HLS
Hemolytic anemia and hemoglobinopathies

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I. Hemolytic anemia

Hemolytic anemia is a class of anemia that is caused by accelerated destruction of red blood cells, increased hemoglobin catabolism, decreased levels of hemoglobin, and an increase in efforts of bone marrow to regenerate product.

Hemolytic Anemia is often subcategorized depend on either :

- acute and chronic disease.
- immune vs. non-immune mediated.
- intravascular or extravascular.
- inherited or acquired.
- intracorpuscular or extracorpuscular.

intracorpuscular vs extracorpuscular.

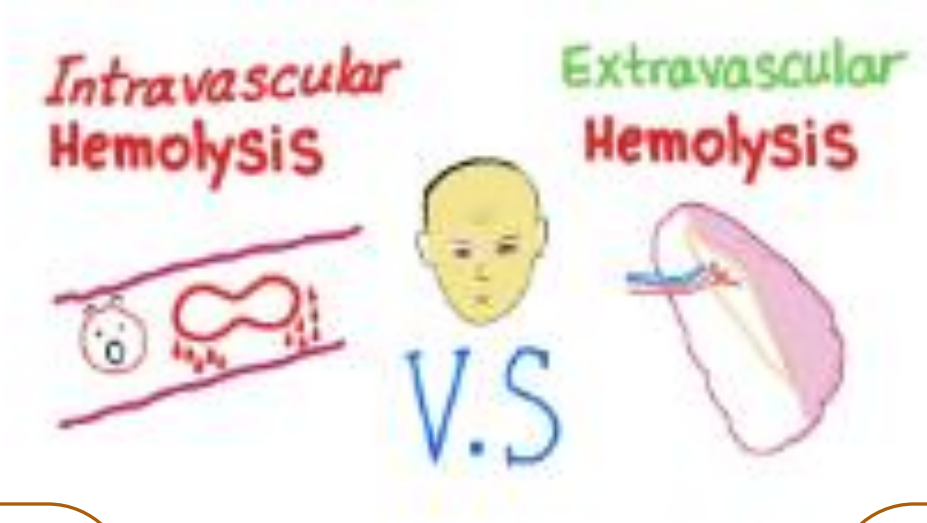
A. Hereditary defects:
- Membranopathy: Spherocytosis.
- Enzymopathy: G6PD Deficiency.
- Hemoglobinopathies: Sickle cell disease
- Deficient globin synthesis: Thalassemia syndromes.

- B. Acquired Defects:
- Membrane defect: PNH.

- Antibody- mediated .
- Mechanical trauma to red cells.
- Infection: Malaria

intravascular vs extravascular.

cell destruction inside the blood vessels.



destruction of red cells by phagocytes, particularly in the liver and spleen

*Hemoglobinemia.
*hemoglobinuria.
*hemosiderinuria .
*Marked decrease in Haptoglobin
"almost absent"

- Hyperbilirubinemia and jaundice,
*Splenomegaly.
*Mild decrease in Haptoglobin.
*No Hburia, Hbemia, and Hemosiderinuria

Intravascular Hemolysis

Activation of Complement on RBC Membrane
Paroxysmal noctural hemoglobinuria
Paroxysmal cold hemoglobinuria
Some transfusion reactions
Some autoimmune hemolytic anemias

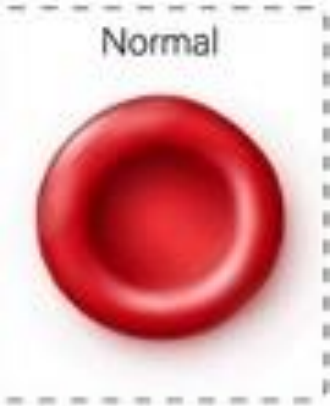
Physical or Mechanical Trauma to the RBC
Microangiopathic hemolytic anemia
Abnormalities of heart vessels
Disseminated intravascular coagulation

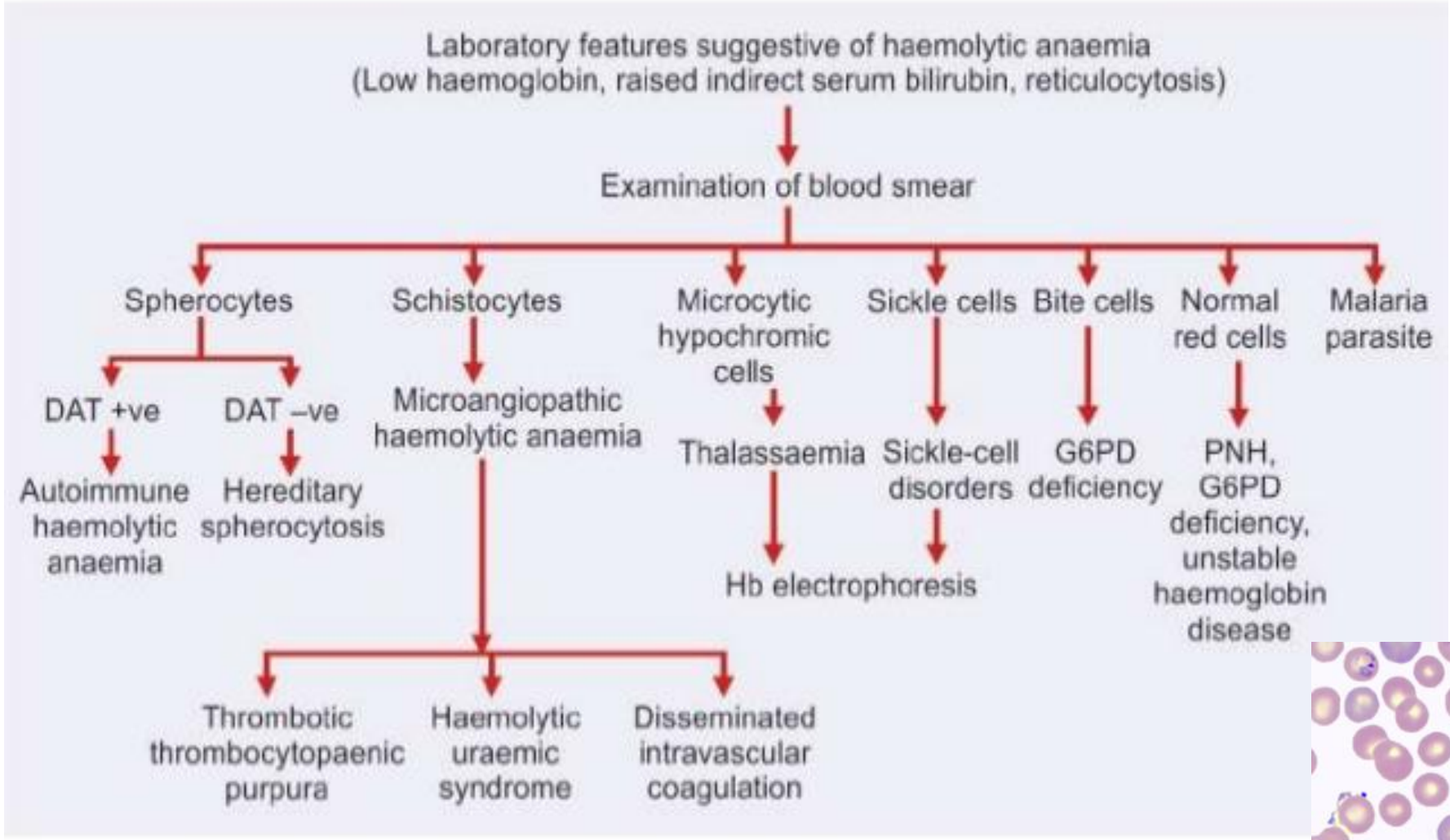
Toxic Microenvironment of the RBC
Bacterial infections
Plasmodium falciparum infection
Venoms
Thermal injury
Acute drug reaction in G6PD deficiency

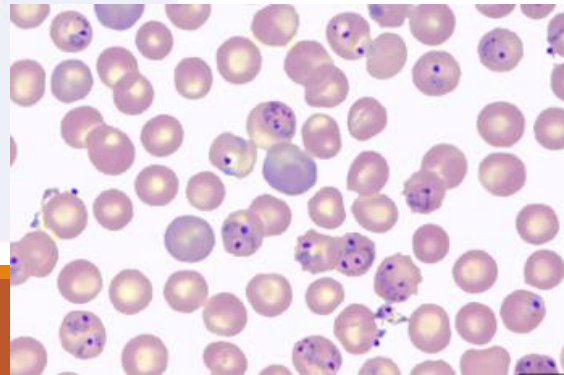
Features of Hemolytic Anemia (Intra- and Extravascular)

- Shortened RBCs survival
- Elevated erythropoietin level leading to increased erythrpoiesis and early release of RBCs from marrow
- Reticulocytosis
- Accumulation of products of Hb. Catabolism
- Elevation in indirect Bilirubin and LDH

A simplified approach to diagnosis of haemolytic anaemias



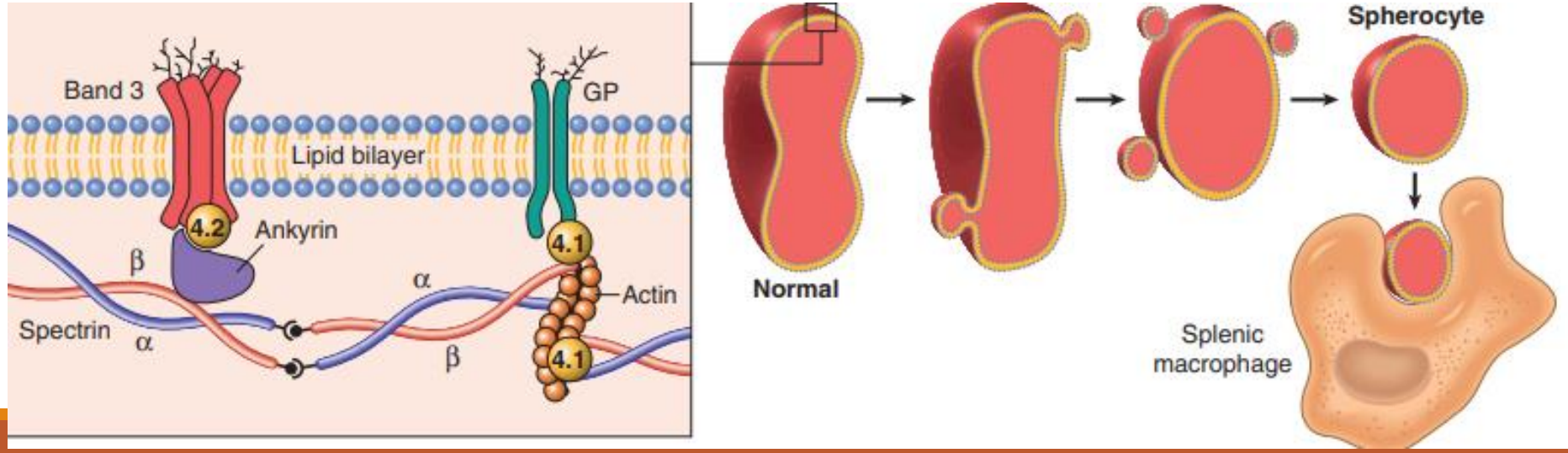




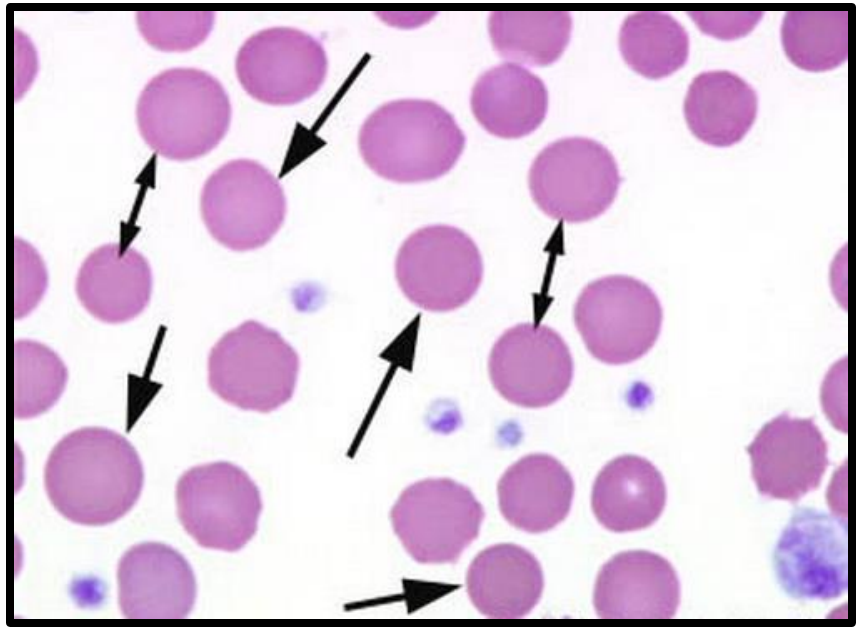
1. HEREDITARY SPHEROCYTOSIS

inherited (intrinsic) defects in the red cell membrane that lead to the formation of spherocytes, nondeformable cells that are highly vulnerable to sequestration and destruction in the spleen.

caused by inherited defects in the membrane skeleton, a network of proteins that stabilizes the lipid bilayer of the red cell



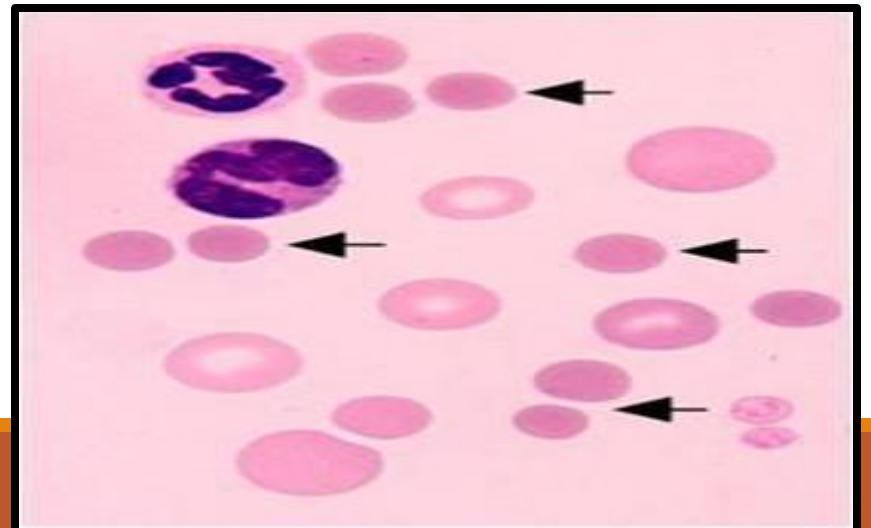
Usually transmitted as Autosomal dominant trait, due to mutations in Spectrin, Ankyrin, and band 3.



Clinically characterized by:

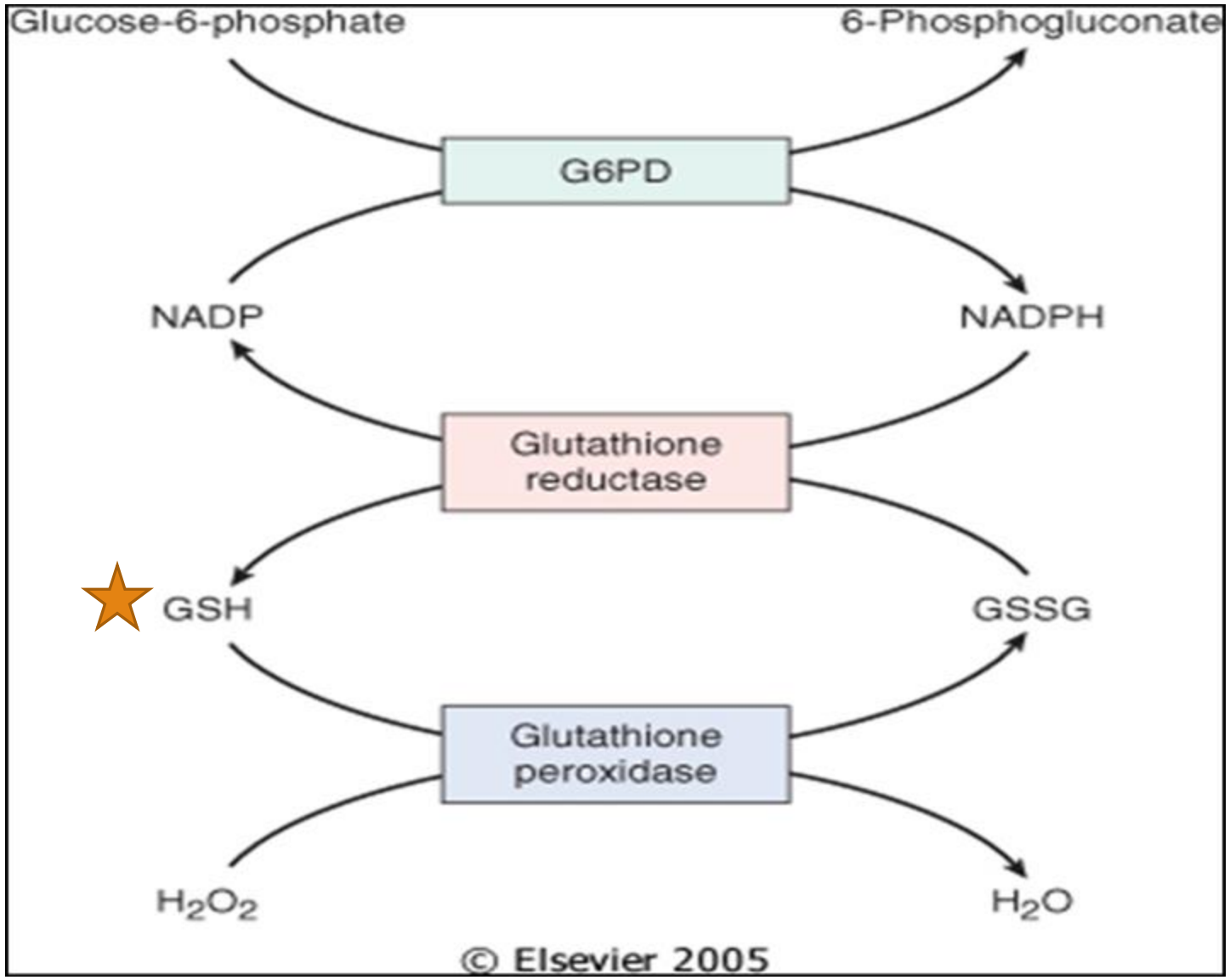
(Severity of anemia correlates with spectrin deficiency):

- Anemia, splenomegaly and jaundice.
- Gallbladder stones
- Aplastic crisis: Due to infection by Parvovirus B19



2. G6PD Deficiency

glucose-6-phosphate dehydrogenase (G6PD, located on chromosome X) has a major role in defense against oxidant injury, mediated by disposal of H2O2, a potential oxidant.

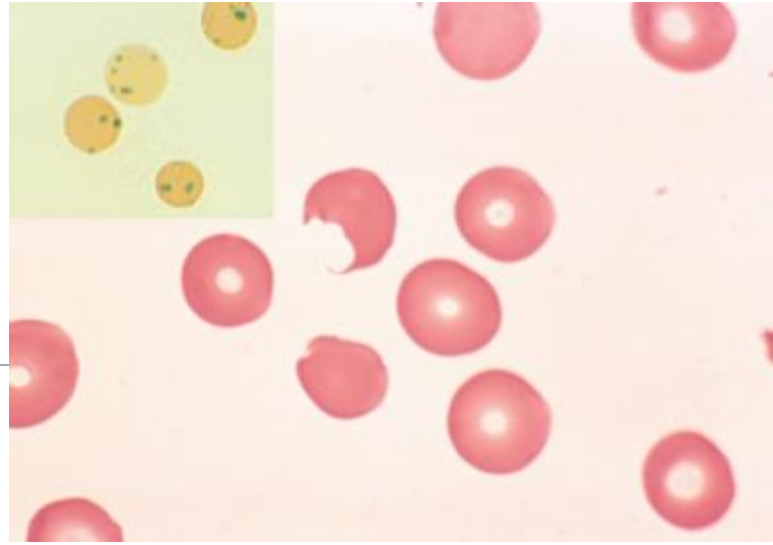


Decrease in GSH causes hemolysis in cells exposed to oxidant agent.

Patients are asymptomatic until exposed to :

* Drugs: eg. Antimalarial, sulfonamides.
* Favism
* Products of free radicals in infections.

Pathogenesis



Because regeneration of GSH is impaired in G6PD-deficient cells.

oxidants are free to “attack” red cell components including globin chains.

Oxidized hemoglobin denatures and precipitates, forming Heinz bodies, which can damage the red cell membrane (intravascular hemolysis).

Other cells with lesser damage lose their deformability and suffer further injury when splenic phagocytes attempt to remove the Heinz bodies, creating bite cells, (extravascular hemolysis).

IMMUNE HEMOLYTIC ANEMIA

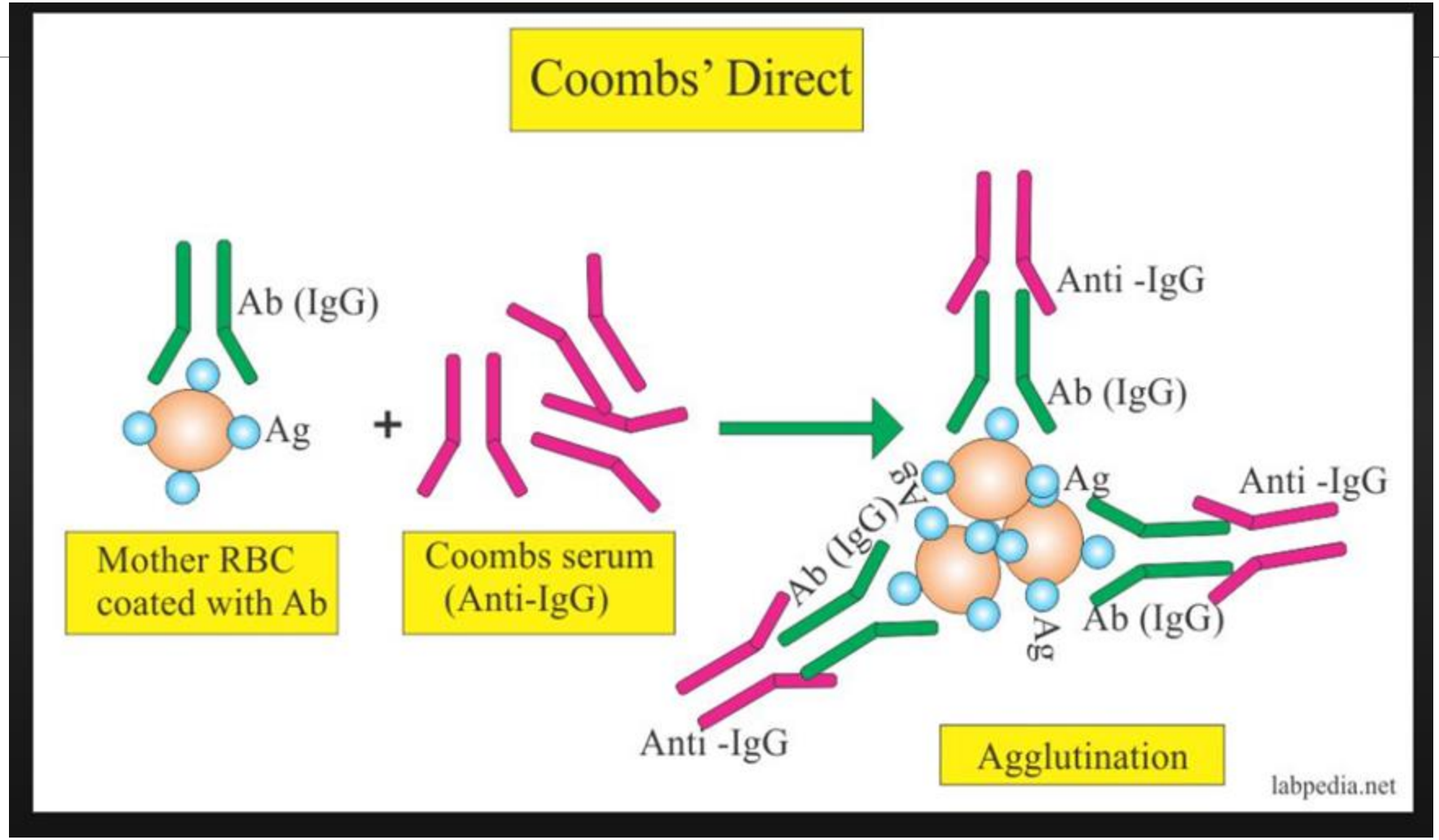
Immunohemolytic anemia is caused by antibodies that bind to determinants on red cell membranes. These antibodies may arise spontaneously or be induced by exogenous agents such as drugs or chemicals.

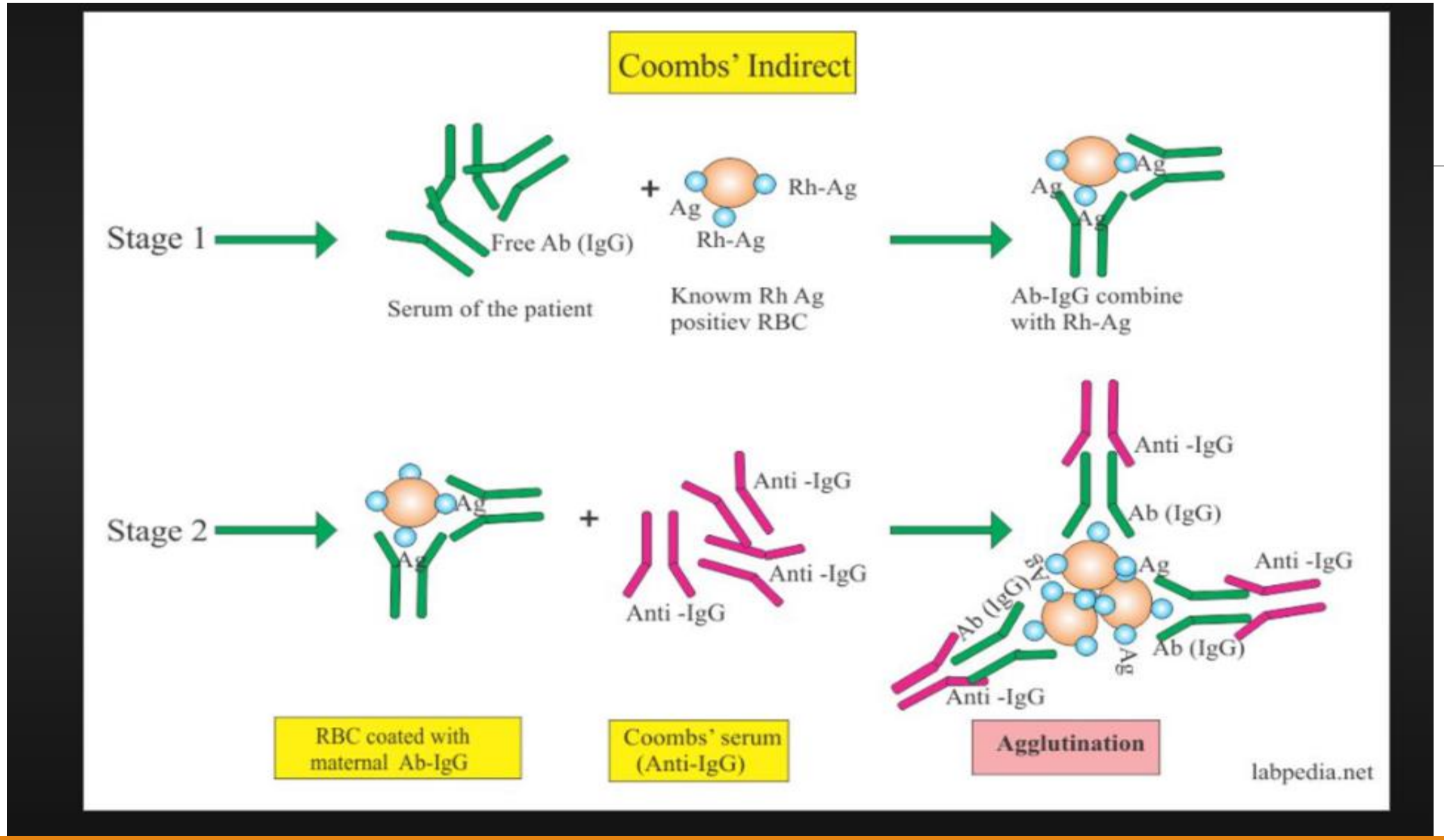
The diagnosis depends on the detection of antibodies and/or complement on red cells. This is done with:

* Direct Coombs test, in which the patient's red cells are incubated with antibodies against human immunoglobulin or complement.

*Iindirect Coombs test, which assesses the ability of the patient's serum to agglutinate test red cells bearing defined surface determinants, can then be used to characterize the target of the antibody.

COOMB's Test


Coombs' Direct
Ab (IgG)
Ag
+
Mother RBC coated with Ab
Coombs serum (Anti-IgG)
Anti -IgG
Ab (IgG)
Ag
Anti -IgG
Ab (IgG)
Ag
Ag
Ab (IgG)
Anti -IgG
Agglutination
labpedia.net


Coombs' Indirect
Stage 1
Free Ab (IgG)
Serum of the patient
+
Ag
Rh-Ag
Rh-Ag
Knowm Rh Ag
positiev RBC
Ag
Ag
Ag
Ab-IgG combine
with Rh-Ag
Stage 2
Ag
Ag
+
Anti -IgG
Anti -IgG
Anti -IgG
Anti -IgG
Ab (IgG)
Ag
Ag
Ag
Ab (IgG)
Ab (IgG)
Anti -IgG
Anti -IgG
RBC coated with
maternal Ab-IgG
Coombs' serum
(Anti-IgG)
Agglutination
labpedia.net

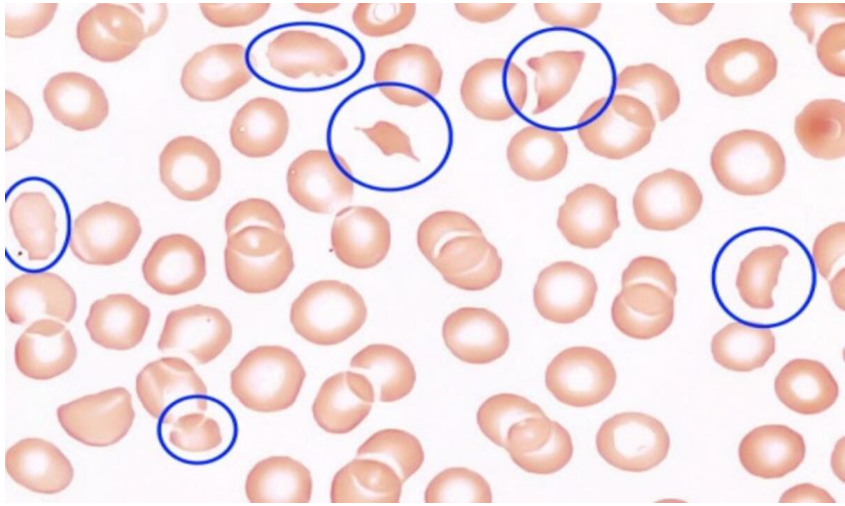
Hemolytic Anemia Due to Mechanical Trauma to RBC

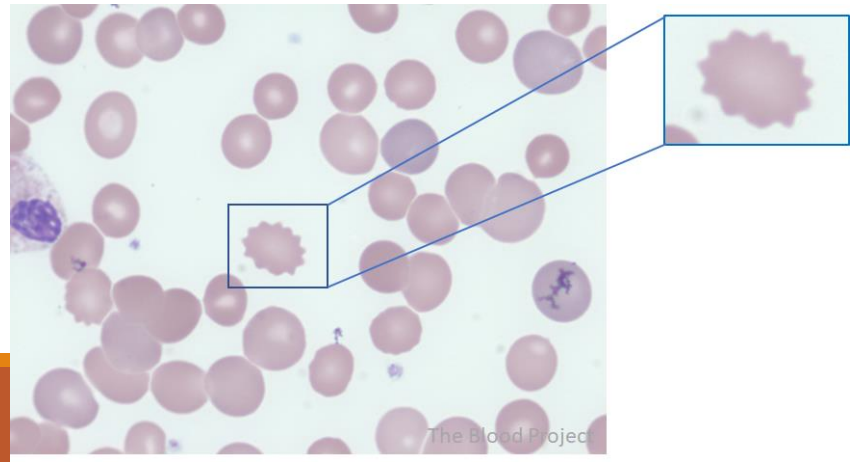
Etiology

- Artificial valves
- Microangiopathic hemolytic anemia
  - DIC
  - Malignant hypertension
  - TTP
  - Hemolytic uremic syndrome

Morphology

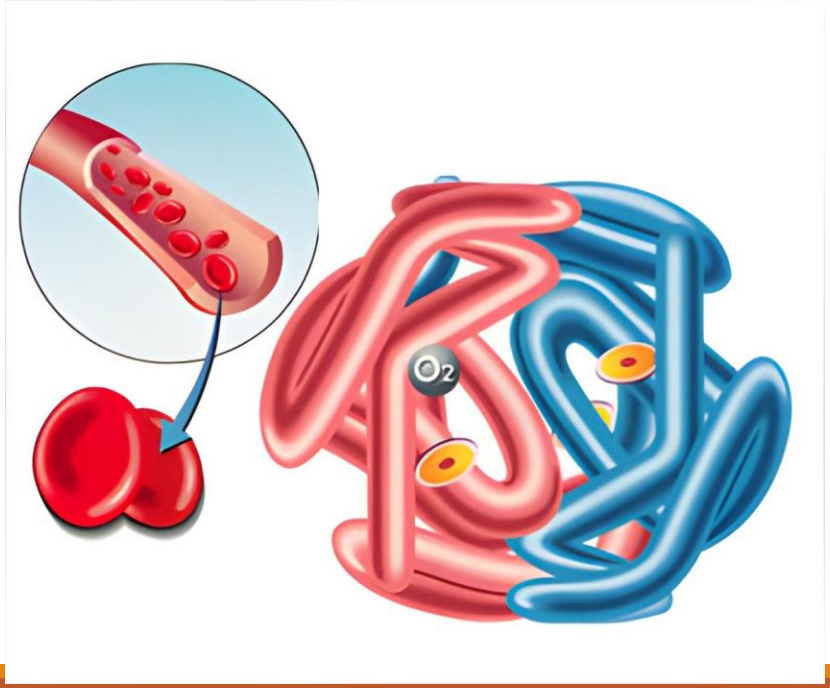
- Significant poikilocytosis with helmet cells/ schistocytes , burr cells, and triangle cells





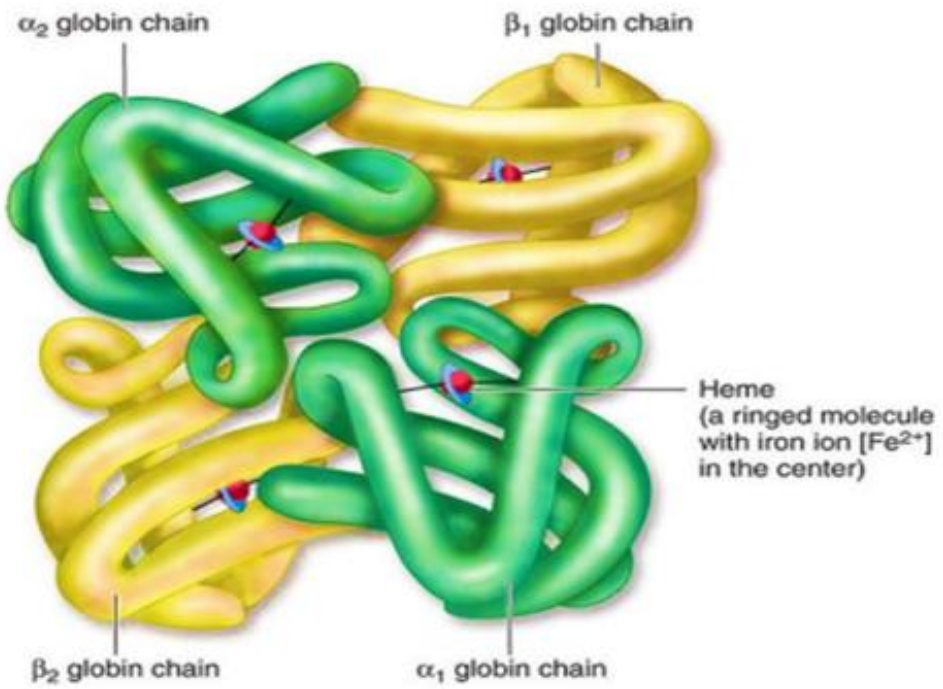
HEMOGLOBINOPATHIES

❖Hemoglobinopathies are a group of hereditary disorders caused by inherited mutations that lead to structural abnormalities in hemoglobin.



NORMAL HUMAN HEMOGLOBINS

- Hemoglobin A ($\alpha 2\beta 2$): 95% of adult hemoglobin.
- Hemoglobin A2 ($\alpha 2\delta 2$): 3% of adult hemoglobin.
- Hemoglobin F ($\alpha 2\gamma 2$) :
  - 75% at birth
  - < 5% at 6 months
  - < 1% in adults

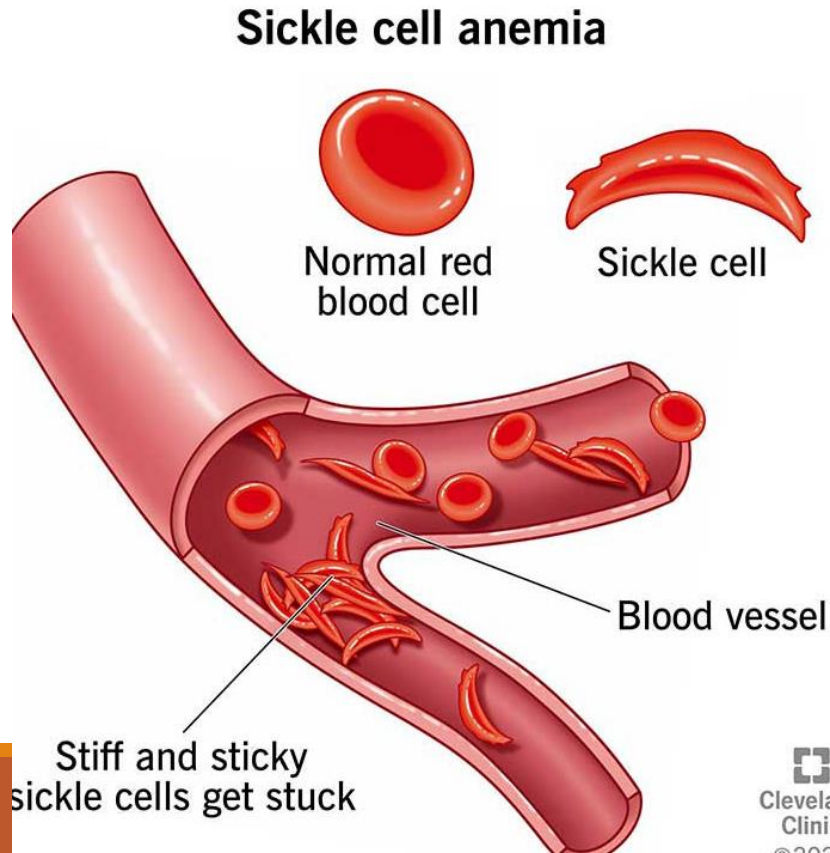


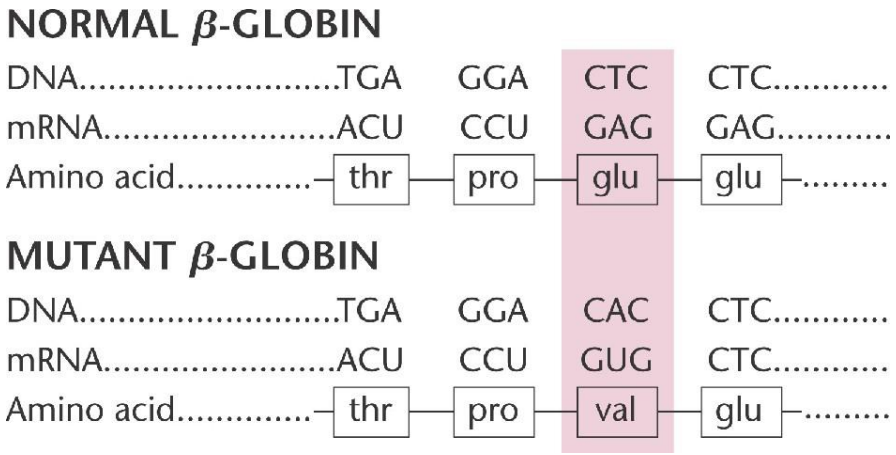
1. SICKLE CELL DISEASE

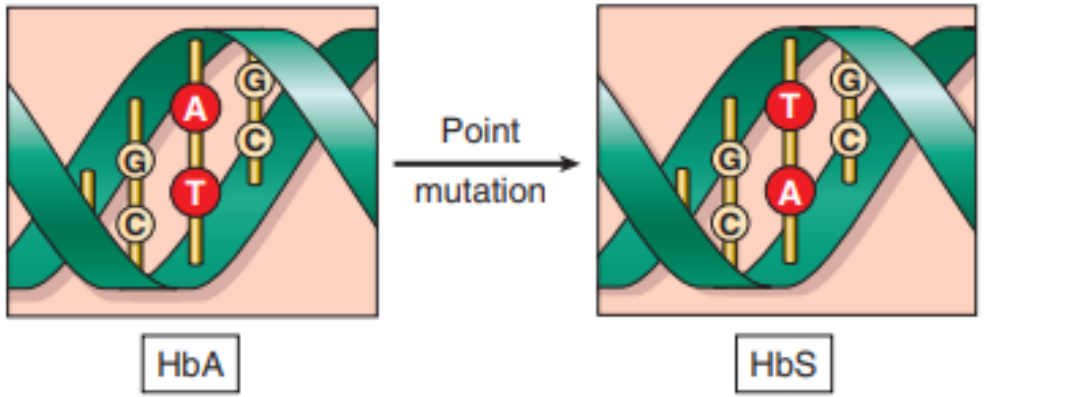
- Sickle cell anemia, the prototypic hemoglobinopathy (and the most common), is caused by a mutation in β-globin that creates sickle hemoglobin (HbS)

- Pathogenesis : one base pair mutation resulting in the substitution of valine for the glutamic acid at the 6th position of the β chain of Hb.

- RBC life span decreased from a normal 120 days to 10-12 days



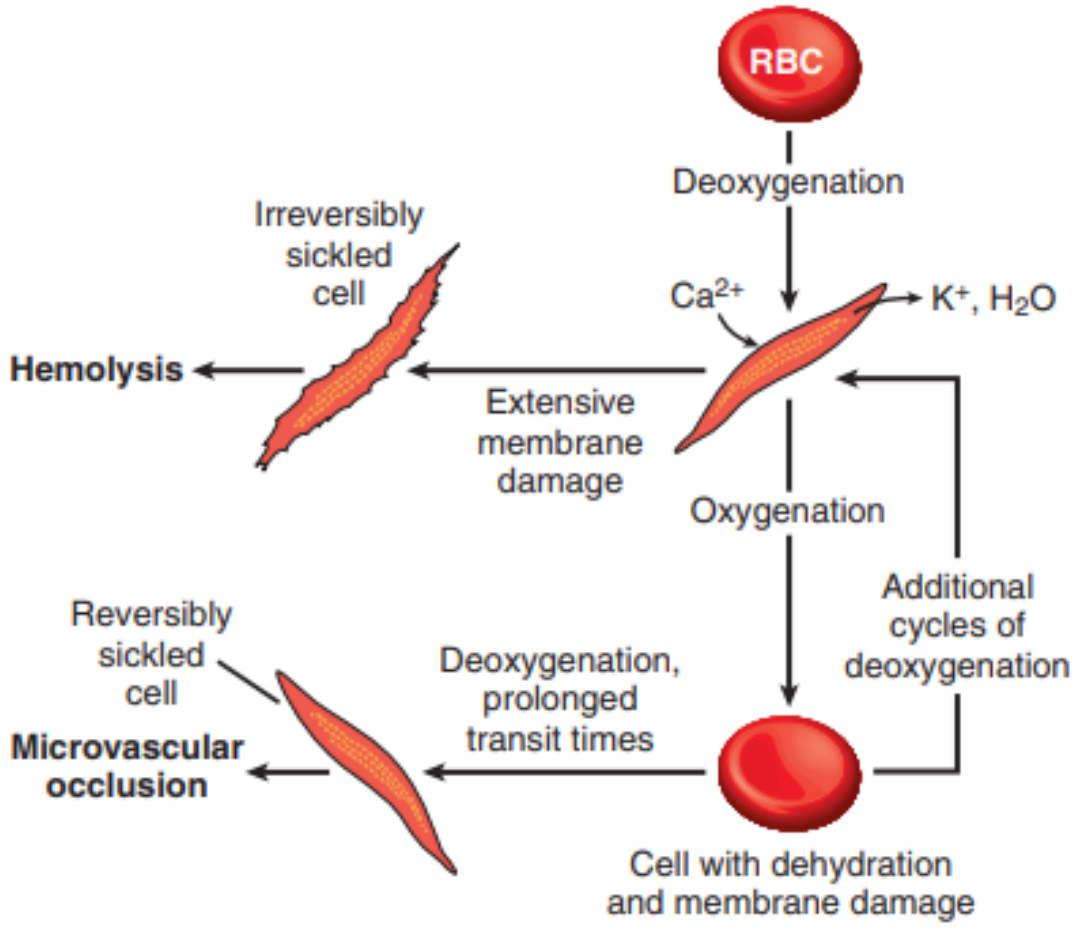




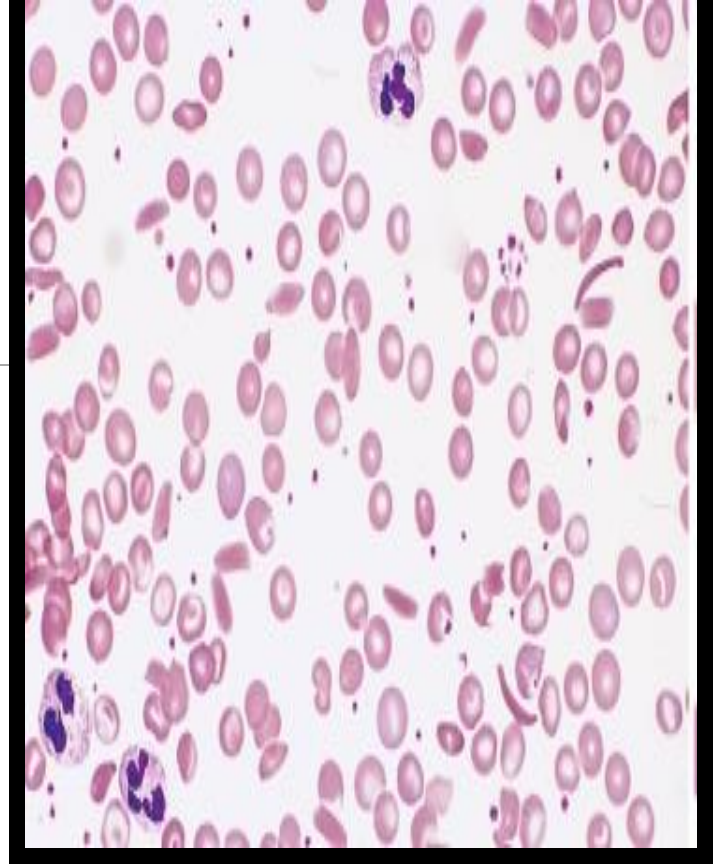
Released Hb

Inactivates NO → vessels narrowing

Vaso-occlusive phenomena.



Clinical presentation



- Asymptomatic till 6 months of age.
- Moderate to severe anemia (6-8 g/dl).
- Unremitting course complicated by sudden crises.
- Laboratory investigation: CBC and blood smear, Hemoglobin electrophoresis.
- Treatment: Adequate hydration / Pain relief/ Antibiotic therapy/ exchange transfusion to reduce the HbS.

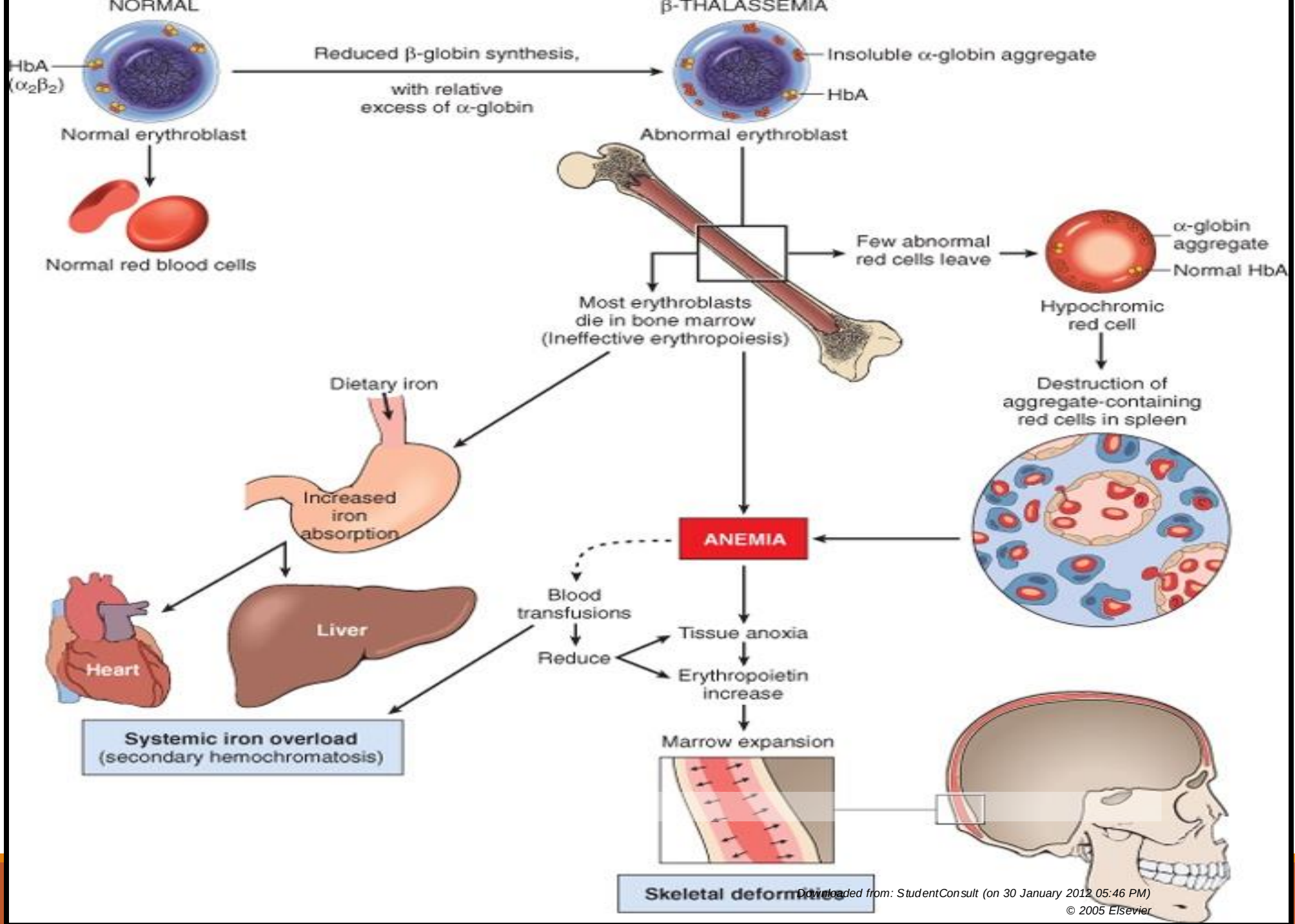
2. Thalassemia

- Thalassemia's are inherited disorders caused by mutations in globin genes that decrease the synthesis of α- or β-globin, leading to deficiency of Hb and red cell damage
- The mutations that cause thalassemia are particularly common in Mediterranean, African, and Asian regions in which malaria is endemic.
- As with HbS, it is hypothesized that globin mutations associated with thalassemia protect against falciparum malaria.

Features of thalassemia

- Decreased globin chain synthesis leading to hypochromic microcytic anemia.

- Imbalance of globin chains → Reduced Hb synthesis and anaemia
- Precipitation of abnormal Hb → haemolysis and ineffective erythropoiesis



β-Thalassemia

Mutations leading to aberrant RNA splicing are the most common cause of β-thalassemia.

Mutations associated with β-thalassemia :

(1) βo: No β-globin chains are produced

(2) β+: Reduced (but detectable) β-globin synthesis.

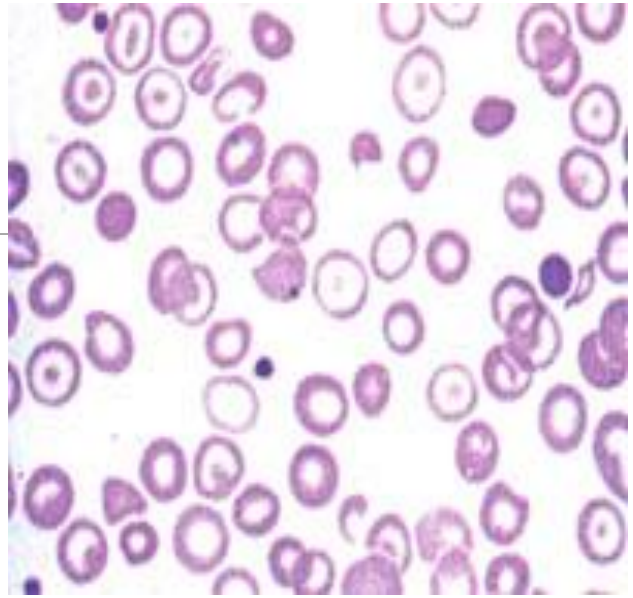
β-thalassemia minor (β-thalassemia trait):

Persons inheriting one abnormal allele

β-Thalassemia major:

- Persons inheriting any two βo and β+ alleles

β–THALASSEMIA MAJOR



- Genotype: β^0/β^0, β^+/β^+, β^0/β^+
- Age of manifestations: 6-9 months
- Hb. Level: 3-6 gm/dl (if un-transfused).
- Very high HbF, absent or decreased HbA, HbA2 Normal or increased
- Transfusion dependent.

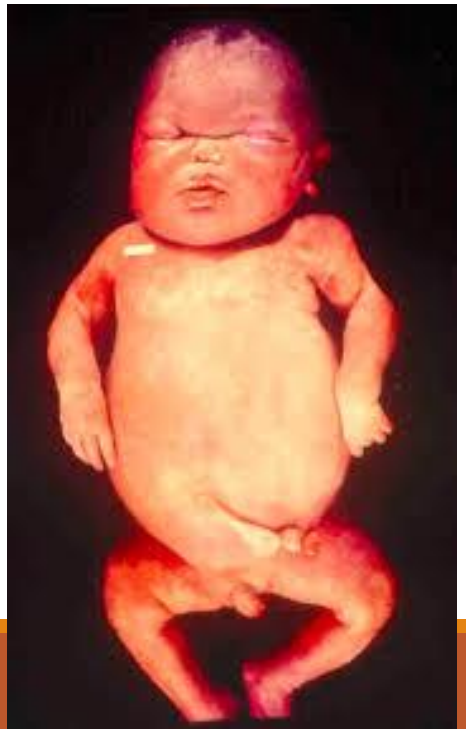
β –THALASSEMIA MINOR

- Heterozygous for β^0 or β^+ gene
- increased HbA2 (> 3.5%) and/or HbF (1- 5%)
- Mild microcytic anemia (Hb 9-11 g/dL)
- Differential Dx: Iron deficiency anemia

α-Thalassemia

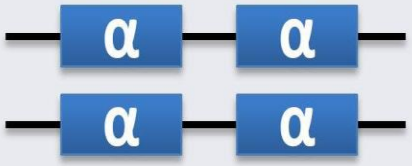
- Caused mainly by deletions involving one or more of the a-globin genes.
- Severity of the disease is proportional to the number of a-globin genes that are missing.

- -α/αα: silent carrier state: asymptomatic
- --/αα, -α/-α : α thalassemia minor: asymptomatic
- --/-α : Excess beta: Beta 4: HbH disease
- --/-- : Excess Gamma : Hb Barts, Death in utero (Hydrops fetalis)

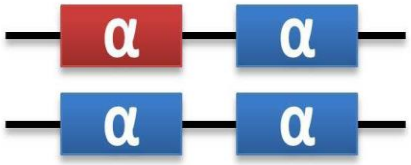


Alpha-thalassemia Genetics and Clinical Consequences

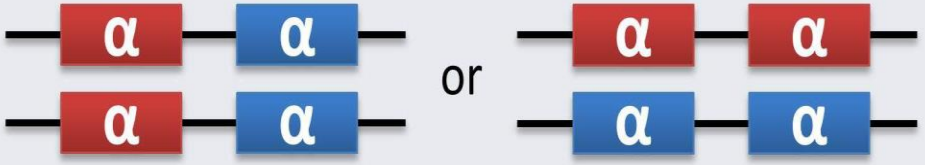
Normal



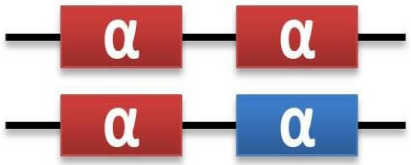
Carrier: Asymptomatic
No abnormalities



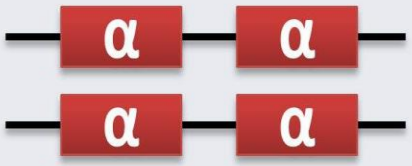
α-thal minor: Asymptomatic
Mild microcytic anemia



Hb H Disease: Symptomatic
Hemolytic and Microcytic anemia
Splenomegaly



Incompatible with Life
Hydrops Fetalis



Peripheral smear

Red cell inclusion bodies