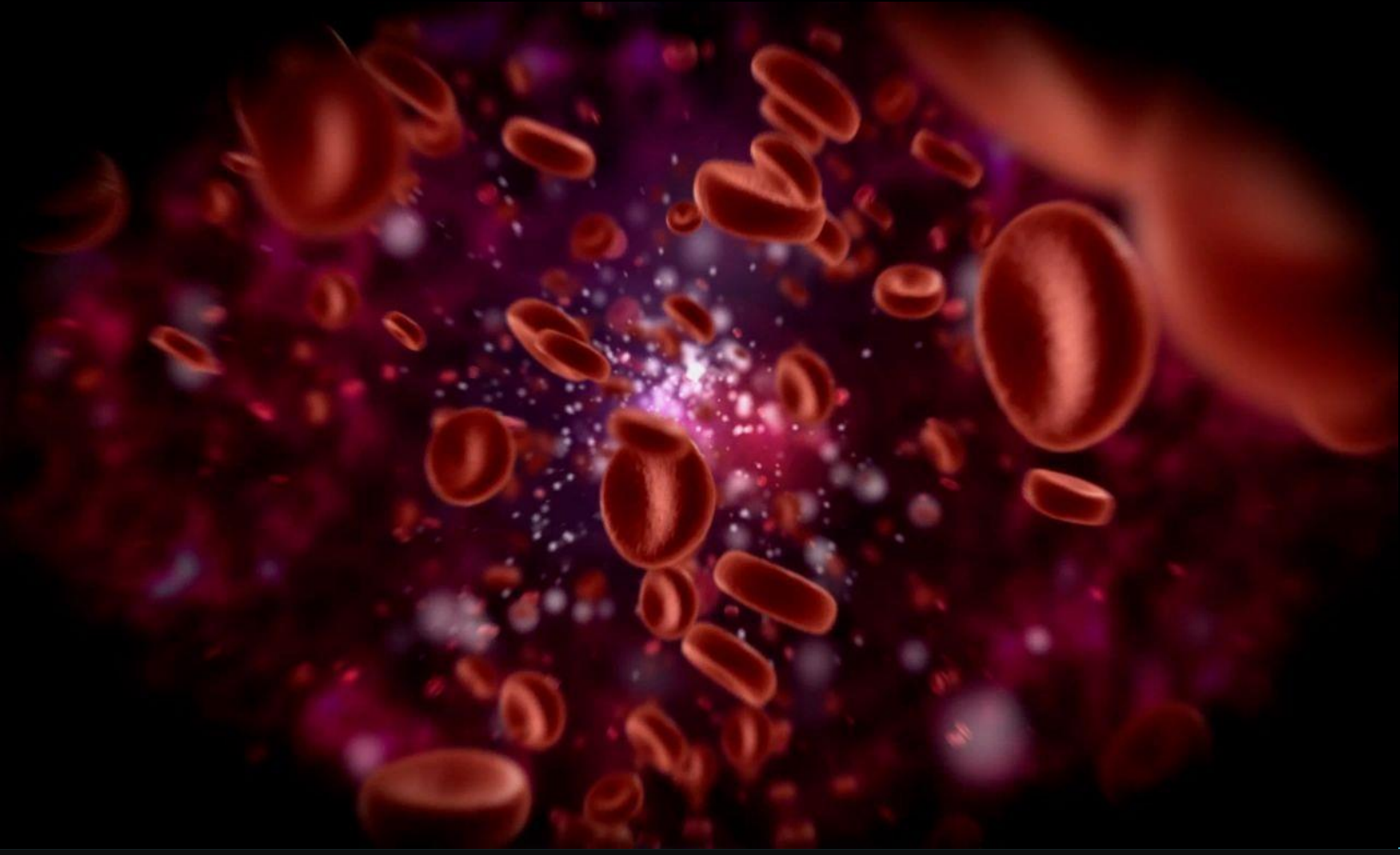


ATHAR BATCH

BIOCHEMISTRY

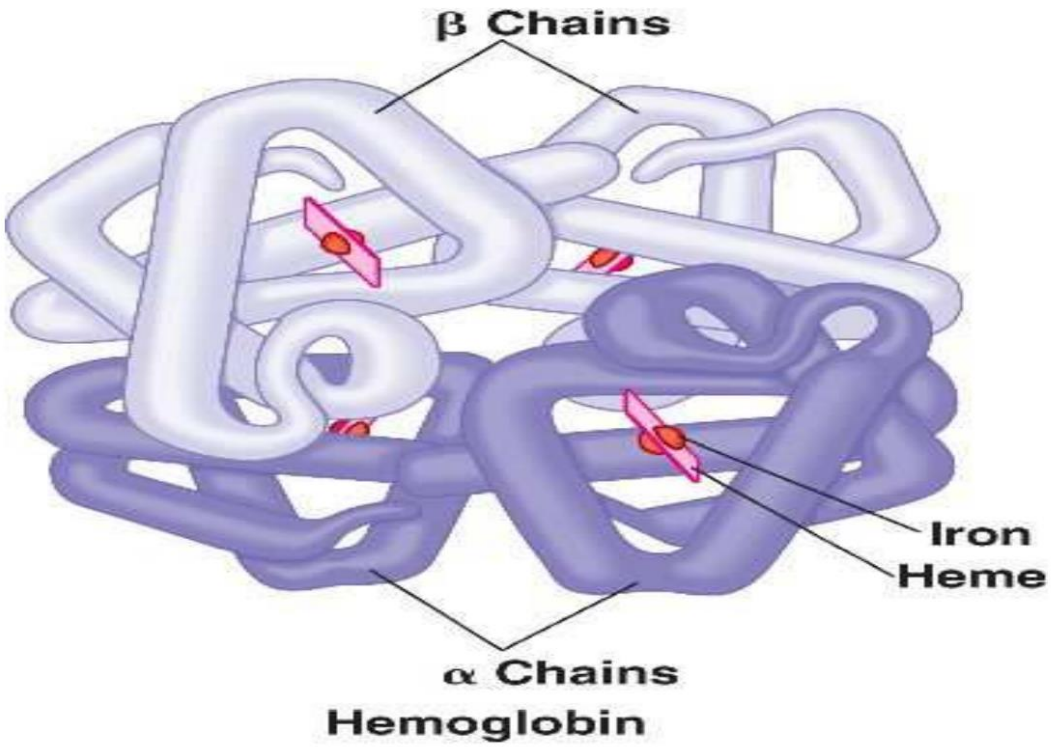
lecture : 3

Done by: Salsabeel Alhawatmeh

النادي الطبي

Hb & Hemoglobinopathies

By
Dr. Walaa Bayoumie El Gazzar



- The iron atom of heme occupies the central position of the porphyrin ring.
- In Hb iron is in the **ferrous state** (Fe^{++})
- Ferrous iron (Fe^{++}) has 6 valencies.
- Iron carries oxygen.

- *Remember: when we say that ferrous iron has 6 valences, we mean that it can bind to 6 atoms or molecules.*

Globin

- **Tetramer : 4 polypeptide chains.**
- **Each polypeptide chain is formed of 7 or 8 helices which are termed A-B-C-D…….**
- **There are 4 types of the polypeptide chains that may enter in the formation of Hb (α-β-γ-δ).**
  - **α –chain → 141 amino acids**

  (α chain gene is on chromosome 16)
  - **β-γ-δ chains → 146 amino acids**

  (β-γ-δ chain genes are on chromosome 11)

- **Hb is composed of 2 α and 2 either β , γ or δ**

Types of Hb

- **Hb A:**

- The Hb of normal adult
- forms about 97-98% of adult Hb
- 2 α and 2 β (α 2 β 2)

- **Hb A1:**

- This is a group of glycated HbA. They are faster than HbA in electrophoresis, and hence the designation A_1 .The most abundant is HbA_{1c} in which glucose is linked to amino groups of the N terminal valine of the β chains. **This glycosylation depends on the blood glucose level .** Since the half -life of the RBCs is about 60 days, Hb A_1 gives an idea about the average blood glucose level over the last 8 weeeks. Normally Hb A_1 forms **4 - 6.5%** of the total Hb . Values higher than 8% indicate poorly controlled diabetes mellitus.

5.6

- *Glycated: bound to sugar (glucose, fructose, galactose)*
- *Electrophoresis: الفصل الكهربائي*
- *Glucose binds to hemoglobin if its level in the blood is high*
- *HbA1 is a measure for controlling diabetes mellitus... if we want to know the effectiveness of the therapy for a diabetic patient, we measure HbA1. If high levels → poorly controlled diabetes mellitus. Low levels → good controlled.*

- **Hb A2:**
- **2-3% of adult Hb**
- **2 α and 2 δ (α 2 δ 2)**
- **Appears in the blood at the age of 3 months.**
- **It increases in β thalassemia.**

- *In beta thalassemia, beta is the defective chain. The body try to compensate the lack of beta chain by formation of HbA2 that constitute of 2 alpha chains and 2 delta hemoglobin.*

- **Hb F:**

- Normal fetal Hb
- 2 α and 2 γ (α 2 γ 2)
- Has higher affinity for O2 than maternal Hb which allows fetal Hb to take oxygen from maternal blood
- Presents during fetal life and disappears gradually after birth and becoms almost completely replaced by Hb A by the age of

6 months

Difference between oxygenation and oxidation

- When Hb carries oxygen, it is oxygenated and the iron atom is still in the ferrous state

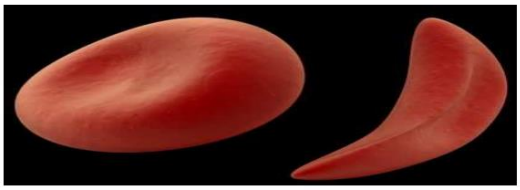
- Oxidised Hb is called Met-Hb and the iron atom is present in the ferric state (the oxygen carrying capacity is lost)

Hemoglobinopathies

- Abnormalities in the primary sequence of globin chains

- *Primary structure of a polypeptide chain: number and sequence of amino acids*

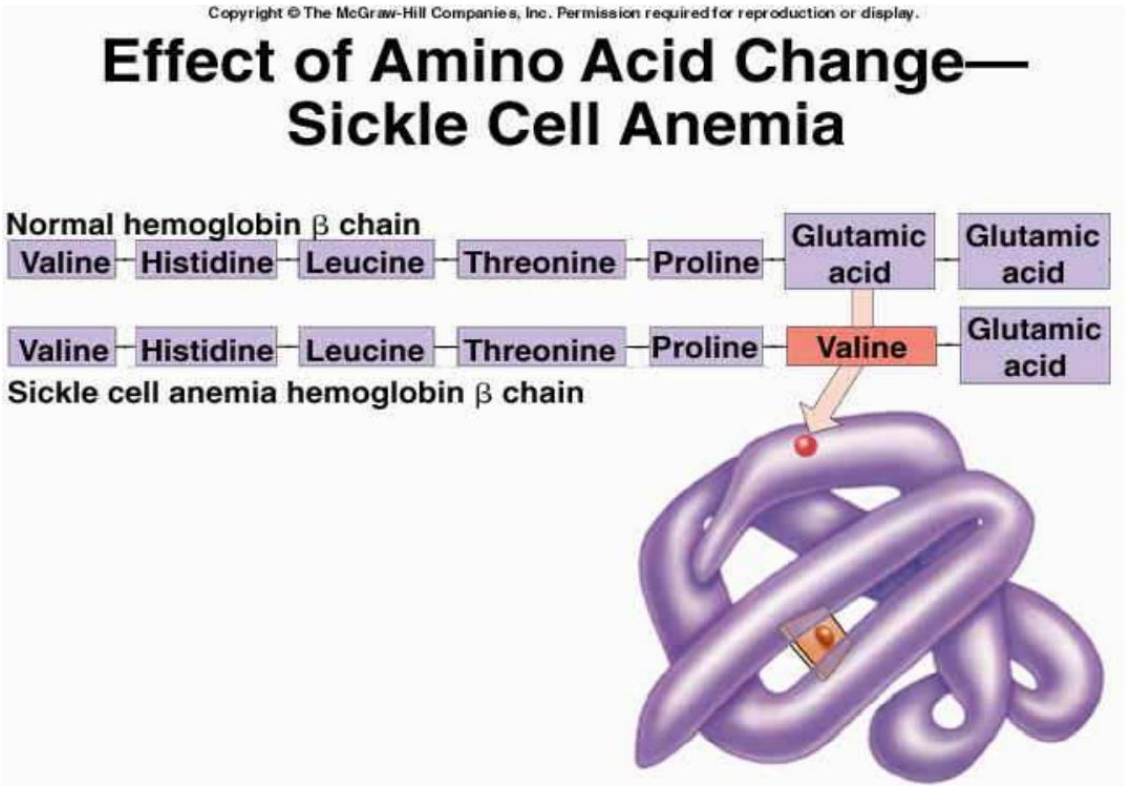
Types :



Hemoglobin S (HbS) / sickle cell hemoglobin:

Genetic disease caused by: Replacement of glutamic acid in the 6th position of beta chain by valin.

- *The sequence of a protein is altered when the sequence of DNA (that encodes for that protein) is altered.*
- *A simple change in the amino acids resulted in formation of abnormal beta chain → abnormal hemoglobin*

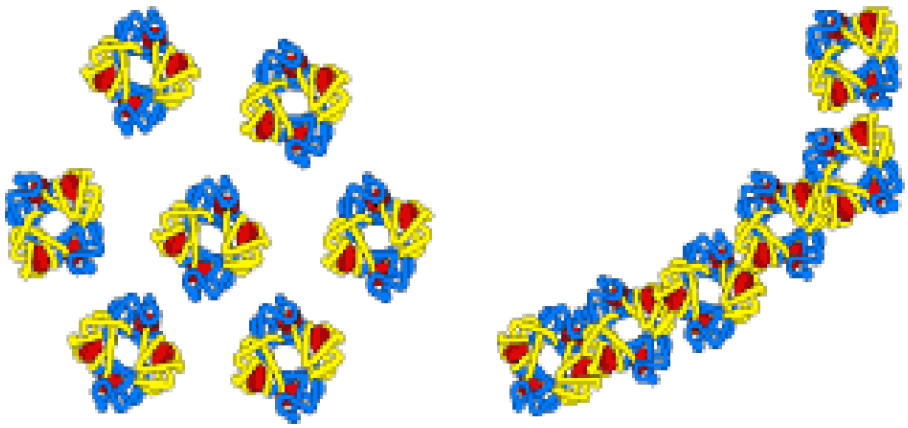


- **Solubility of HbS in the deoxygenated form is 50 times less than oxygenated form leading to crystallization.**

- **HbS polymerize when <u>deoxygenated</u> leading to the formation of a fibrous precipitate in the RBCs which collapes and aquire the shape of a sickle.**

- **Thus the red blood cells become sickled in the peripheral circulation and reaquire the normal shape in the lungs. After repeated sickling and unsickling the red cells become permanently sickled.**

- *Oxygenated HbS is soluble → no crystallization → no polymerization*
- *Deoxygenated HbS is insoluble → crystallization → polymerization*



NORMAL HEMOGLOBIN

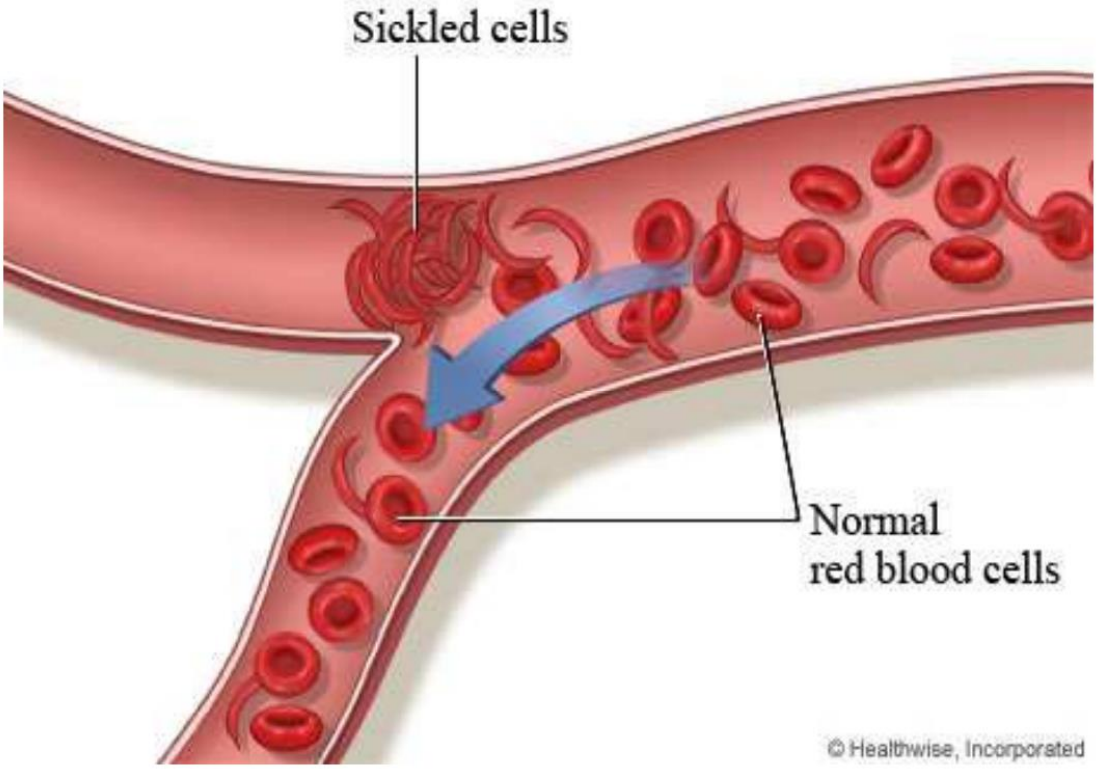
CLUMPED HEMOGLOBIN

- **Sickle cells aggregate in microcirculation and may occlude it leading to infarctions in different organs (crisis in the form of sever pain)**

- **The spleen removes sickle cells at a faster rate than normal cells leading to hemolytic anemia.**

- **HbS is slower than HbA in electrophoresis.**

➢ *since sickle cells are abnormal cells, the spleen removes these cells at faster rate → short life span of sickle cells*



- **Individual who is heterozygous for HbS do not acquire the symptoms of the sickle cell disease, they have both HbA and HbS in their blood cells. They are only carriers (sickle cell trait).**
- **They are resistant to parasites that causes malaria**
- **These parasites do not survive in erythrocytes containing HbS because these cells have shorter life span than normal cells so the parasite can not complete its development.**
- **Also the infected cells require larger amounts of oxygen than uninfected ones so cells tend to be sickled sooner and thus be removed from circulation.**

- *heterozygous: one of the two genes is defected*
- *homozygous: the two genes are defected*
- *parasites need oxygen for metabolism, thus infected cells with parasites requires more oxygen → faster sickling → faster removal by the spleen*

يعني ال parasites تقضي على نفسها بنفسها

Hemoglobin C :

- **Genetic disease caused by replacement of glutamic acid in the 6th position of beta chain of HbA by lysine.**
- **Homozygotes suffer from mild hemolytic anemia**

Thalassemias

- **Group of diseases characterized by reduced formation of the α- or the β- globin chains.**
- **It is due to mutations in the genes responsible for the synthesis of the globin chain producing abnormal Hb with impaired oxygen binding properties.**

➢ *in pediatrics*

Types of thalassemia:

- **α- thalassemia**
- **β- thalassemia**

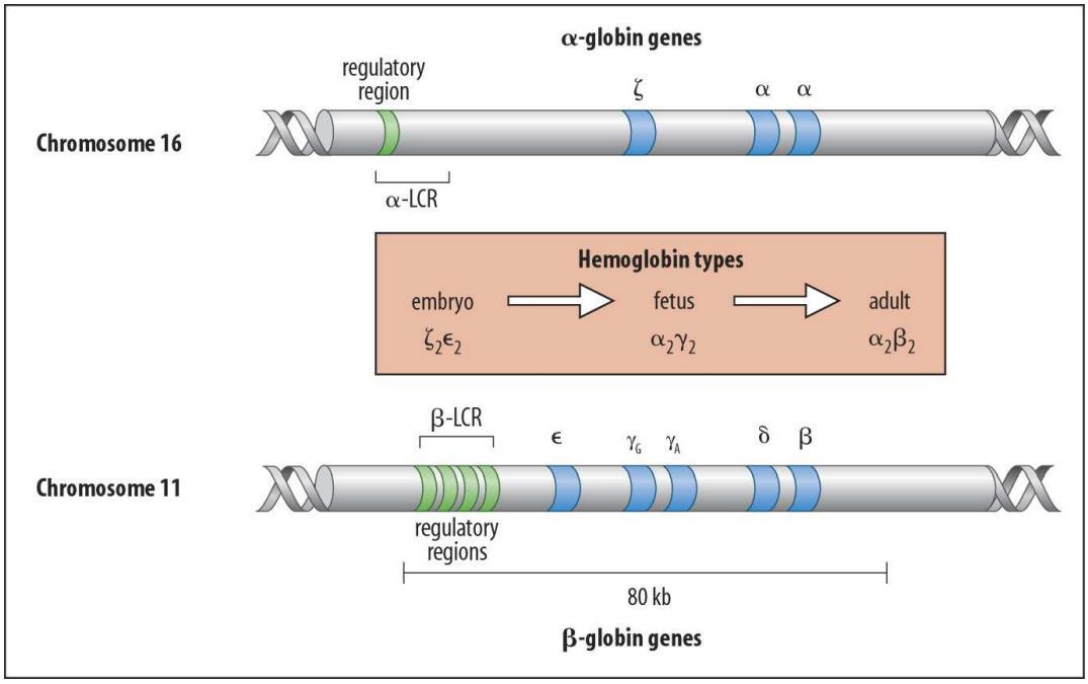
The α- gene family

- This family is present on chromosome 16.
- It contains a number of genes for α- globin-like chains .
- It includes 2 α-genes and one ζ-gene(zeta-gene). The zeta-gene is expressed during embryonic life. It stops working by the end of the first 3 months of pregnancy, its function being gradually replaced by the α- genes.

- *two alpha genes in one chromosome. 4 alpha genes in the two chromosomes.*
- *zeta-gene: alpha globin like chain*

The β- gene family

- This family is present on chromosome 11.
- It contains a number of genes for β-globin-like chains.
- These include the β-gene, the γ-genes, the δ-gene, and the ε-gene (epsilon-gene). the ε-gene, like the ζ-gene, is expressed during embryonic life. It stops working by the end of the first 3 months of pregnancy, its function being gradually replaced by the γ - genes.
- Thus by the end of the first 3 months of pregnancy **HbF** is the major Hb in the blood of the fetus.



- *during the first 3 months of pregnancy: alpha, gamma and beta genes are turned off. Zeta and epsilon genes are turned on.*
- *After 3 months of pregnancy: alpha and gamma genes are turned on to encode for alpha and gamma chains → HbF*

α- thalassemia

- **Results from mutations in one or more of the 4 α- chain genes.**
- **The α- globin genes are duplicated (four) so one to four α- globin genes may be mutated:**

1-patients deficient in one α- globin gene are completely normal and are only carriers of α- thalassemia.

2- patients deficient in 2 α- globin genes are said to have α- thalassemia trait with mild anemia

3- patients deficient in 3 α- globin genes are said to have α- thalassemia major with sever anemia that is present since birth due to deficient formation of HbF.

4- patients deficient in the four α- globin genes are said to have homozygous α-thalassemia . They usually die soon after birth or in the uterus as HbF can not be synthesized we get hydrops fetalis.

- Homozygous alpha thalassemia → the fetus cannot produce HbF → die in the uterus (if survive in the uterus, die after birth)
- The fetus is anemic
- Hydrops fetalis: anemia causes heart failure leading to edema (ascites, pleural effusion, pericardial effusion…)

β - thalassemia

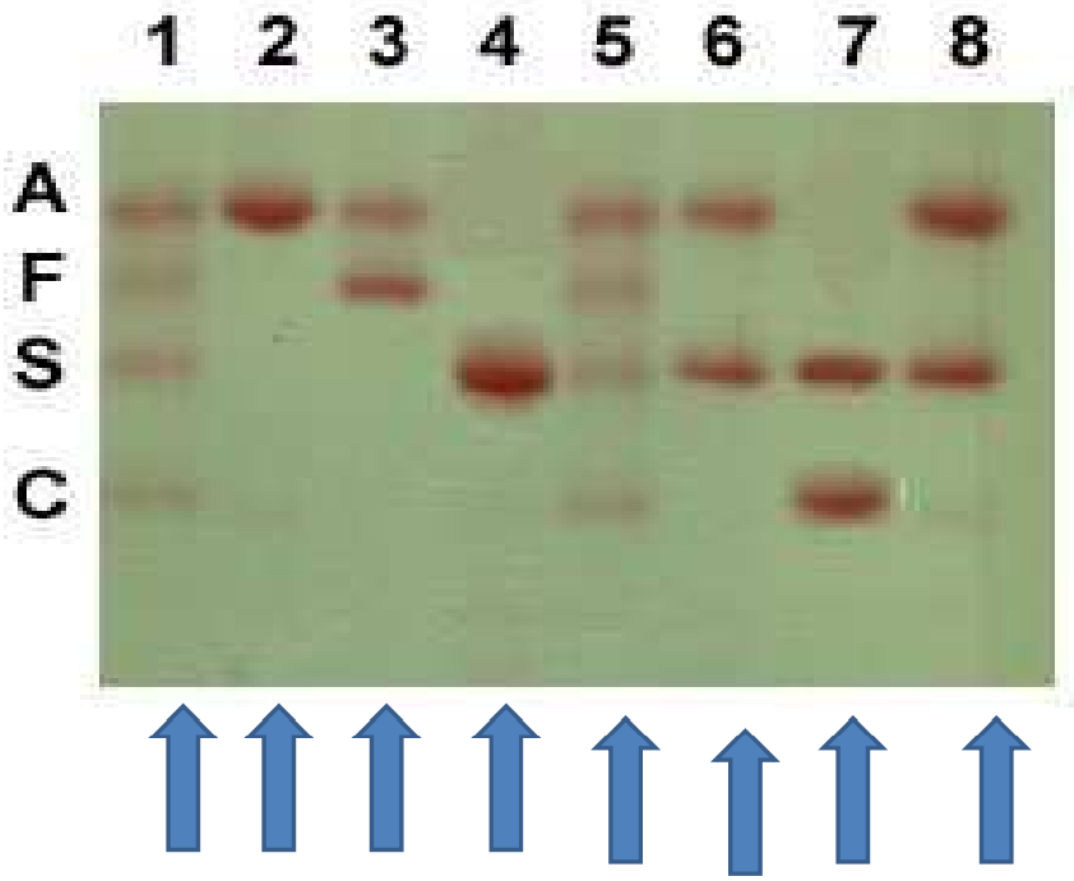
- **Results from mutations in one or the 2 β- chain genes.**
- **If only one gene is defective we get <u>β – thalassemia trait or β – thalassemia minor</u> with mild anemia**
- **If the 2 genes are defective we get <u>β – thalassemia major</u> with sever anemia. They rarely live to adulthood.**
- **The fetus appears normal at birth because HbF is formed at the normal rate.**

➢ *patients with beta thalassemia major need frequent blood transfusion which causes many problems.*

Normal and abnormal hemoglobins can be identified by electrophoresis:

The arrangement of hemoglobins , fastest to slowest , is A, F, S and C. HbA_2 runs with HbC

Hb electrophoresis

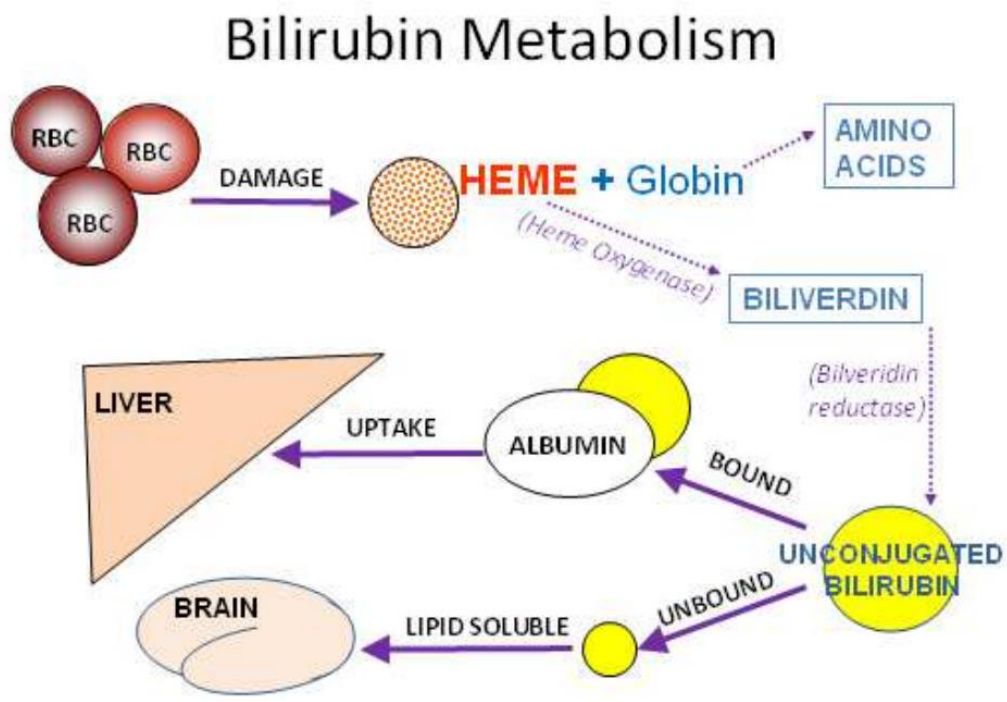


1) the marker
2) ز
3) Normal child
4) Homozygous sickle cell anemia
5) .
6) Heterozygous sickle cell anemia
7) ده غريب جدا
8) Heterozygous sickle cell anemia

Hemoglobin derivatives

- **Oxyhemoglobin: carries oxygen present in arterial blood.**
- **Reduced hemoglobin: present in venous blood.**
- **Carboxyhemoglobin: carries carbon monoxide which is toxic.**
- **Methemoglobin: can not carry oxygen because iron is present in ferric state.**

- **NADPH+H$^+$ resulting from HMP shunt keeps the iron of Hb in the ferrous state.**



- *After hemolysis, globin is hydrolyzed to amino acids (then reused), and heme is converted to biliverdin*
- *Biliverdin is converted to indirect bilirubin (unconjugated bilirubin)*
- *Indirect bilirubin may be conjugated with albumin → uptake by the liver → conjugation with glucuronic acid (detoxification) → excreted in bile*

- Or may remain free (unconjugated) → cross the blood brain barrier → if high levels of unbound bilirubin are present in the body, it causes mental retardation