

# Anemia



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## Definition:

- **Anemia:** is a reduction in the oxygen carrying capacity of blood.
- **Classification of anemia:**
  - a. Etiological classification**
    1. Increase RBC loss (bleeding)
    2. Increase red cell destruction (hemolysis)
    3. Decrease red cell production

**b. Morphological classification:**

1. Cell size (normocytic, microcytic, macrocytic)
2. Degree of hemoglobinization reflected by the color of the cell (normochromic, hypochromic)
3. Shape of the cells: normal shape, spherocyte, sickle cell shape.

## Clinical features of patient with anemia:

It largely depends on the type of anemia and hemoglobin level.

- **General features include:** pallor, tiredness, palpitation, change in skin, hair and fingers, decrease in concentration
- Jaundice and change in color of urine and stool with loin pain = **intravascular hemolytic anemia**
- Jaundice +special face character splenomegaly and signs of iron deposition= **extravascular hemolytic anemia**

# What are the symptoms of anemia?



**Fatigue.**



**Chest pain.**



**Dizziness.**



**Heart palpitations.**



**Headache.**



**Pallor  
(pale skin).**



**Shortness  
of breath.**



**Pulsatile  
tinnitus.**



**Frequent  
infections.**

## Investigations:

- **Complete blood count:** detect the number of each blood cell+ Hb + PCV +special indices of RBC
- **TSB: total serum bilirubin** which include both indirect (unconjugated) and direct (conjugated) bilirubin. In hemolytic anemia there was indirect (unconjugated) hyperbilirubinemia.
- **Blood film:** detect the shape and size of the blood cells
- **Hb electrophoresis** if hemoglobinopathies (thalassemia, sickle cell anemia, ....) suspected
- **Bone marrow:** state of bone marrow cellularity, examine blood cell precursors, iron store and any pathological abnormality.

## I-Anemia of blood loss:

**a. Acute blood loss (hemorrhage):** acute massive blood loss result in hypovolemic shock rather than anemia. Anemia in acute blood loss is normochromic normocytic. The body reacts by hemodilution and increase erythropoietin level which stimulates bone marrow to increase RBC production. The onset of marrow response is marked by reticulocytosis (reticulocyte is anew RBC)

**b. Chronic blood loss:** here the iron store gradually depleted, iron essential for hemoglobin synthesis and effective erythropoiesis. Anemia is hypochromic anemia (iron deficiency anemia) corrected by treating the cause and iron supplementation.

## II- Anemia of increase RBC destruction (hemolytic anemia):

- Normal RBCs have a life span of about 120 days. If RBC destroyed earlier, hemolytic anemia will occur.

General features of all hemolytic anemia: all characterized by:

1. Increase rate of RBC destruction
2. Compensatory increase in erythropoiesis result in reticulocytosis

3. Retention by the body products of red cell destruction e.g. iron overload in extravascular hemolytic anemia.

4. Almost invariably hemolytic anemia associated with erythroid hyperplasia in the bone marrow and increased retic count in the peripheral blood. In severe hemolytic anemia extramedullary hematopoiesis often develops eg in spleen liver and lymph nodes.

## Site of RBC destruction:

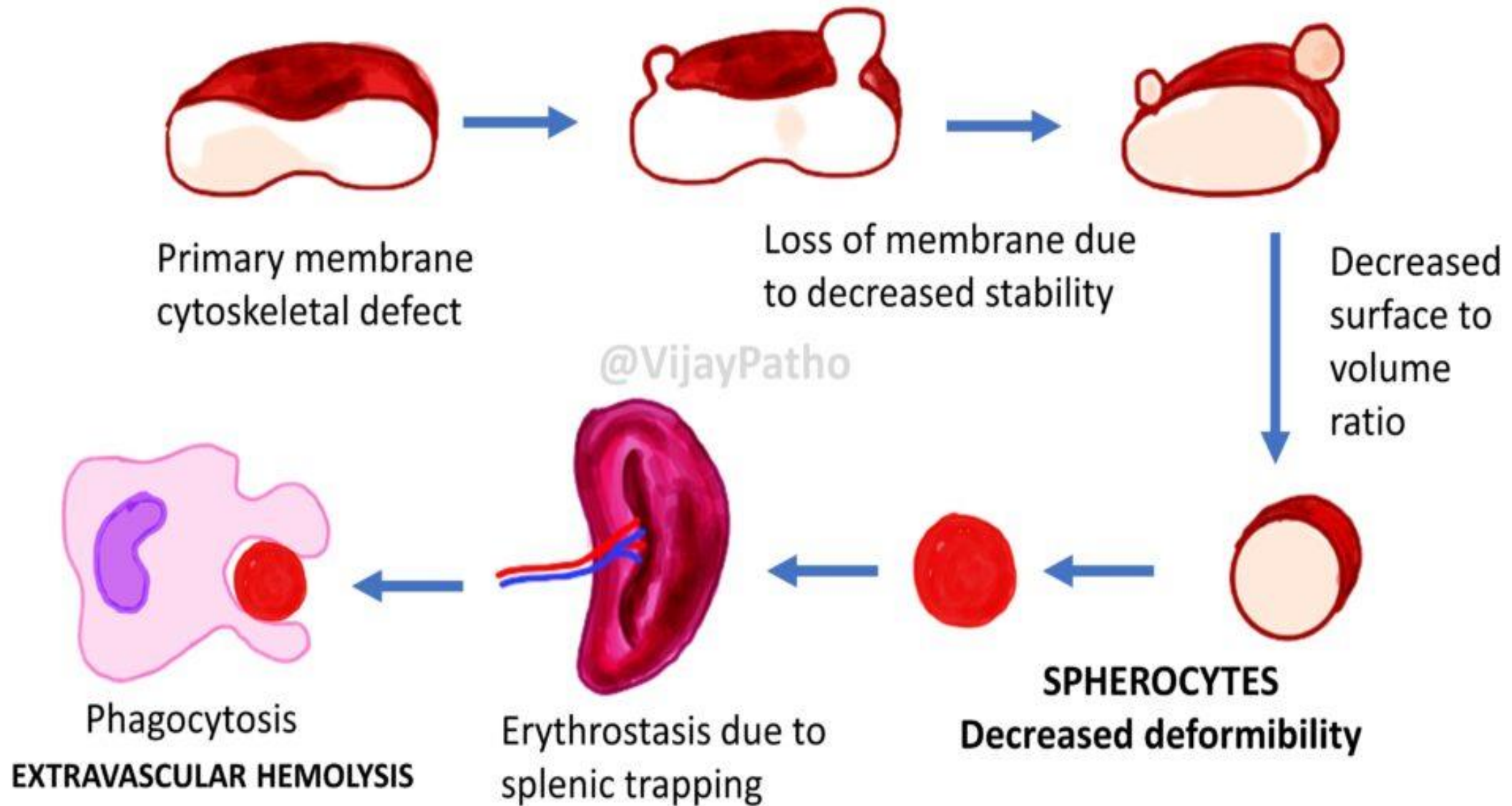
- **Intravascular RBC destruction:** hemolysis occurs within blood vessels. It results from mechanical destruction of the RBC (prosthetic valve), physical agent (heat), chemical agent (bacterial toxin, drugs), G6PD deficiency, microorganism (malaria), immunological (type II hypersensitivity reaction, ABO mismatch). Regardless the cause, the anemia characterized by the followings: hemoglobinemia, hemoglobinuria, unconjugated hyperbilirubinemia (jaundice) and severe deficiency or absent haptoglobin from plasma (circulating protein that bind and clear Hb). Intravascular Hemolytic anemia may lead to acute tubular necrosis and renal failure.
- The patient present with sudden attack of loin pain, change in color of urine and drop in Hb.

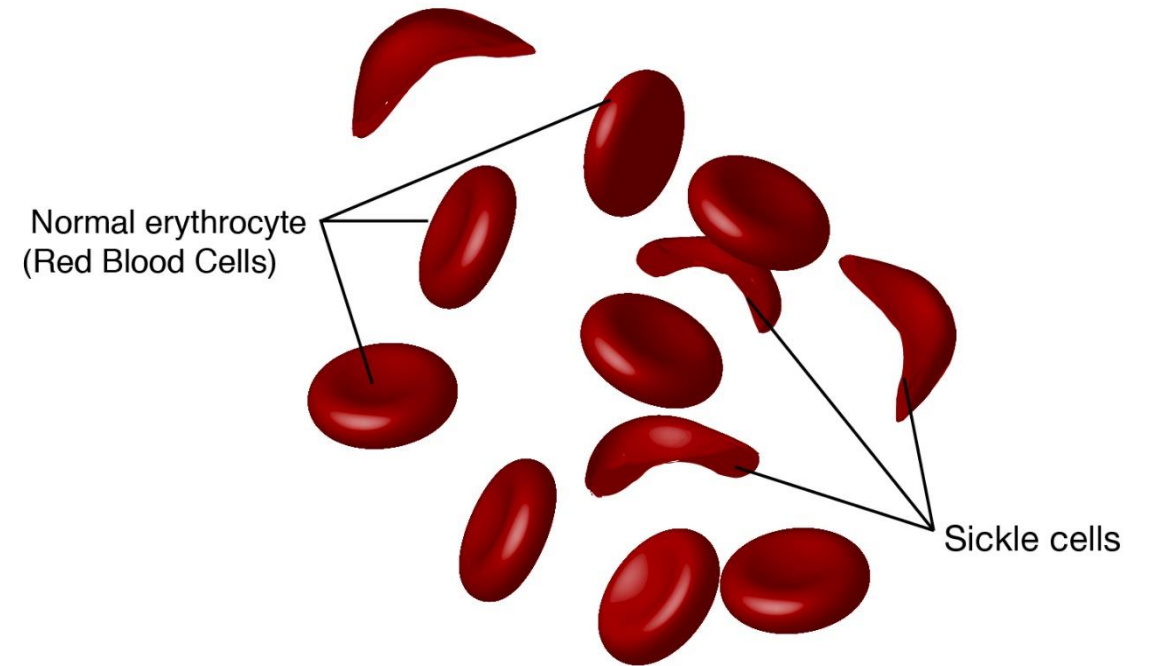
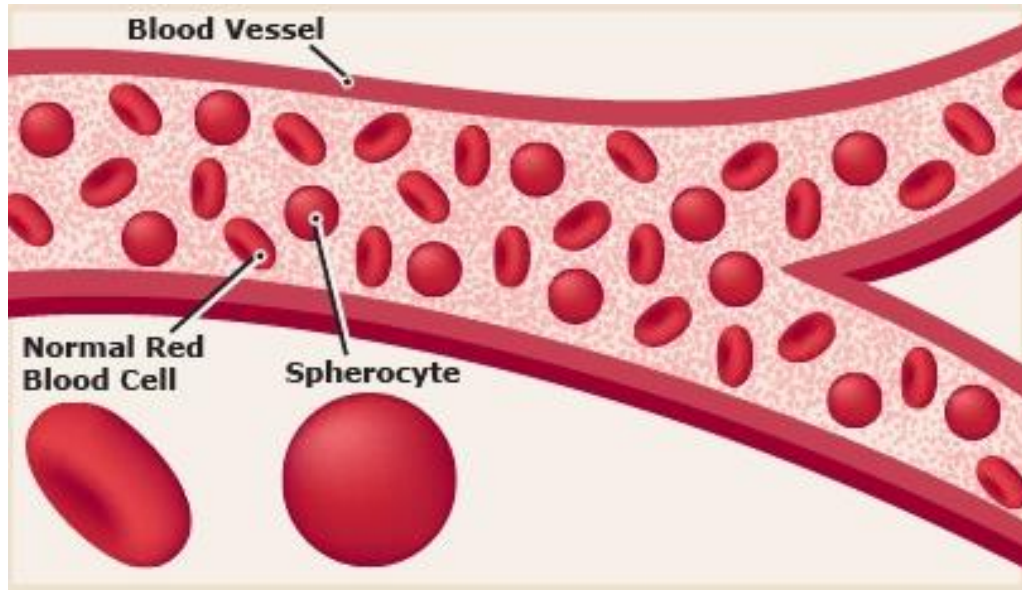
- **Extravascular RBC destruction:** hemolysis takes place largely within the phagocytic cells of the spleen. The phagocytic cells remove abnormal RBCs from the circulation (spherocytosis, sickle cell anemia, thalassemia). Abnormal RBC shape makes their passage difficult through splenic sinusoids and leads to splenic sequestration followed by phagocytosis. Extravascular hemolysis characterized by:
  - Unconjugated hyperbilirubinemia (jaundice) with iron that released from Hb by phagocytic cells accumulated in tissues lead to secondary hemosiderosis. **no** hemoglobinemia, **no** hemoglobinuria. The spleen was enlarged in most cases and pigmented gall stone formed.
  - The patients usually presented with severe anemia, signs of multiple organs dysfunctioning due to hemochromatosis and splenomegaly.

## Common examples of hemolytic anemia:

- **Hereditary spherocytosis (HS):** is characterized by autosomal dominant inherited defect in RBC membrane that renders the cells spheroidal less deformable and vulnerable to splenic sequestration and destruction (extravascular hemolysis).
- **Sickle cell anemia:**
- Normal infant RBC contains HbF (Fetal hemoglobin HbF  $\alpha_2\gamma_2$ ). Adult RBC contain 96% HbA ( $\alpha_2\beta_2$ ), 3% HbA2 ( $\alpha_2\delta_2$ ) and 1% of HbF ( $\alpha_2\gamma_2$ ).

# HERIDETARY SPHEROCYTOSIS- PATHOPHYSIOLOGY





- In Sickle cell anemia HbS will be produced by substitution of **valine** for **glutamic acid** of **β chain**. In homozygotes all HbA is replaced by HbS, whereas in heterozygotes only about half is replaced. Upon deoxygenation, HbS molecules undergo polymerization (crystallization) these polymers distort RBC which assume an elongated crescentic or sickle shape (sickling) and become sticky less deformable then destructed by splenic macrophages. Sickling initially reversible then with recurrent episodes it become irreversible. The hemolysis is extravascular hemolysis.

# Thalassemia:

- Thalassemia is heterogeneous group of inherited disorders caused by mutations that decrease the rate of synthesis of  $\alpha$  or  $\beta$  chains.
- Adult Hb (HbA) is a tetramer composed of two  $\alpha$  and two  $\beta$  chains ( $\alpha_2\beta_2$ ). The  $\alpha$  chains are encoded by two  $\alpha$  globin genes, while the  $\beta$  chains are encoded by a single  $\beta$  globin gene. If mutation in  $\alpha$  globin gene,  $\alpha$  thalassemia will occur. If mutation in  $\beta$  globin gene,  $\beta$  thalassemia will occur.

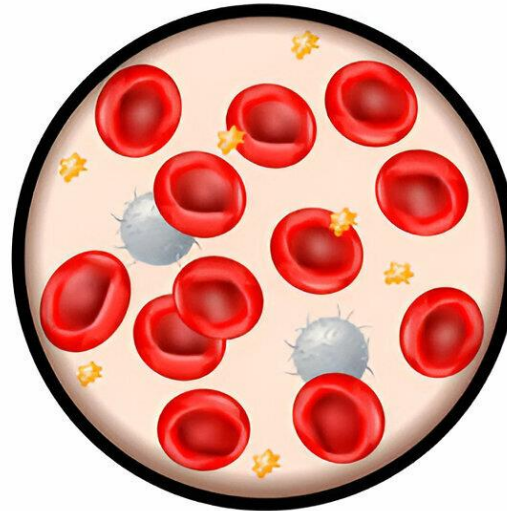


Clinical Features of Thalassemia Major

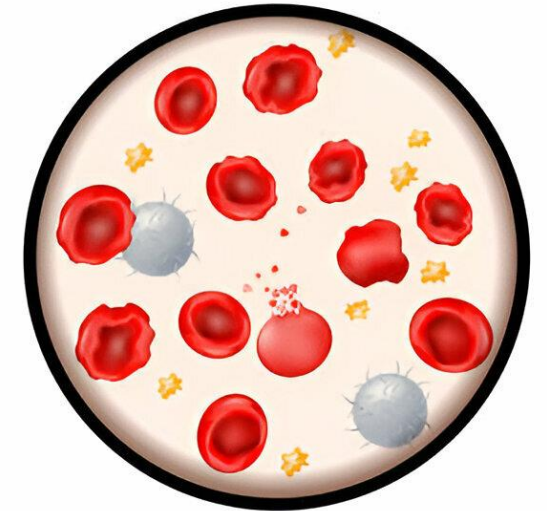


## Thalassemia

Normal



Thalassemia



## - $\beta$ thalassemia:

$\beta$  thalassemia resulted when the  $\beta$  globin gene was mutated. Individuals inheriting one abnormal gene (i.e. from one parent) have **thalassemia minor**, which is asymptomatic or mildly symptomatic. If individuals inheriting two mutated genes (i.e. from both parents)  **$\beta$  thalassemia major** will occur.

In  $\beta$  thalassemia there is:

- a. Reduced synthesis of  $\beta$  globin leads to inadequate HbA formation and the RBC will be **hypochromic microcytic**
- b. Reduced synthesis of  $\beta$  globin leads to unbalance between  $\alpha$  and  $\beta$  of globin chains. Unpaired  $\alpha$  chain will form insoluble precipitate on the red cell membrane which leads to extravascular hemolysis.

## - $\alpha$ thalassemia:

- The molecular basis of  $\alpha$  thalassemia is quite different from that of  $\beta$  thalassemia. Most of  $\alpha$  thalassemia are caused by deletion that remove one or more of the  $\alpha$  globin gene loci. The severity of the disease that result from these lesions is directly proportional to the number of  $\alpha$  globin genes that are missing. For example the loss of single  $\alpha$  globin gene is associated with a **silent carrier state**, whereas the deletion of all four  $\alpha$  globin genes is associated with **fetal death in utero**.

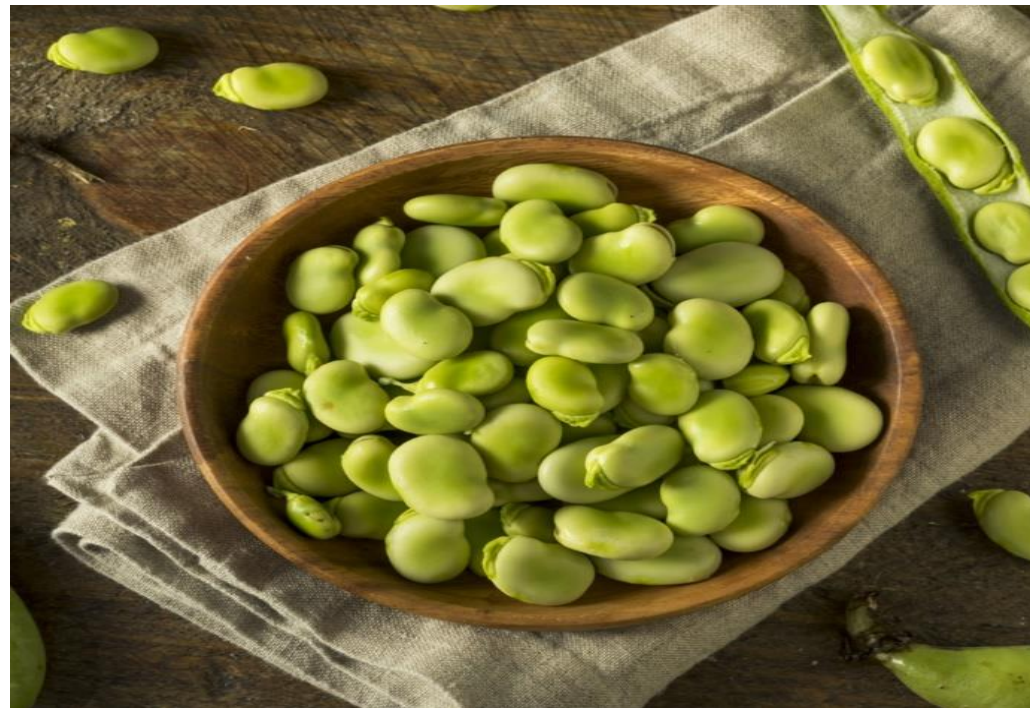
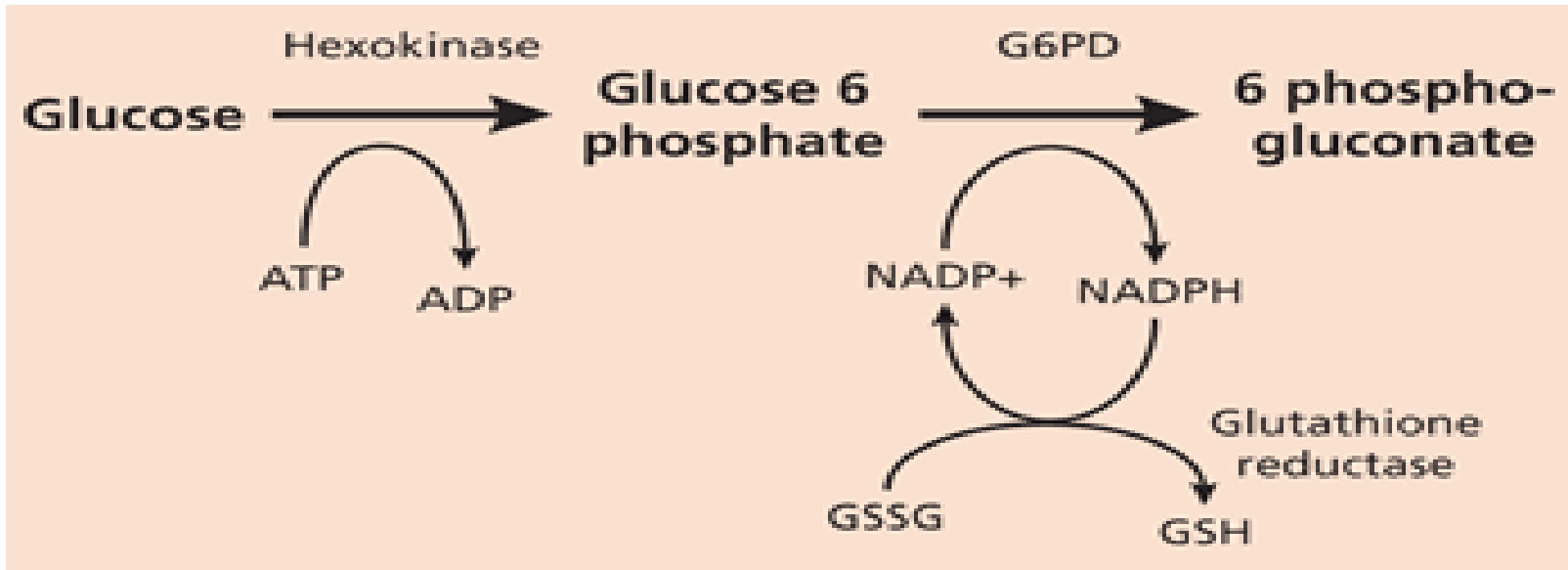
- Hemolytic anemia due to  $\alpha$  thalassemia less severe than that of  $\beta$  thalassemia because excess  $\beta$  globin chains form relatively stable  $\beta_4$  tetramers (HbH) and  $\gamma_4$  tetramers (HbBart) that cause less membrane damage than do free  $\alpha$  globin chains. But unfortunately both HbH and HbBart have an abnormal high affinity for oxygen, which renders them ineffective at delivering oxygen to the tissues

# Glucose 6 Phosphate Dehydrogenase Deficiency (G6PDD) (Favism) :

- X-linked recessive inherited disorder, i.e males affected and the females become carrier. This genetic disorder affects the enzymes glucose 6 phosphate dehydrogenase which required to convert **NADP** (Nicotinamide Adenine Dinucleotide Phosphate) to **NADPH** which in turn required for **glutathione (GSH)** production. **GSH protect RBC membrane from oxidative stress**. The G6PD deficiency makes the RBC vulnerable to hemolysis.

- The patients have no symptoms until the patient is exposed to oxidant stress which include:
  - a. Drug: antimalarial drug premaquine, sulfonamide, nitrofurantoin, aspirin, phenacetin.
  - b. Food especially broad beans.
  - c. infection and inflammation

- Oxidative stress will produce free radicals, these free radicals encountered by GSH. GSH is impaired in G6PDD red cells so the free radicals attack the red cells including and intravascular hemolysis will occur.
- Hemolysis is intravascular hemolysis.



## Immuno-hemolytic anemia:

- Antibodies recognize antigens on red cell membrane cause the uncommon form of hemolytic anemia. Example of immune hemolytic anemia:
  1. Rh incompatibility: mother with Rh -ve blood group bearing fetus with Rh +ve blood group. RBC will escape from the fetus to mother circulation lead to Ab formation against Rh antigen. In the following pregnancy, if the fetus with Rh +ve antigen, anti Rh antibody in the mother circulation that formed in the first pregnancy cross the placenta and attack the fetus RBC Rh antigen lead to hemolysis of fetal RBC.

2. ABO incompatibility when the patient receive incompatible blood group. Antibodies in the recipient patient react with antigens of the incompatible donor blood and the vice versa e.g patient with blood group A which have anti B antibodies in his blood receive blood from group B donor which have anti A antibodies.

3. Blood transfusion reaction: her the blood is compatible but the patient have antibodies in his serum may react with the received compatible blood. This can commonly occur in multiparous women and patients with multiple blood transfusions. Cross match test will decrease the occurrence of this reaction.