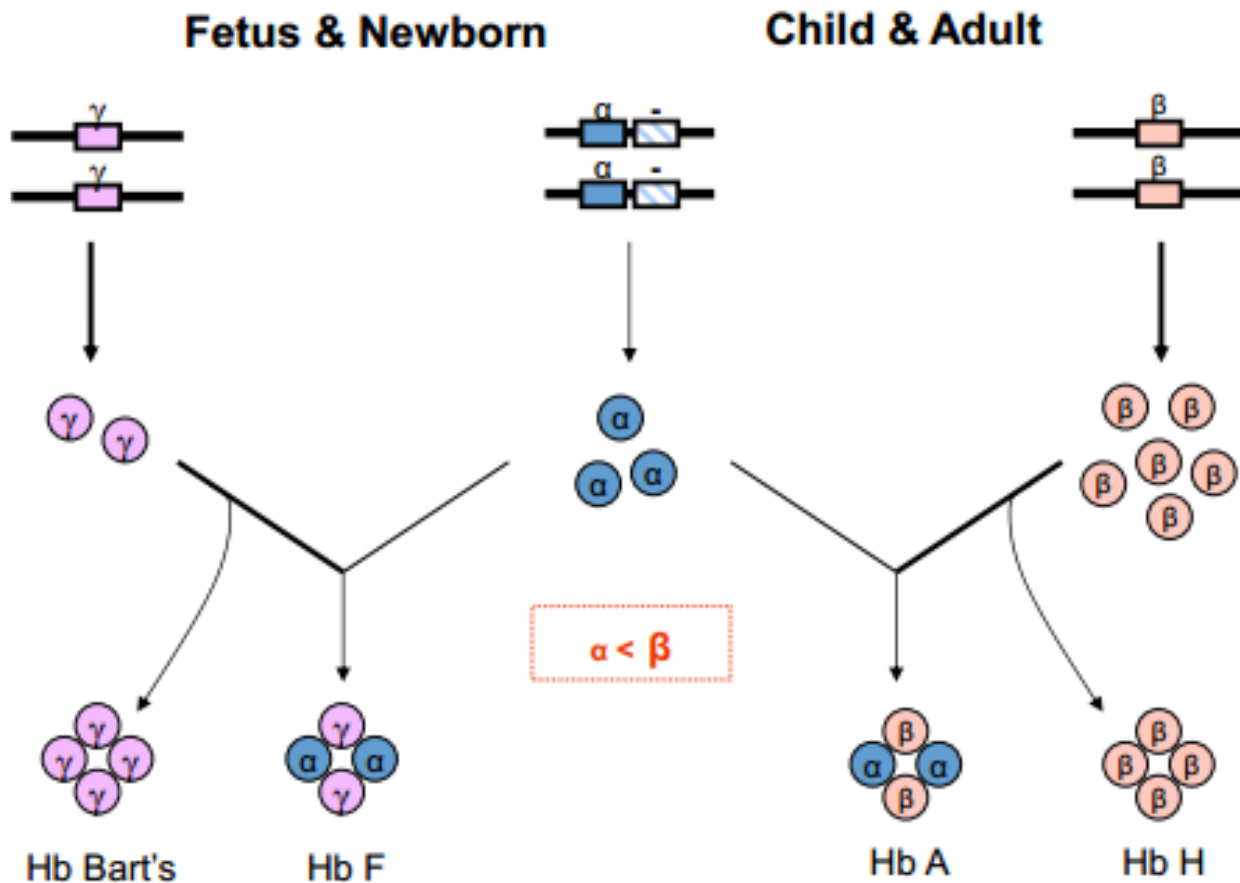
Inherited deletions that result in reduced or absent synthesis of α -globin chains.

There are four α -globin genes, and the severity of α -thalassemia depends on how many α -globin genes are affected.

Unpaired globin chains are either β , γ or δ based on patient's age, γ -globin In newborns form tetramers called hemoglobin Barts while β chain tetramers formed in adults are called HbH.

Hemolysis and ineffective erythropoiesis are less severe than in β -thalassemia because free β and γ chains are more soluble than free α chains and form fairly stable homotetramers

Alpha Thalassemia



α -Thalassemias

Clinical Syndromes

Silent Carrier State

- A single α -globin gene deletion
- No symptoms but have slight microcytosis

α -Thalassemia Trait

- Caused by the deletion of two α -globin genes
- The clinical picture in α -thalassemia trait is identical to β -thalassemia minor, minimal or no anemia, and no abnormal physical signs, **HbA2 levels are normal or low**

α -Thalassemias

Clinical Syndromes

Hemoglobin H Disease

- Deletion of three α -globin genes.
- The synthesis of α chains is markedly reduced and tetramers of β -globin forms, called HbH
- HbH precipitates and form intracellular inclusions that promote red cell sequestration and phagocytosis in the spleen. The result is a moderately severe anemia resembling β -thalassemia intermedia

α -Thalassemia

Clinical Syndromes

Hydrops Fetalis

- Deletion of all four α -globin genes
- In the fetus, excess γ -globin chains form tetramers (hemoglobin Barts) that have a very poor oxygen delivery
- Fetal distress usually become evident by the third trimester of pregnancy, tissue anoxia lead to death in utero or shortly after birth, the fetus shows severe pallor, generalized edema, and massive hepatosplenomegaly

Risk of Hydrops Fetalis in Offspring Depends on Trait Genotype in Parents

Immuno-hemolytic Anemias

Caused by antibodies that bind to red cells, leading to their premature destruction

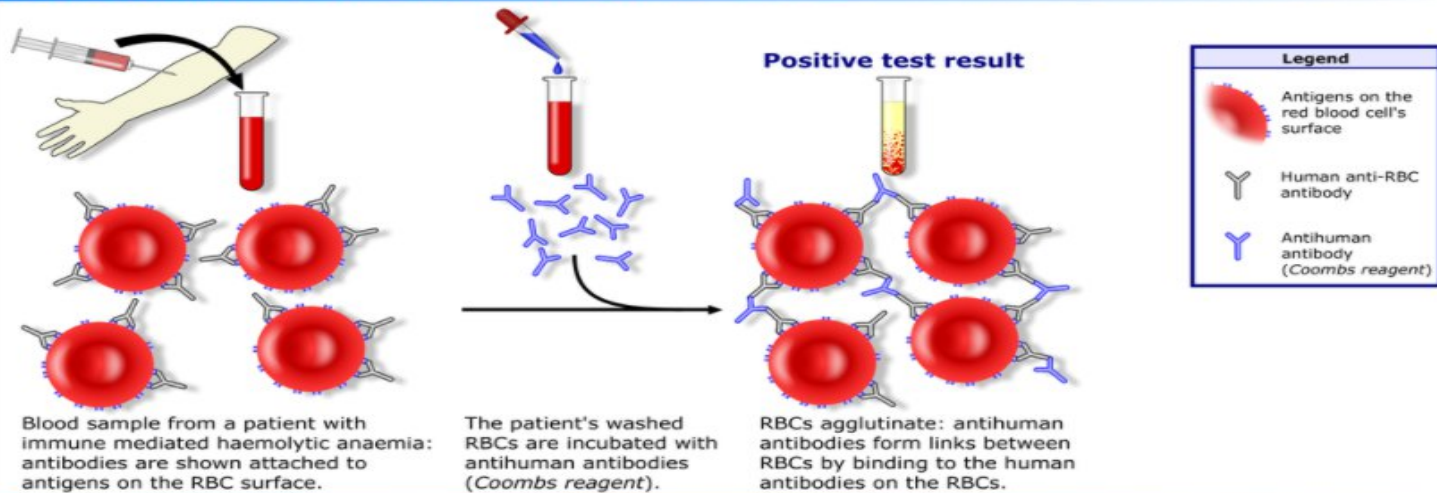
Divided into warm reacting antibody, clod agglutinin and cold hemolysin type

The diagnosis of immuno-hemolytic anemia requires the detection of antibodies and/or complement on red cells from the patient

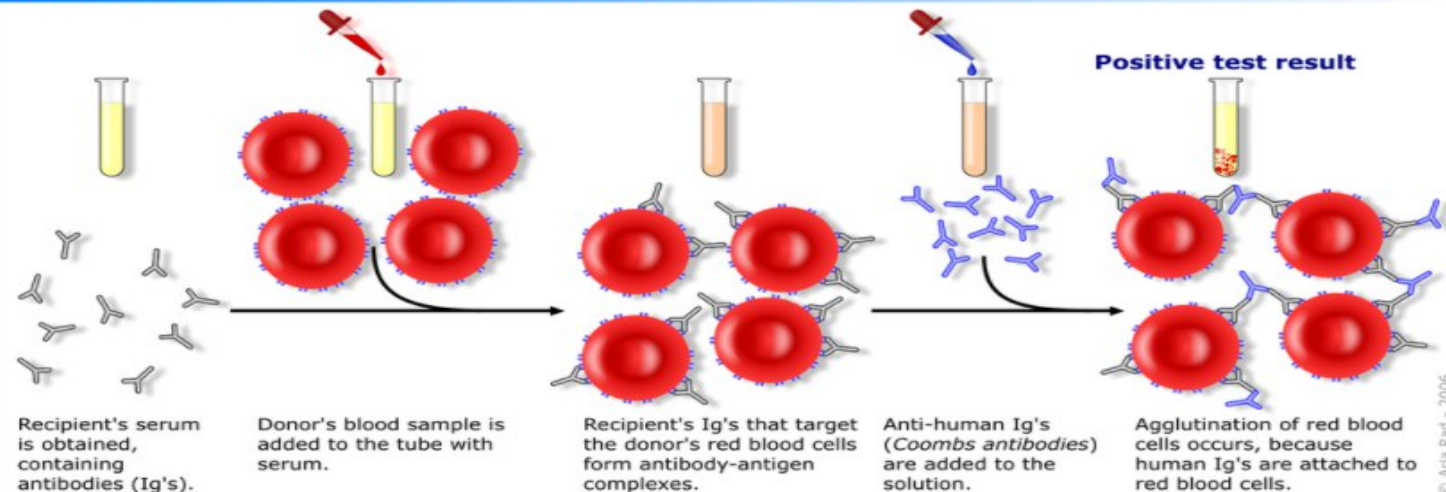
This can be done using the direct and indirect coomb's test

Coomb's test

Direct Coombs test / Direct antiglobulin test



Indirect Coombs test / Indirect antiglobulin test



Immuno-hemolytic Anemias

Direct Coombs antiglobulin test

- Patient's red cells are mixed with sera containing antibodies that are specific for human immunoglobulin or complement
- If either immunoglobulin or complement is present on the surface of the red cells, the antibodies cause agglutination, which is easily appreciated visually as clumping.

Indirect Coombs antiglobulin test

- Patient's serum is tested for its ability to agglutinate commercially available red cells bearing particular defined antigens

Immunoheolytic Anemias

Warm Antibody Type (IgG Antibodies Active at 37°C)

Primary (idiopathic)

Secondary

Autoimmune disorders (particularly systemic lupus erythematosus)

Drugs

Lymphoid neoplasms

Cold Agglutinin Type (IgM Antibodies Active Below 37°C)

Acute (mycoplasmal infection, infectious mononucleosis)

Chronic

Idiopathic

Lymphoid neoplasms

Cold Hemolysin Type (IgG Antibodies Active Below 37°C)

Rare; occurs mainly in children following viral infections

Warm Antibody Type

The most common form

About 50% of cases are idiopathic, others are related to predisposing conditions or drugs e.g. penicillin, ceftriaxone and methyldopa

Antibodies are of the IgG class; less commonly, IgA

Partial phagocytosis of antibody covered RBCs leads to loss of their membrane converting them to **spherocytes**

The red cell hemolysis is mostly extravascular

Splenomegaly due to hyperplasia of splenic phagocytes is usually seen.

Cause of idiopathic immunohemolytic anemia is unknown, but antibodies are directed **to Rh antigens** in many cases

Drug-induced immunohemolytic anemia

Antigenic drugs

- e.g. penicillin and cephalosporins
- Hemolysis happens 1 to 2 weeks after large, intravenous doses of the offending drug
- The antibody may bind the drug only or complex of the drug and membrane protein

Tolerance-breaking drugs

- e.g. α -methyldopa
- Alteration of the immunogenicity of native epitopes and circumvention of T cell tolerance

Cold Agglutinin Type

Less common than warm antibody
immunohemolytic anemia

Caused by IgM antibodies occasionally called
Cold Agglutinins

Idiopathic chronic disease in adults over 50 years
of age

Cold agglutinin antibodies in children and young
adults appear transiently following certain
infections, such as with **Mycoplasma
pneumoniae**, Epstein Barr virus, cytomegalovirus,
influenza virus, and human immunodeficiency
virus (HIV) leading to self-limited disease and
rarely causing clinically important hemolysis

Cold Agglutinin Type

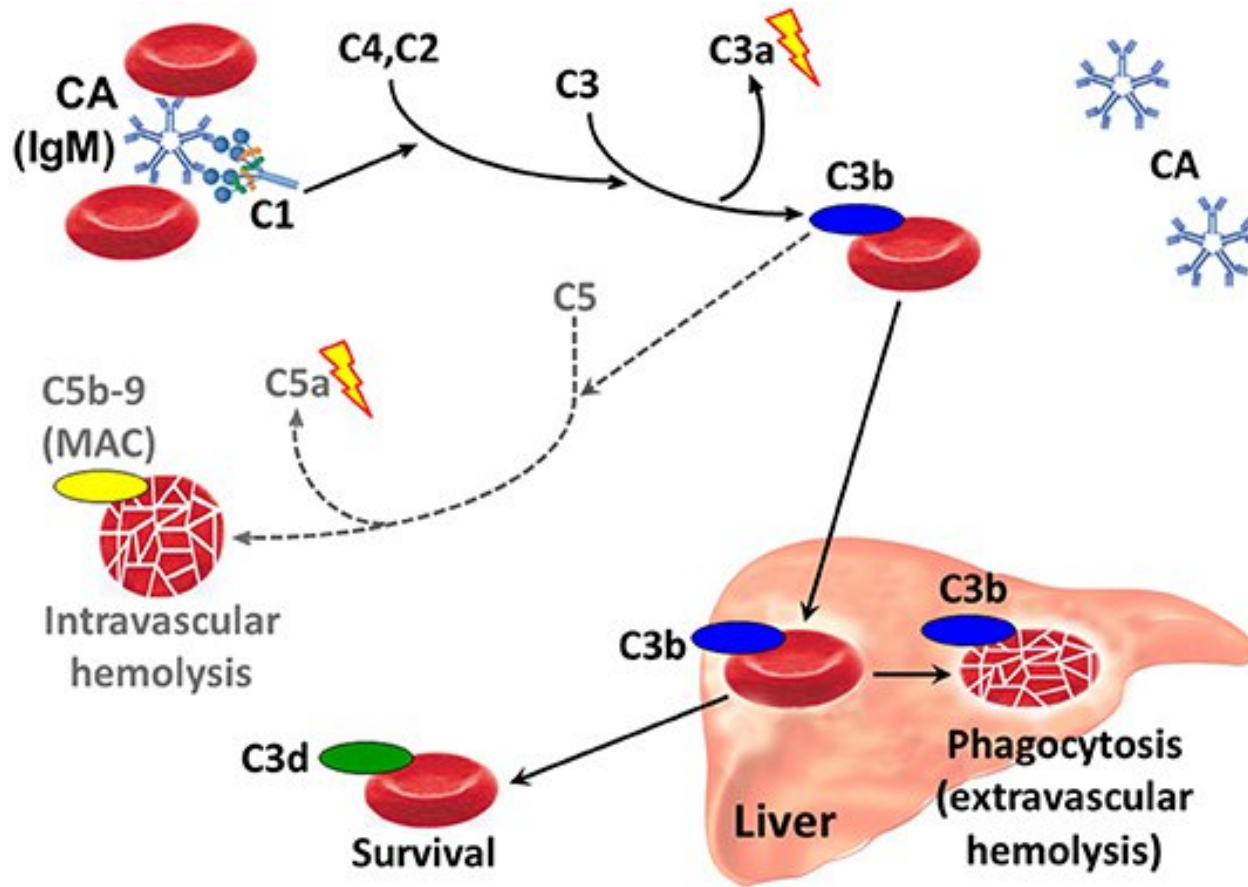
IgM binds red cells in vascular beds where the temperature may fall below 30°C, such as in exposed fingers, toes, and ears

IgM binding agglutinates red cells and fixes complement rapidly so C3b is deposited on the red cell membrane.

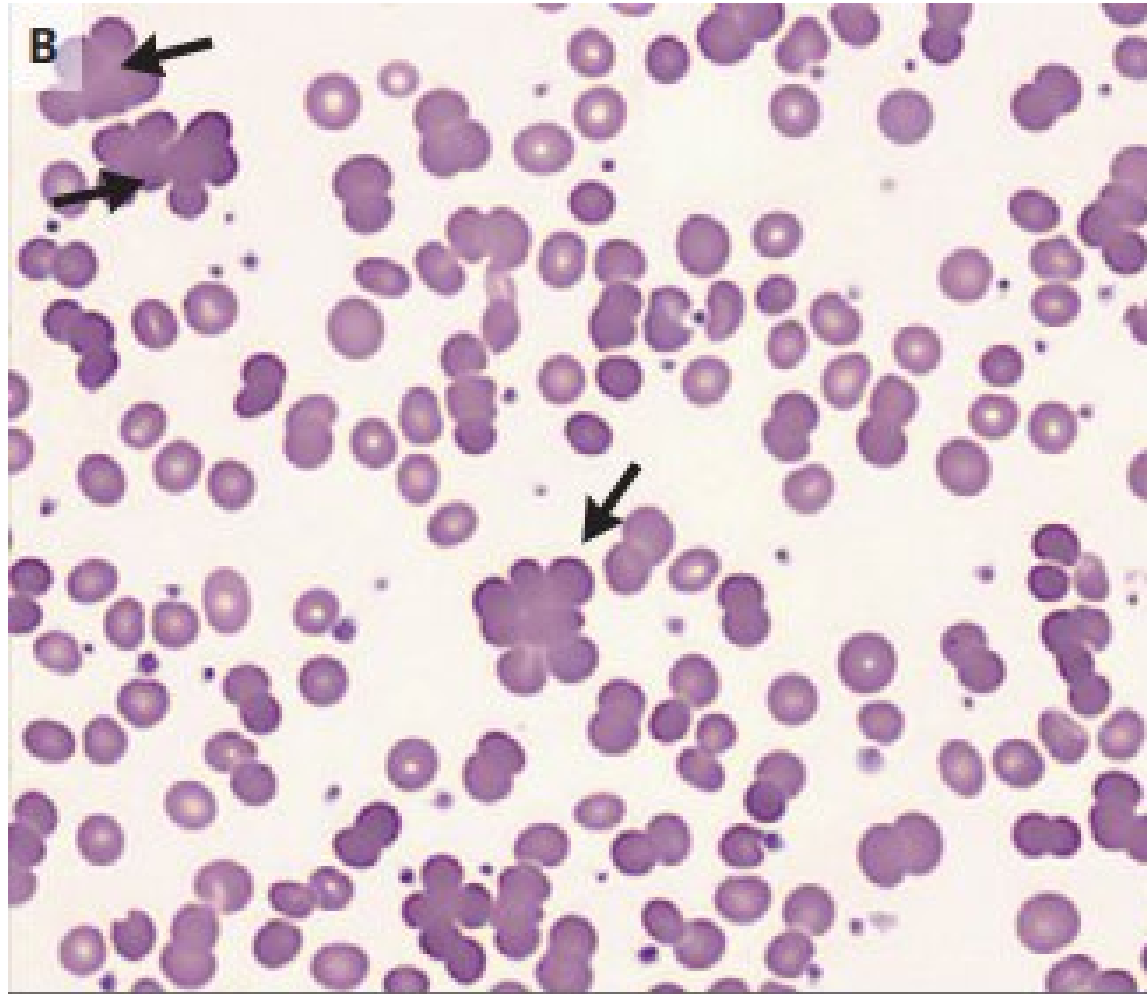
When blood warms, IgM dissociates and C3b mediate phagocytosis or occasionally the entire complement cascade is activated to the membrane attack complex

Vascular obstruction caused by agglutinated red cells results in pallor, cyanosis, and Raynaud phenomenon in body parts exposed to cold temperature

Cold Agglutinin Type



Cold Agglutinin Type



Cold Hemolysin Type

Rare , occasionally called paroxysmal cold hemoglobinuria

Primarily a disease of children

Cold reacting IgG against RBCs, initiates aggressive hemolysis through activation of the entire complement cascade

Patients experience a severe anemia, decreased haptoglobin levels, and hemoglobinuria secondary to **intravascular hemolysis**

Mechanical Red Cell Fragmentation Syndrome

Red cells are fragmented within the blood vessels (intravascular hemolysis)

Macroangiopathic hemolytic anemia occurs in larger vessels

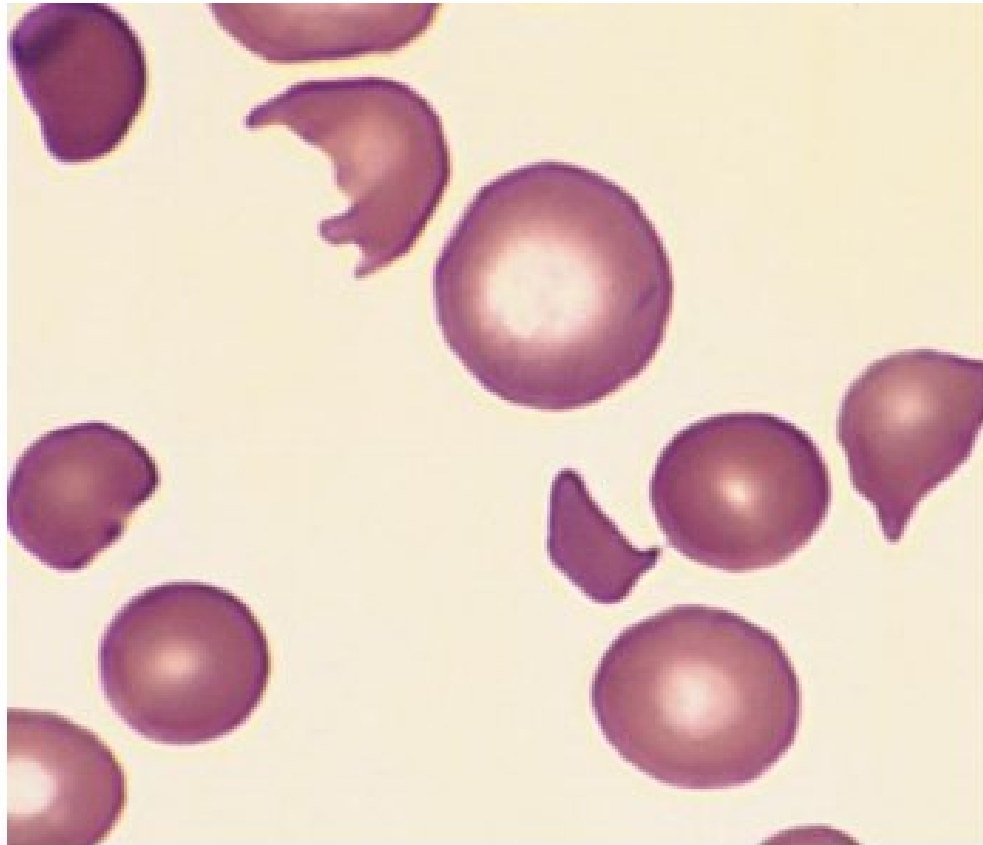
- Synthetic vascular graft
- Prosthetic valve

Microangiopathic hemolytic anemia occurs in smaller vessels that become partially obstructed or narrowed

- Disseminated intravascular coagulation
- Malignant hypertension,
- Thrombocytopenic purpura (TTP)
- Hemolytic uremic syndrome (HUS)

Examination of the blood reveals a mild to moderate anemia, reticulocytosis, and fragmented red blood cells (schistocytes) and helmet cells.

Microangiopathic hemolytic anemia



Megaloblastic Anemia

Caused by impaired DNA synthesis, which often is secondary to vitamin B12 or folate deficiency.

B12 and folate are required for the formation of thymidine, one of the four bases found in DNA molecules

Megaloblastic Anemia

Causes

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

 - Competitive parasitic uptake

 - Fish tapeworm infestation

- Bacterial overgrowth in blind loops and diverticula of bowel

Anemias of Vitamin B12

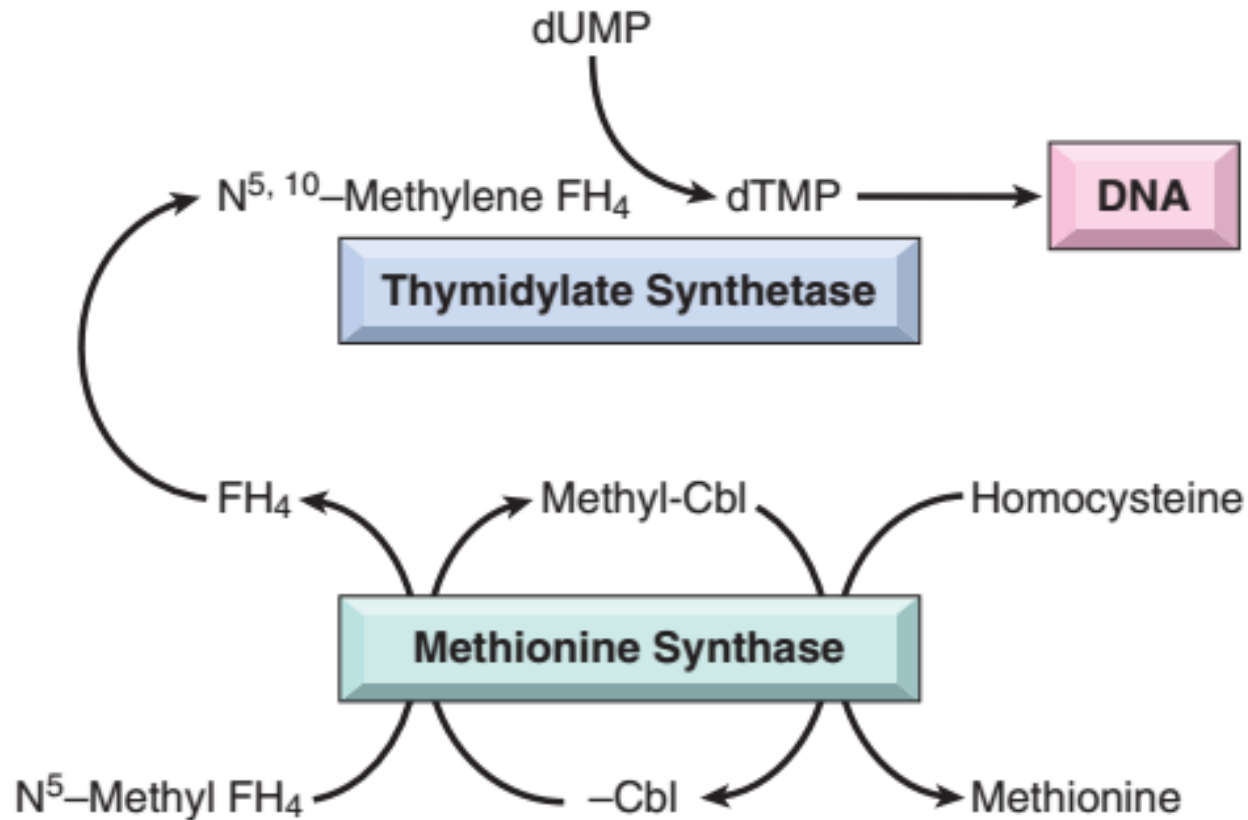
Deficiency: Pernicious Anemia

A form of megaloblastic anemia caused by an autoimmune gastritis that impairs the production of intrinsic factor, which is required for vitamin B12 uptake from the gut.

Vitamin B12 is found in many animal food sources and is synthesized by intestinal organisms, plants and vegetables contain little cobalamin

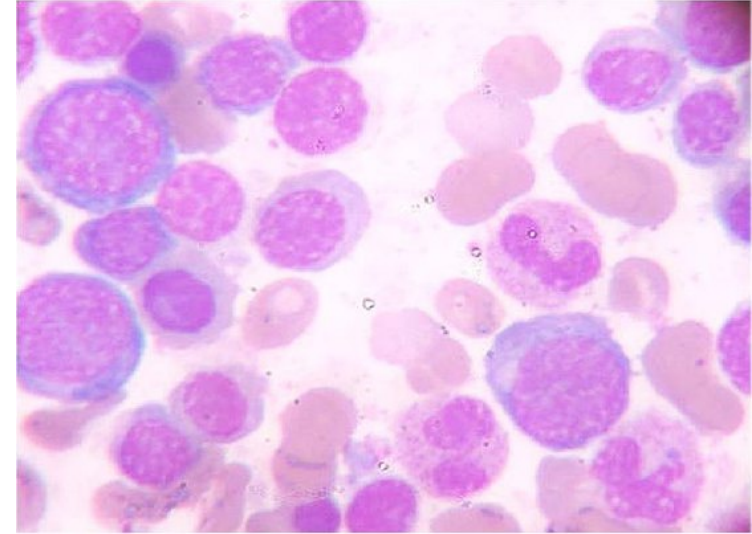
After ingestion, vitamin B12 binds to intrinsic factor (IF) secreted by gastric parietal cells and is ultimately absorbed in the distal ileum and transferred to the carrier molecule transcobalamin II in the blood

Biochemical Functions of Vitamin B12

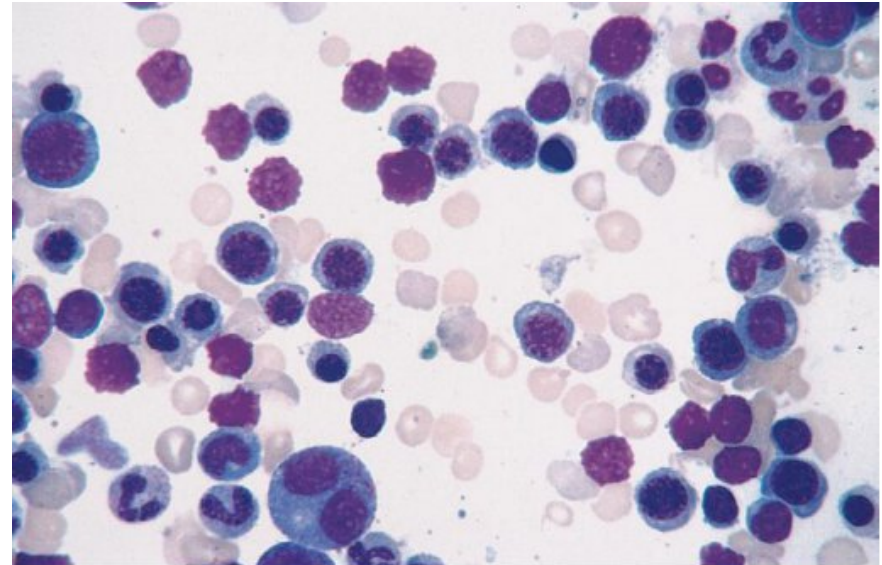


Megaloblastic Anemia

MORPHOLOGY



Erythroid hyperplasia
with normal maturation



MORPHOLOGY

Peripheral blood features shared by all megaloblastic anemias

- **Macro-ovalocytes** mostly lacking the normal central pallor anisocytosis and poikilocytosis
- The reticulocyte count is low
- **Nuclear hypersegmentation** (five or more nuclear lobules)

MORPHOLOGY

The marrow is usually markedly hypercellular and **Megaloblastic changes** are detected at all stages of erythroid development.

- Most primitive cells are large, with a deeply basophilic cytoplasm, prominent nucleoli, and a distinctive, fine nuclear chromatin pattern
- Cytoplasmic maturation and hemoglobin accumulation proceed at a normal pace but the nucleus retains its finely distributed chromatin and fails to develop the clumped pyknotic chromatin typical of normoblasts, leading to nuclear-to-cytoplasmic asynchrony.
- DNA synthesis is impaired in all lines
giant metamyelocytes and band forms
Megakaryocytes can be abnormally large and have bizarre, multilobate nuclei

Pernicious Anemia

Pathogenesis

Pernicious anemia is believed to result from an autoimmune attack on the gastric mucosa. Histologically, there is a chronic atrophic gastritis marked by a loss of parietal cells, a prominent infiltrate of lymphocytes and plasma cells

Autoantibodies are present either preventing the binding of B12 to intrinsic factor or prevent its internalization

Other Causes of B12 deficiency

Achlorhydria

Gastrectomy

Loss of exocrine pancreatic function

Ileal resection or diffuse ileal disease

Certain tapeworms

Pernicious Anemia

Clinical Features

It is a disease of older adults; the median age at diagnosis is 60 years, and it is rare in people younger than 30.

Insidious in onset

The diagnosis is based on

- a moderate to severe megaloblastic anemia
- leukopenia with hypersegmented granulocytes
- low serum vitamin B12
- Elevated serum levels of homocysteine and methylmalonic acid

Response to parenteral administration of vitamin B12 confirms the diagnosis

B12 deficiency can also lead to neurologic complications postulated to be due to myelin sheath break down and degeneration of the posterior and

Pernicious Anemia

Complications

Gastric carcinoma

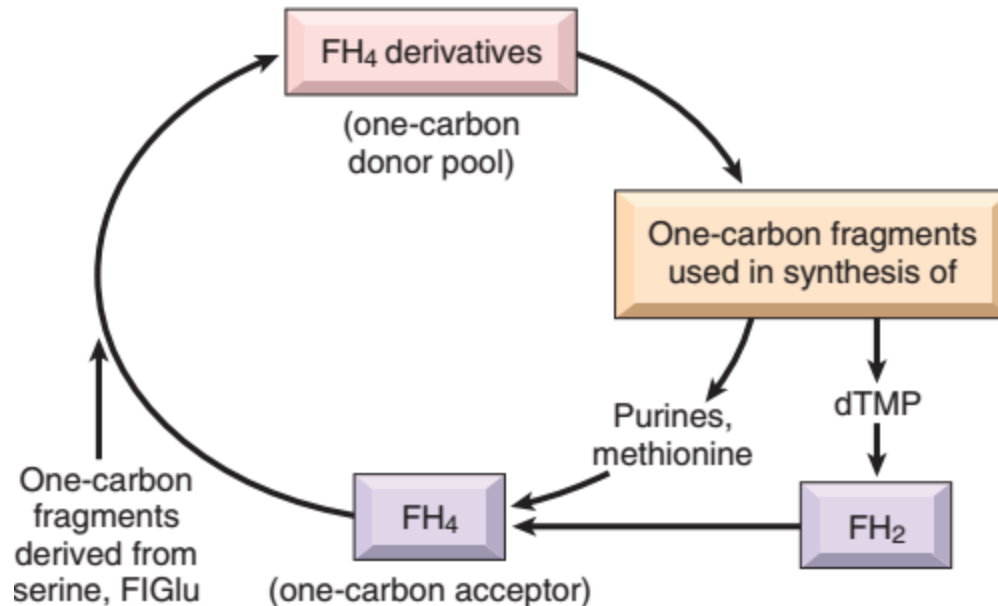
Atherosclerosis

With parenteral or high-dose oral vitamin B12, the anemia is cured and the progression of the peripheral neurologic disease can be reversed or at least halted, changes in the gastric mucosa and the risk of carcinoma are unaffected

Anemia of Folate Deficiency

A deficiency of folic acid results in a megaloblastic anemia having the same pathologic features as that caused by vitamin B12 deficiency

FH₄ derivatives act as intermediates in the transfer of one-carbon units such as formyl and methyl groups to various compounds



Anemia of Folate Deficiency

Suppressed synthesis of DNA, the common denominator of folic acid and vitamin B12 deficiency, is the immediate cause of megaloblastosis

Folate Deficiency Causes

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 Utilization
Folic acid antagonists
Unresponsive to Vitamin B₁₂ or Folic Acid Therapy
Metabolic Inhibitors of DNA Synthesis and/or Folate Metabolism (e.g., Methotrexate)

Folate Deficiency

Megaloblastic anemia that results from a deficiency of folic acid and vitamin B12 are identical, but neurological pathology is not found in folate deficiency

The diagnosis of folate deficiency can be made only by demonstration of decreased folate levels in the serum or red cells

Homocysteine levels are increased, methylmalonate concentrations are normal

Iron Deficiency Anemia

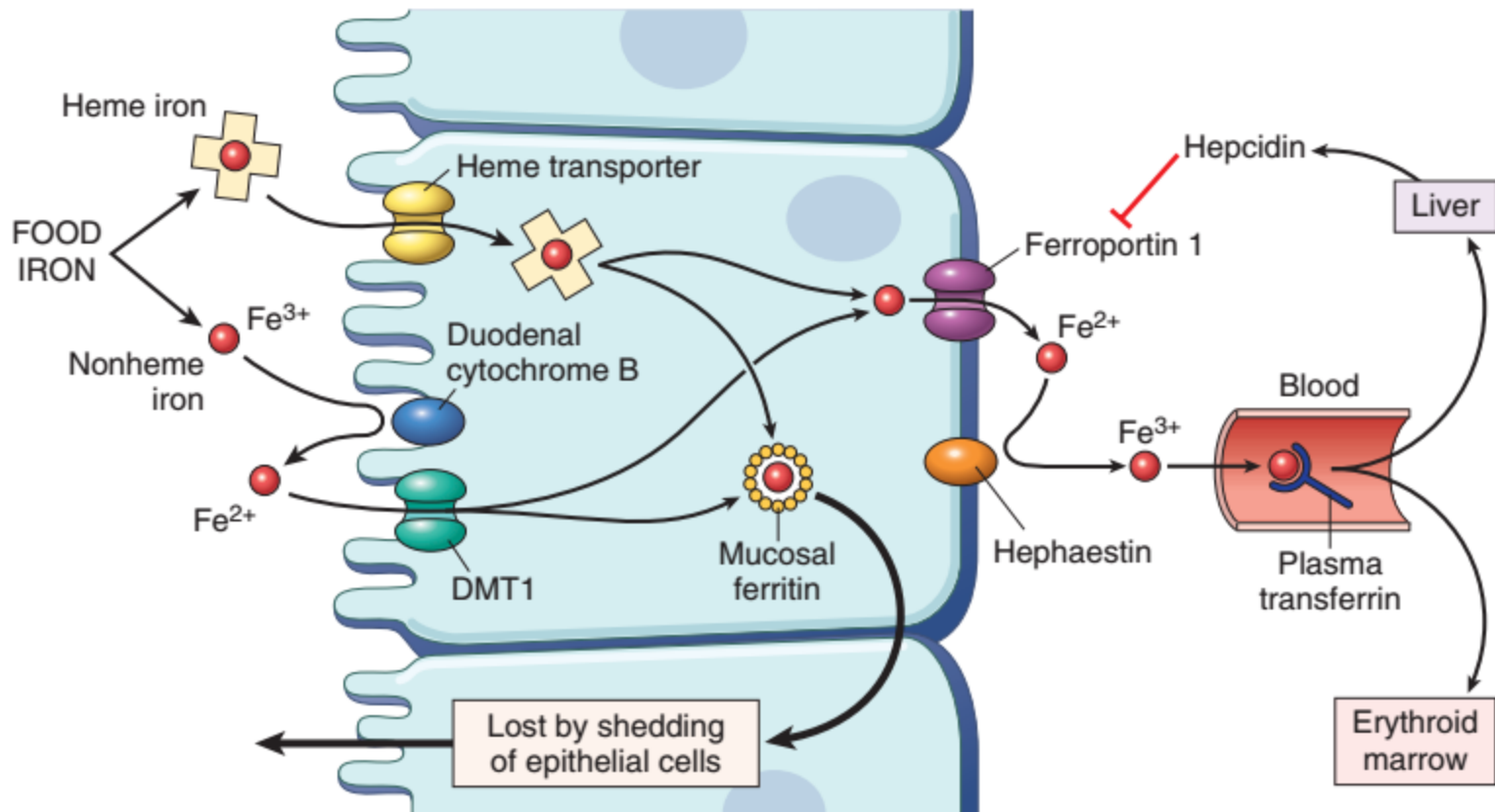
The most common nutritional disorder in the world

Dietary iron presents in 2 forms

- Heme contained in animal products, in the Fe^{2+} (ferrous) state About 20% of it is absorbable
- Inorganic nonheme iron in vegetables, is mostly in the Fe^{3+} (ferric) 1% to 2% is absorbable after reduced to Fe^{2+}

Body iron is either

- Functional, 80% of total body iron, found in hemoglobin; myoglobin and iron-containing enzymes
- Storage pool, 15% to 20% of total body iron represented by hemosiderin and ferritin



Iron Deficiency Anemia

Iron in the body is recycled between the functional and storage pools. It is transported in plasma by an iron-binding glycoprotein called **transferrin**, which is synthesized in the liver.

Free iron is highly toxic, and it is therefore important that storage iron be sequestered. This is achieved by binding of iron in the storage pool to either **ferritin** or hemosiderin.

Plasma ferritin levels correlate well with body iron stores, in iron deficiency, serum ferritin is below 12 µg/L, whereas in iron overload values approaching 5000 µg/L may be seen.

Luminal nonheme iron is mostly in the Fe^{3+} (ferric) state and must first be reduced to Fe^{2+} (ferrous) to be absorbed

Iron Deficiency Anemia

Iron that enters the duodenal cells can either be transported to the blood or stored in the mucosa if body iron stores are adequate, to be shed with mucosal cell later

Iron absorption is regulated by **hepcidin**, a small circulating peptide that is synthesized and released from the liver in response to increases in intrahepatic iron levels.

when the body is replete with iron, high hepcidin levels inhibit its absorption into the blood.

Conversely, with low body stores of iron, hepcidin synthesis falls and this in turn facilitates iron absorption.

Iron Deficiency Anemia

Etiology

Dietary lack

- Common in developing countries
- The absorption of inorganic iron is enhanced by ascorbic acid, citric acid, amino acids, and sugars in the diet, and inhibited by tannates (found in tea), carbonates, oxalates, and phosphates.
- Groups at risk are infants, the impoverished, older adults and teenagers

Iron Deficiency Anemia

Etiology

Impaired absorption

- Celiac disease, other causes of malabsorption and chronic diarrhea
- Gastrectomy decreasing the acidity of the proximal duodenum (which enhances uptake), and also by increasing the speed with which gut contents pass through the duodenum.
- Certain dietary items e.g. tannates and phosphate

Increased requirement

- Growing infants, children, and adolescents
- Premenopausal women, particularly during pregnancy

Iron Deficiency Anemia

Etiology

Chronic blood loss

- The most common cause of iron deficiency in the Western world
- External hemorrhage
- Bleeding into the gastrointestinal, urinary, or genital tracts
- Iron deficiency in adult men and postmenopausal women in the Western world must be attributed to gastrointestinal blood loss until proven otherwise, not to miss an occult gastrointestinal cancer or other bleeding lesion

Iron Deficiency Anemia

Pathogenesis

Whatever the cause, the following consequences happen in a row

- Depletion of stores, i.e. ferritin and hemosiderin
- Lowered serum iron and transferrin saturation
- Anemia appears only when iron stores are completely depleted

Whatever its basis, iron deficiency produces a hypochromic microcytic anemia

Iron Deficiency Anemia

Clinical Features

Features of underlying cause e.g. gastrointestinal or gynecologic disease, malnutrition, pregnancy, and malabsorption

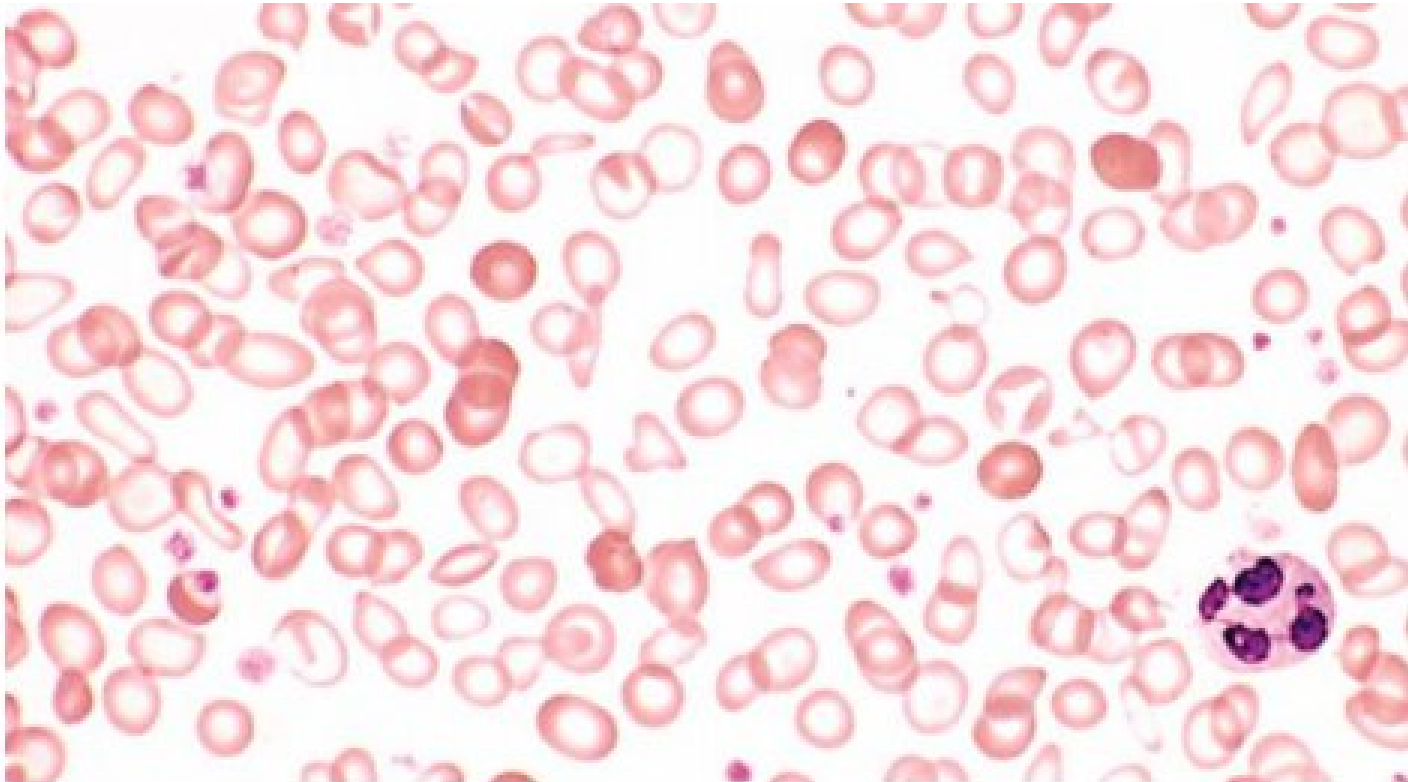
Plummer-Vinson syndrome rare triad of Esophageal webs, microcytic hypochromic anemia and atrophic glossitis

Long standing depletion affect enzymes causing other changes e.g. **koilonychia, alopecia, atrophic changes in the tongue and gastric mucosa, and intestinal malabsorption**

Pica

- Depletion of iron from the central nervous system
- Consume non-food stuffs such as clay

Iron Deficiency Anemia Morphology



Iron Deficiency Anemia

Diagnosis

Based on laboratory studies

- Both the hemoglobin and hematocrit are depressed
- Hypochromia, microcytosis, anisocytosis and modest poikilocytosis
- The serum iron and ferritin are low
- Total plasma iron-binding capacity (TIBC) is high
- Transferrin saturation (serum iron divided by TIBC, expressed as percentage) decreased below 15%

In uncomplicated iron deficiency, oral iron supplementation produces an increase in reticulocytes in about 5 to 7 days that is followed by a steady increase in blood counts and the normalization of red cell indices

Paroxysmal nocturnal hemoglobinuria (PNH)

(PNH) is a hemolytic anemia caused by an **acquired somatic mutation** of a gene (PIGA) that encodes an anchor called GPI for proteins (CD55 and CD59) in the cell membrane,

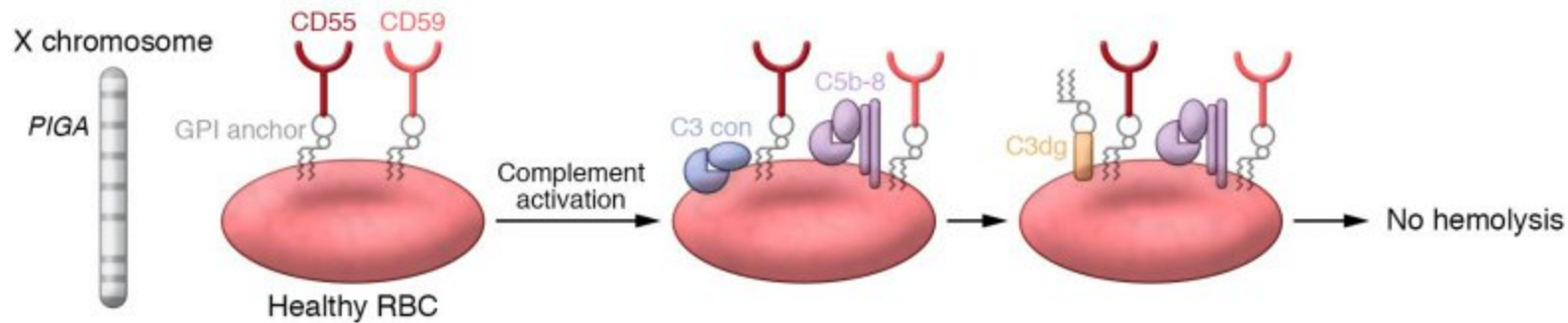
Deficiency in CD 55 and CD59 **cause complement-mediated lysis in red cells** , white cells, and platelets.

The condition causes episodes (paroxysms) of **IV hemolysis** at night.

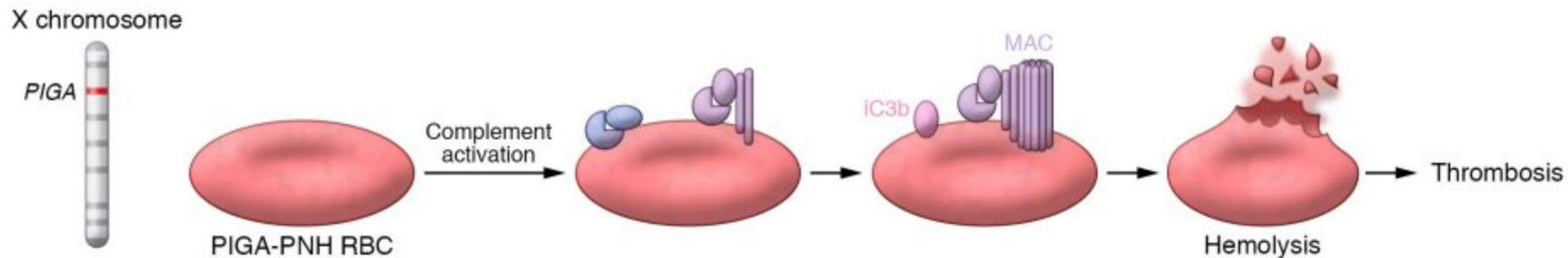
Acidosis in vivo occurs during sleep (breathing slowly retains CO₂) and exercise (lactic acidosis), and the acidosis in turn causes activation of complement.

Hemolysis mechanism of paroxysmal nocturnal hemoglobinuria (PNH) via the complement system

A



B



Paroxysmal nocturnal hemoglobinuria (PNH)

PNH is a clonal stem cell disorder that affects all blood cell lines, leading to pancytopenia (**anemia, leukopenia, and thrombocytopenia**) that is apparent in the peripheral blood.

Venous thrombosis may ensue, the leading cause of death.

Susceptibility to Myelodysplastic syndrome and subsequent acute myeloid leukemia

Most PNH patients have mild disease and don't require treatment, but a monoclonal antibody against complement protein C5 can be therapeutic. Bone marrow transplantation is another therapeutic option

Good Luck