

→⁴ polypeptides chain (2 α , 2 β)

Globular proteins

پروتینات کروہ

Hemeproteins

- Hemeproteins are group of specialized proteins that contains heme as tightly bound prosthetic group

مجموعات متضاهة للبروتين

- Function in

- Oxygen binding myoglobi
- Oxygen transport Hb
- Electron transport
- Photosynthesis
- catalyst enzymes

↳ cytochromes

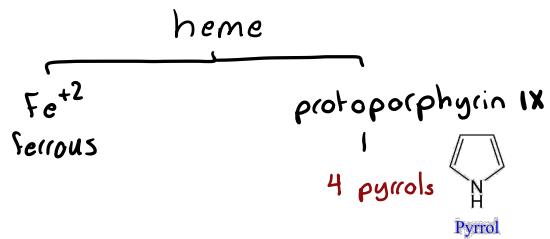
- The most abundant hemeproteins are Myoglobin and hemoglobin

O_2 reservoir
"storage"

Hb
carries O_2

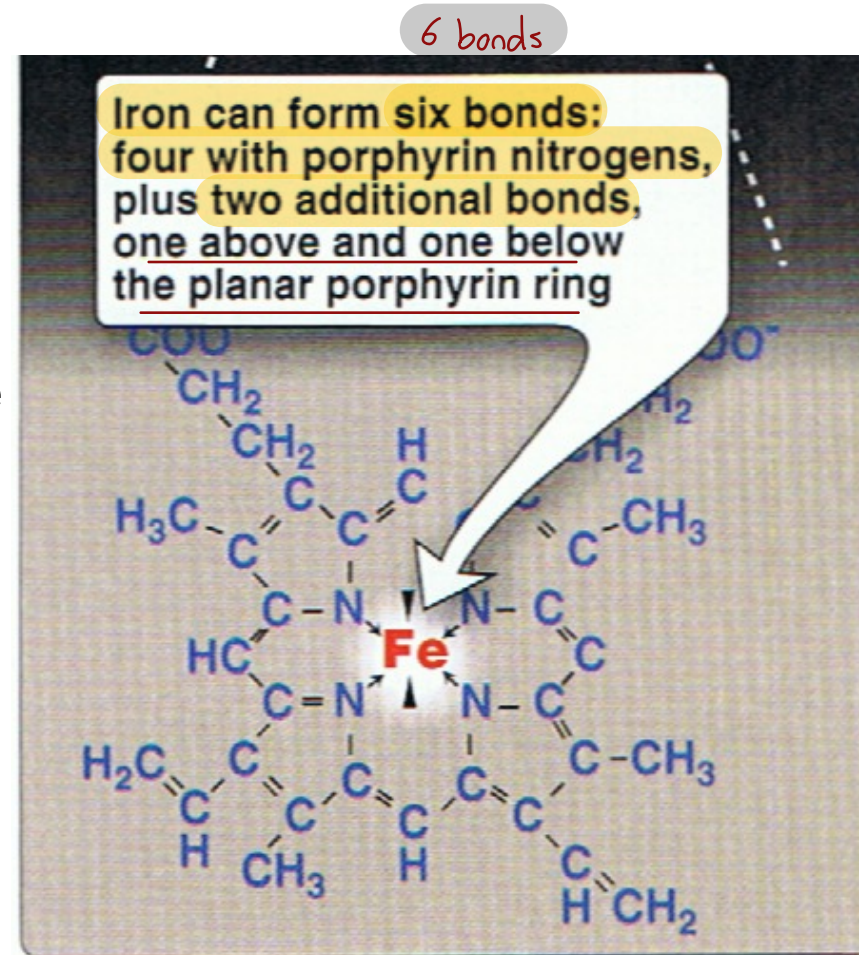
Which group of proteins do virtually all enzymes belong to?

- Globular
- Fibrous
- Structural
- Membrane



Structure of heme

- Function according to the protein it binds
- Heme is a complex of **protoporphyrin IX** and **ferrous iron (Fe⁺²)**. The iron is held in the center of the heme molecule by bonds to the four nitrogens of the porphyrin ring.
- The heme Fe⁺² can form two additional bonds, one on each side of the planar porphyrin, in myoglobin and hemoglobin, one of these positions is coordinated to the side chain of a histidine residue of the globin molecule whereas the other position is available to bind oxygen



ما يقدر ينقل O₂ Ferric لو تاكسد ل
 5 bonds Fe⁺³

1. Which statement about heme is correct?

A. Contains Fe^{3+} in functional hemoglobin

B. Iron binds 6 ligands total

C. Oxygen binds to proximal histidine

D. None of the choices

E. All of the choices

جلبت سؤال انه ال myoglobin يكون الحديد الي عليه Fe^{+3}

Fe^{+2}

Fe^{+4}

Fe^{+1}

Each haemoglobin molecule contains

- A) One iron atom
- B) Two iron atoms
- C) Four iron atoms
- D) Six iron atoms

ANSWER = C

EACH myoglobin molecule contains

- A) One iron atom
- B) Two iron atoms
- C) Four iron atoms
- D) Six iron atoms

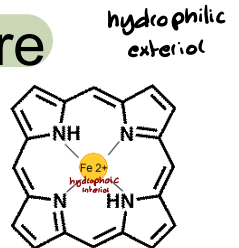
ANSWER = A

1 heme

Structure of myoglobin

- In heart and skeletal muscle
- Functions as ^①reservoir for oxygen and as ^②oxygen carrier to muscles
- Consists of single polypeptide that is structurally similar to hemoglobin subunit.

- Consist of eight α -helices which represent 80% of the structure which are ended by proline or β -bends stabilized by ionic and hydrogen bonding



- Polar and charged aa are present on the surface of the molecule which form hydrogen bonding with water

- with the exception of two histidines, nonpolar aa's form the interior structure

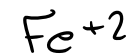
polar

interior aa's

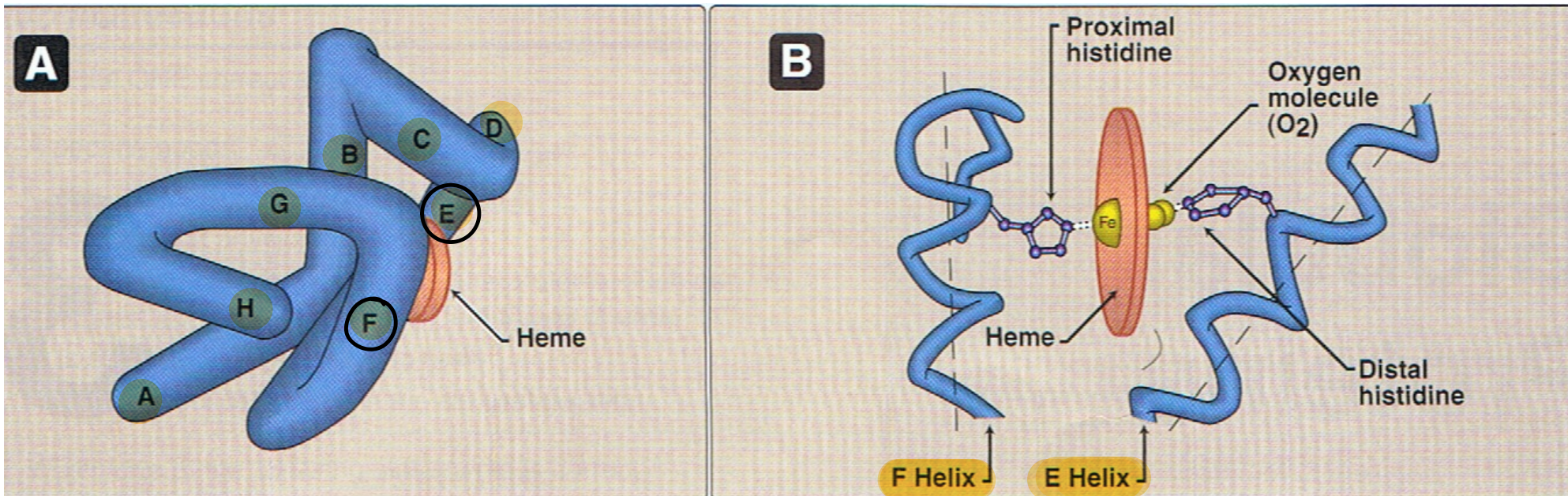
polar aa's

Binding of O₂ to myoglobin

➤ The proximal histidine binds the iron of the heme while the distal histidine helps to stabilize the binding of oxygen to the ferrous iron.



➤ The globin portion of myoglobin thus creates a special microenvironment for the heme that permits the reversible binding of one oxygen molecule (oxygenation).



3. The distal histidine function is:

A. Directly binds Fe^{2+}

B. Stabilizes oxygen binding

C. Breaks heme structure

D. All of the choices

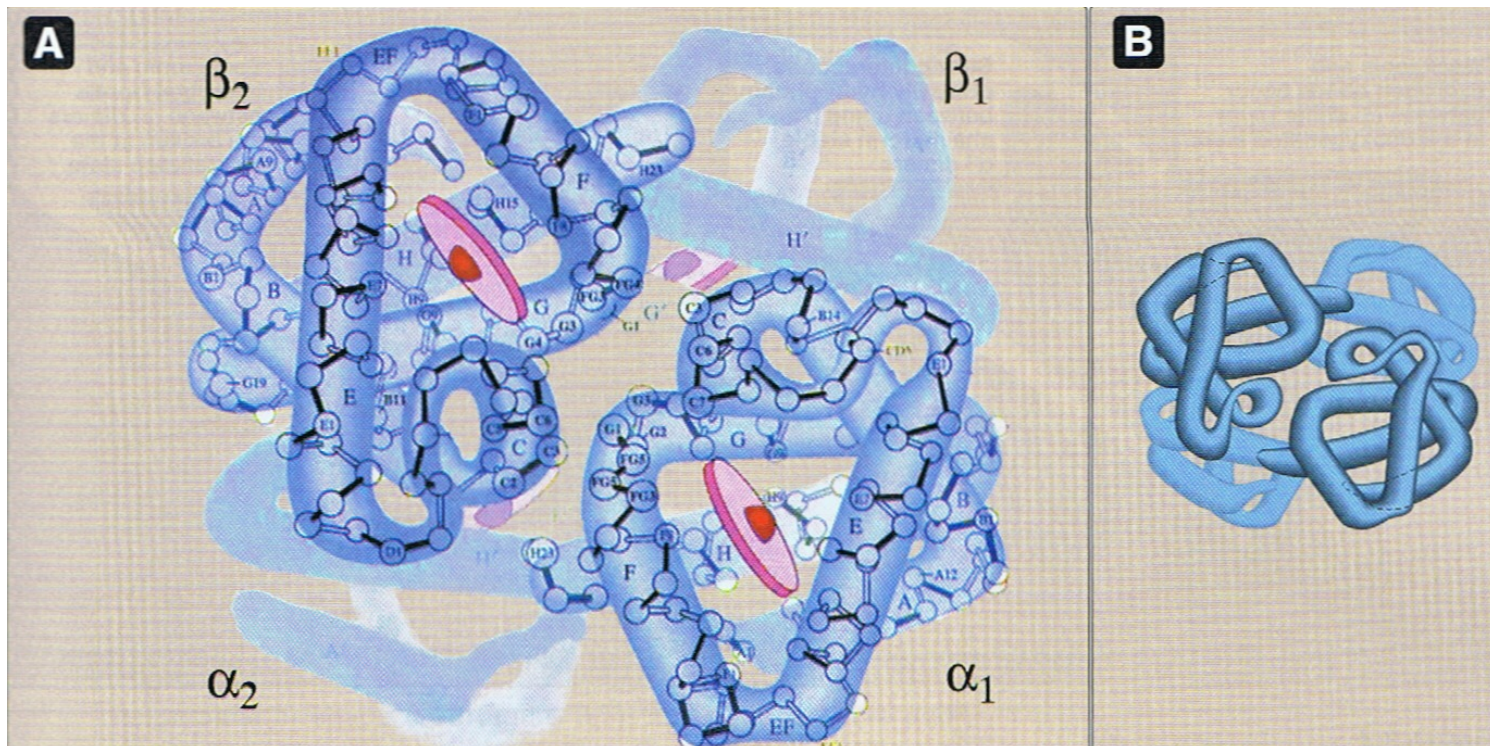
E. None of the choices

Hemoglobin

- In red blood cells RBCs
- Transport oxygen from lung to the capillaries of tissues as well as CO₂ in the reverse direction
- HbA ^{اختصار} A_{dult}, mainly in adults, composed of four polypeptide chains (2 α and 2 β) held together non-covalently
- Oxygen binding is regulated by interaction with allosteric effectors
- The subunits occupy different relative positions in deoxyhemoglobin compared with oxyhemoglobin

Structure of hemoglobin

- The hemoglobin tetramer composed of two identical dimers, ($\alpha\beta_1$) and ($\alpha\beta_2$). The two polypeptide chains within each dimer are held tightly together, primarily by hydrophobic interactions
- Interchain hydrophobic interactions form strong associations between α -subunits and β -subunits in the dimers, ionic and hydrogen bonds also occur between the members of the dimer.



How many heme groups are attached to four polypeptide chains in hemoglobin?

- A Two heme groups attached to two polypeptide chains
- B Three heme groups attached to three polypeptide chains
- C One heme group attached to four polypeptide chains
- D Four heme groups attached to four polypeptide chains

D

deoxy oxy
 T (taut) R (relaxed)
 O₂ Affinity ↓ O₂ Affinity ↑

W O₂ binds to Hb → Hb shift T → R
 low Affinity → high affinity

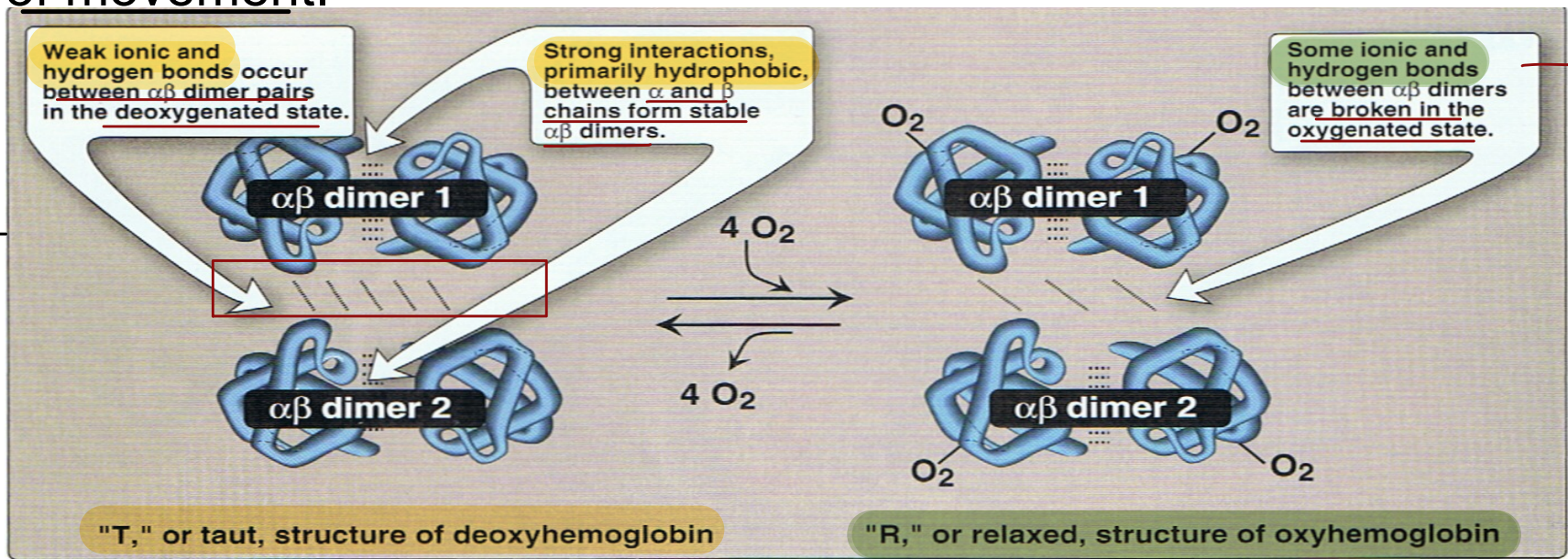
Hemoglobin

➤ The **deoxy form** of hemoglobin is called the **“T or taut (tense) form**, a constrained structure that limits the movement of the polypeptide chains, has a **low oxygen-affinity**.

➤ The binding of oxygen to hemoglobin **causes rupture of some of the ionic and hydrogen bonds**. This leads to a structure called the **‘R’ or relaxed form**, in which the polypeptide chains have more freedom of movement.

روابط ضعيفه
 between αβ
 dimers
 deoxy
 affinity ↓

روابط قويه
 between β / α
 chains



كانت
 ضعيفه
 some got broken

hemoglobin sigmoidal

myoglobin hyperbolic

Hemoglobin

- The R form is the high oxygen affinity form of hemoglobin.
- The oxygen-dissociation curve for hemoglobin is sigmoidal in shape (in contrast to that of myoglobin, which is hyperbolic), indicating that the subunits cooperate in binding oxygen.
- يُساعدوا بعضاً على الارتباط Cooperative binding of oxygen by the four subunits of hemoglobin means that the binding at one heme group increases the oxygen affinity.
- The steep slope of the oxygen-dissociation curve permits hemoglobin to carry and deliver oxygen efficiently from sites of high to sites of low pO₂.
- A molecule with a hyperbolic oxygen-dissociation curve could not achieve the same degree of oxygen release within this range of partial pressures of oxygen. Instead, it would have maximum affinity for oxygen throughout this oxygen pressure range and so would deliver no oxygen to the tissues. it would store it

Sigmoidal O₂-dissociation curve

steep

A small drop in pO₂ → large release of O₂

Hb

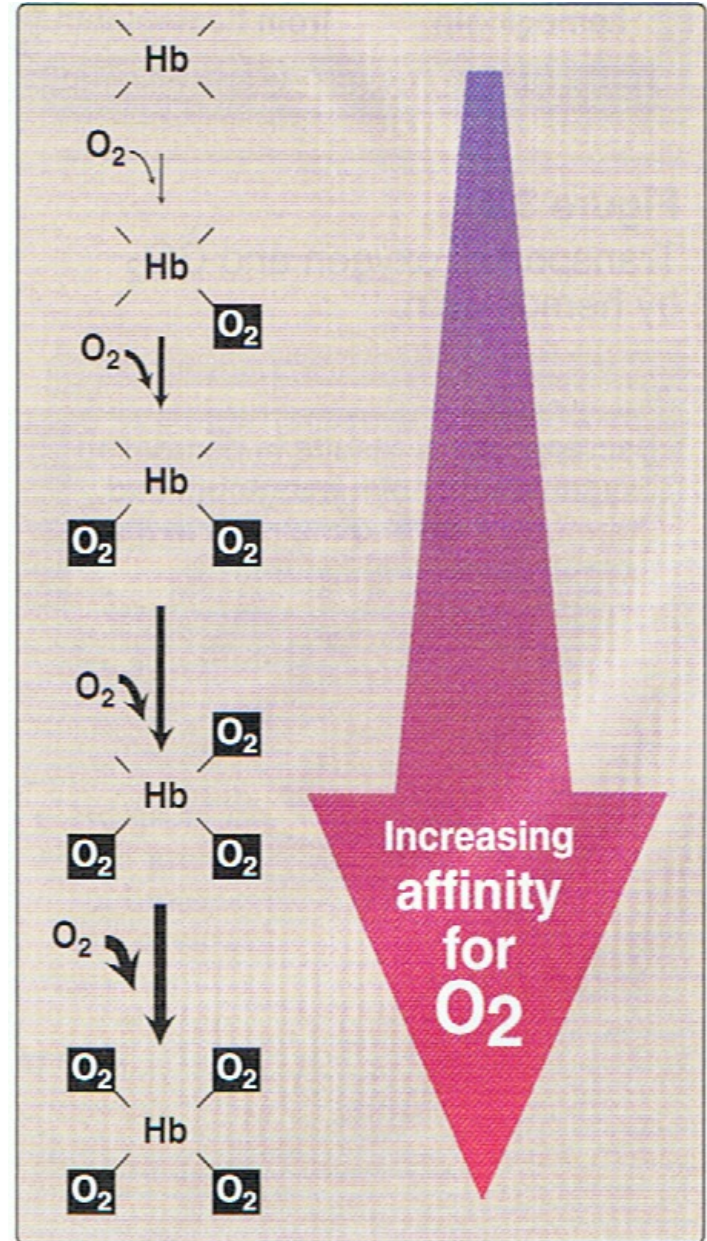
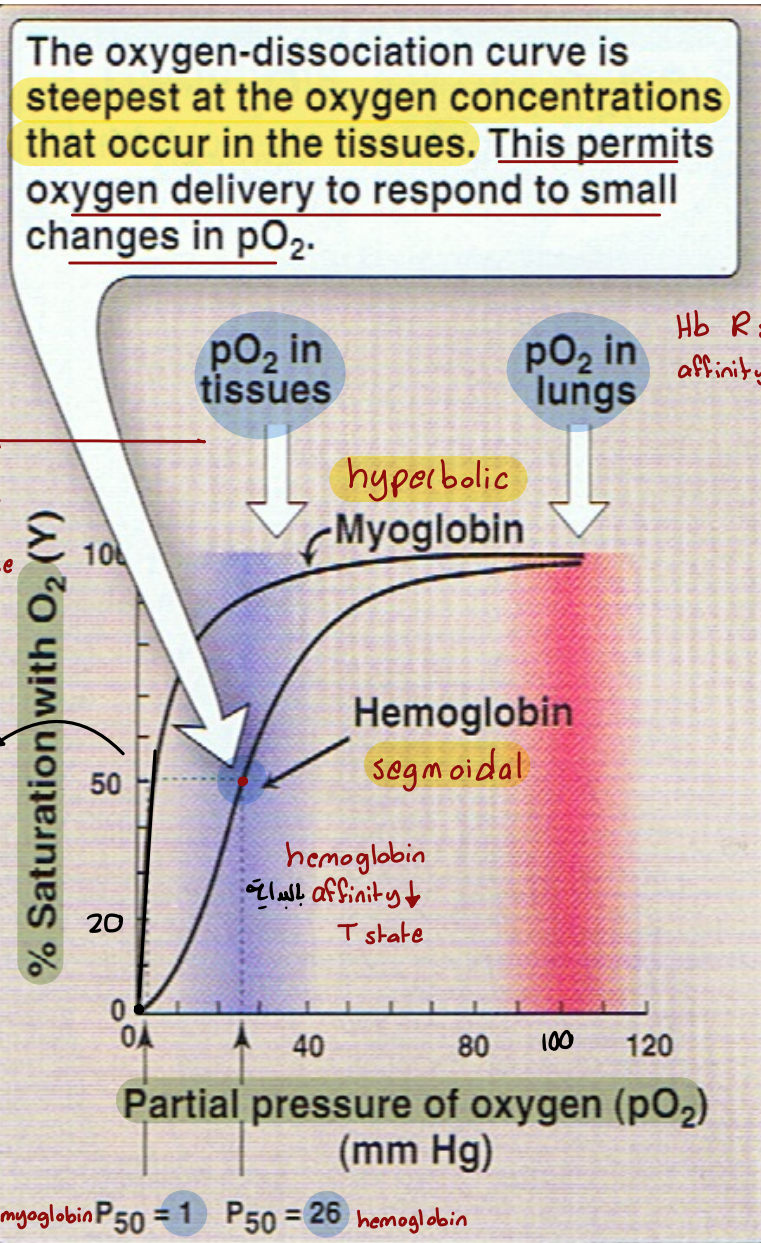
بمطابقة
tissues
المخى
حاد
عقبات اي
تغير بسيط
يوضر
للانسجة
بسرعة

The oxygen-dissociation curve is steepest at the oxygen concentrations that occur in the tissues. This permits oxygen delivery to respond to small changes in pO₂.

pO₂ in tissues pO₂ in lungs
Hb R state affinity ↑

myoglobin affinity ↑
No O₂ release

يوتج بسوية



2. Myoglobin differs from hemoglobin because it:

- A. Has quaternary structure
- B. Shows cooperative binding
- C. Has a hyperbolic curve
- D. Two of the choices
- E. None of the choices

C

5. Cooperative binding means:
- A. Subunits bind independently
 - B. Binding of one O_2 increases affinity of others
 - C. Hemoglobin binds only one O_2
 - D. None of the choices
 - E. All of the choices

In the binding of oxygen to myoglobin, the relationship between the concentration of oxygen and the fraction of binding sites occupied can best be described as:

- A) hyperbolic.
- B) linear with a negative slope.
- C) linear with a positive slope.
- D) random.
- E) sigmoidal

ANSWER = A

In hemoglobin, the transition from T state to R state (low to high affinity) is triggered by

- A) Fe²⁺ binding.
- B) heme binding
- C) oxygen binding
- D) subunit dissociation
- E) subunit association

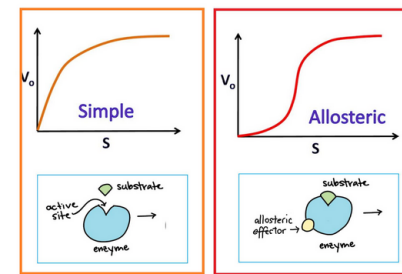
ANSWER = C

An allosteric effector is something that:

- Binds to hemoglobin at a site **OTHER than the oxygen-binding site**
- Changes hemoglobin's shape
- This either:
 - increases O₂ release (↓ affinity → right shift)
 - or increases O₂ binding (↑ affinity → left shift)

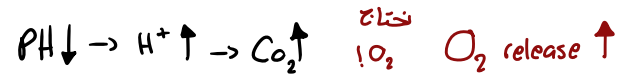


Allosteric effector



create some type of change

➤ ① The **pH of the environment** (the decrease in the pH enhances the release of O₂ from Hb)



➤ ② The **pCO₂** (increase in pCO₂ enhances the release of O₂ (Bohr effect))

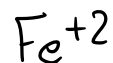
➤ ③ The availability of **2,3-bisphosphoglycerate**. **2,3-BPG** binds to the Hb and decreases its oxygen affinity and shifts the oxygen-dissociation curve to the right



➤ The oxygen-dissociation curve of Hb is shifted to the right to cope long-term with the effects of chronic hypoxia or anemia



➤ **Carbon monoxide (CO)** binds tightly (but reversibly) to the hemoglobin iron, forming carbon monoxyhemoglobin, HbCO.



Allosteric effectors increase O_2 release \uparrow
(affinity \downarrow)

- pH of the environment $pH \downarrow$
 $CO_2 \uparrow$ $\rightarrow O_2$ release \uparrow

- $PCO_2 \uparrow \rightarrow O_2$ release \uparrow

- 2,3-BPG $\uparrow \rightarrow O_2$ release \uparrow

- chronic hypoxia/anemia = body adopts

by increasing 2,3-BPG

- curve shifts to right

- Co binds tightly to Hb

(stronger than O_2)

= HbCo

- blocks O_2 binding sites

- Affinity \uparrow

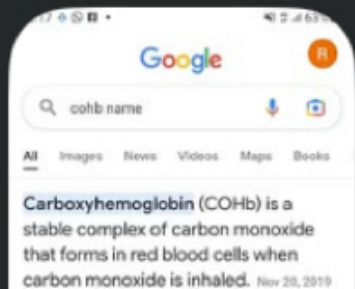
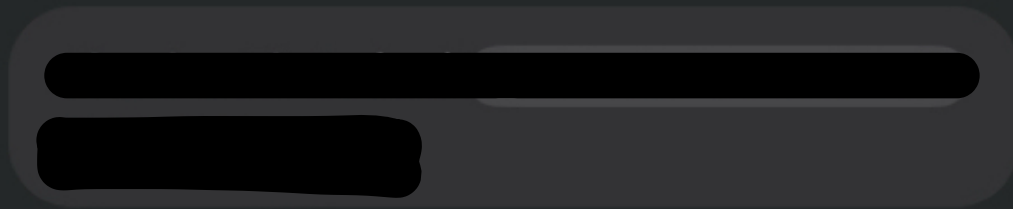
- O_2 release \downarrow

سؤال

Carboxyhemoglobin:

جوابه : CO2Hb

2y Like Reply



و سؤال اي نوع من allosteric effectores يقلل affinity of O2

O_2 release ↑

1y Like Reply

Effect of pH

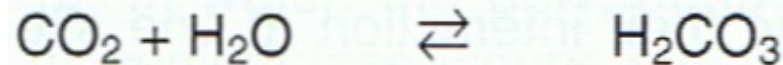
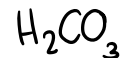


➤ Source of the protons that lower the pH:

➤ The concentration of both CO₂ and H⁺ in the capillaries of metabolically active tissues is higher than that observed in alveolar capillaries of the lungs, where CO₂ is released into the expired air.

➤ Organic acids, such as lactic acid, are produced during anaerobic metabolism in rapidly contracting muscle

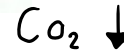
➤ In the tissues, CO₂ is converted by carbonic anhydrase to carbonic acid:



➤ which spontaneously loses a proton, becoming bicarbonate (the major blood buffer):



➤ This differential pH gradient (lungs having a higher pH, tissues a lower pH) favors the unloading of oxygen in the peripheral tissues, and the loading of oxygen in the lung which makes hemoglobin a more efficient transporter of oxygen.



O₂ release ↑

affinity ↓

↑

Acid = release of O_2
affinity ↓ T

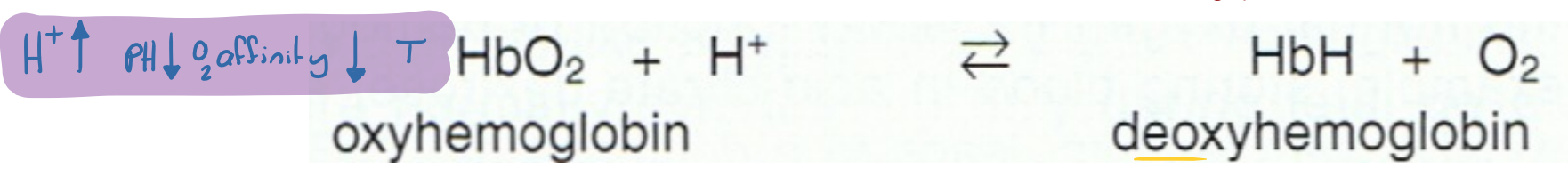
Effect of pH

Mechanism of the Bohr effect

O₂ affinity ↓ Taut *H⁺ affinity ↑*

➤ The Bohr effect reflects the fact that the deoxy form of hemoglobin has a greater affinity for protons than does oxyhemoglobin. This effect is caused by ionizable groups, such as the N-terminal α-amino groups, and specific histidine side chains that have higher pKas in deoxyhemoglobin than in oxyhemoglobin.

➤ Therefore, an increase in the concentration of protons (resulting in a decrease in pH) causes these groups to become protonated (charged) and able to form ionic bonds (also called salt bridges). These bonds preferentially stabilize the deoxy form of hemoglobin, producing a decrease in oxygen affinity. *affinity ↓*



➤ where an increase in protons (or a lower pO₂) shifts the equilibrium to the right (favoring deoxyhemoglobin), whereas an increase in pO₂ (or a decrease in protons) shifts the equilibrium to the left.

H⁺ ↓ pH ↑ shift to left
affinity ↑ R

7. Bohr effect is mainly due to:

A. CO binding

B. Proton binding to Hb

C. Iron oxidation

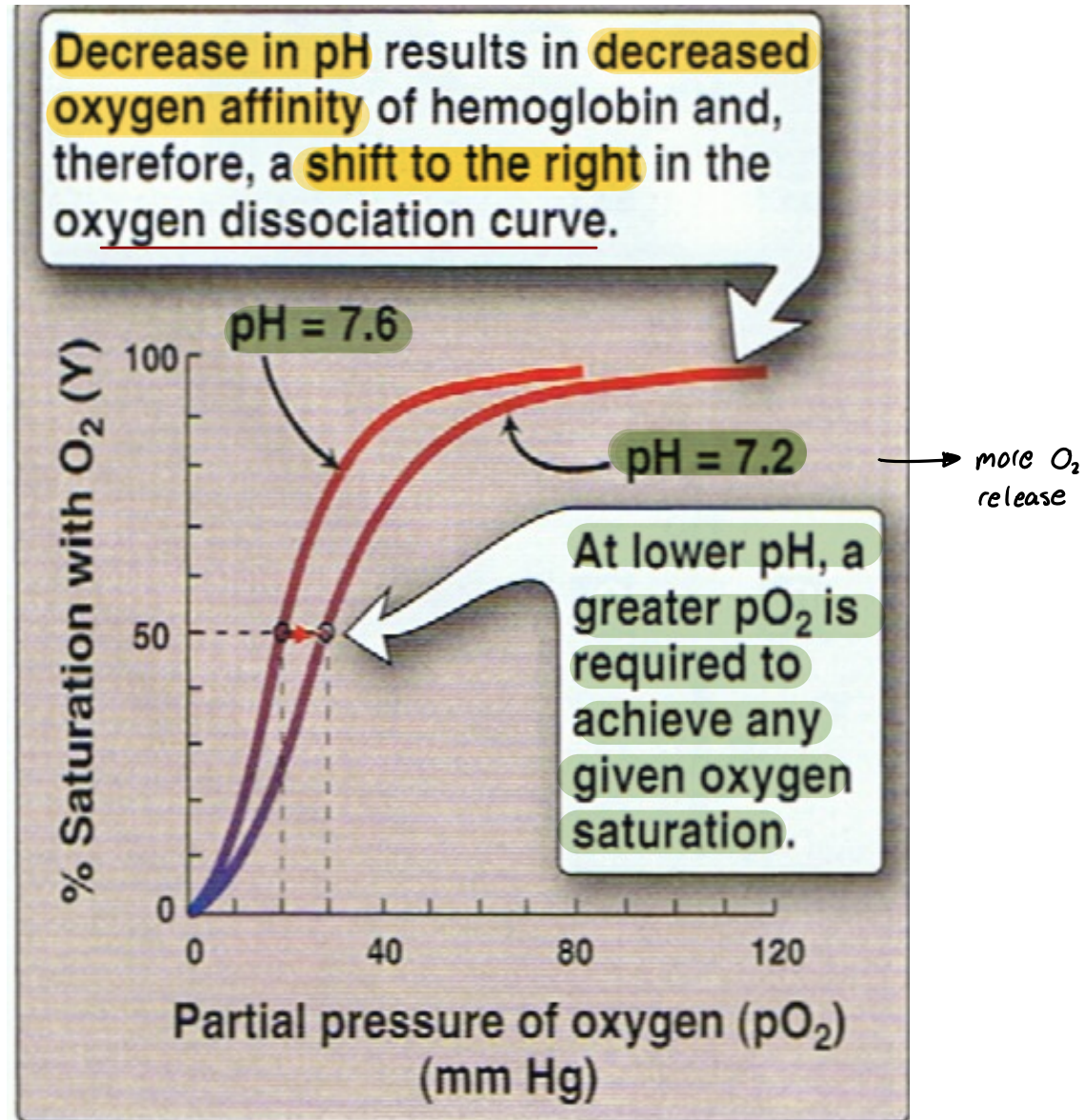
D. None of the choices

E. Two of the choices

affinity ↑ pH
فتحك O_2

Effect of pH

shift to the right → need more pO_2



4. The T form of hemoglobin:

A. High O₂ affinity

B. Stabilized by salt bridges

C. Found in lungs

D. Two of the choices

E. None of the choices

وسؤال ما عرفته عن dissociation curve
من الخيارات كأنه

HbA1 ,pH =7,6

CO₂ bind to Hb

Afinity ↓ T

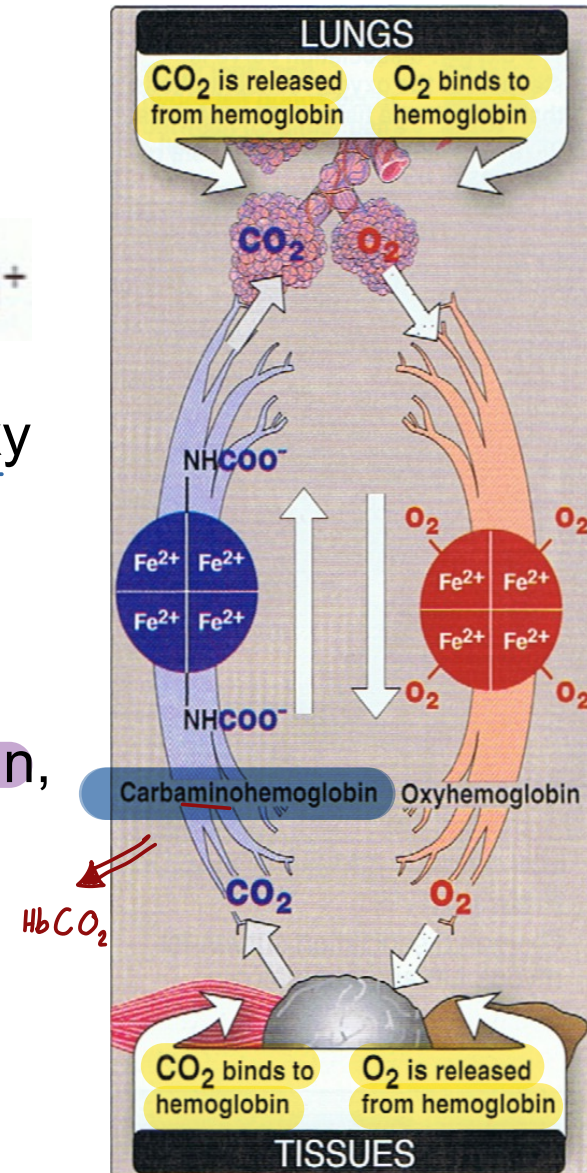
O₂ release ↑

Effect of CO₂

- some CO₂ is carried as **carbamate** bound to the uncharged α-amino groups of hemoglobin (**carbamino-hemoglobin**)



- The binding of CO₂ stabilizes the T (taut) or deoxy form of hemoglobin, resulting in a decrease in its affinity for oxygen.
- In the lungs, CO₂ dissociates from the hemoglobin, and is released in the breath.



After releasing O₂ at the tissues, hemoglobin transports

- A) CO₂ and protons to the lungs
- B) O₂ to the lungs
- C) CO₂ and protons to the tissue
- D) Nutrients

ANSWER = A

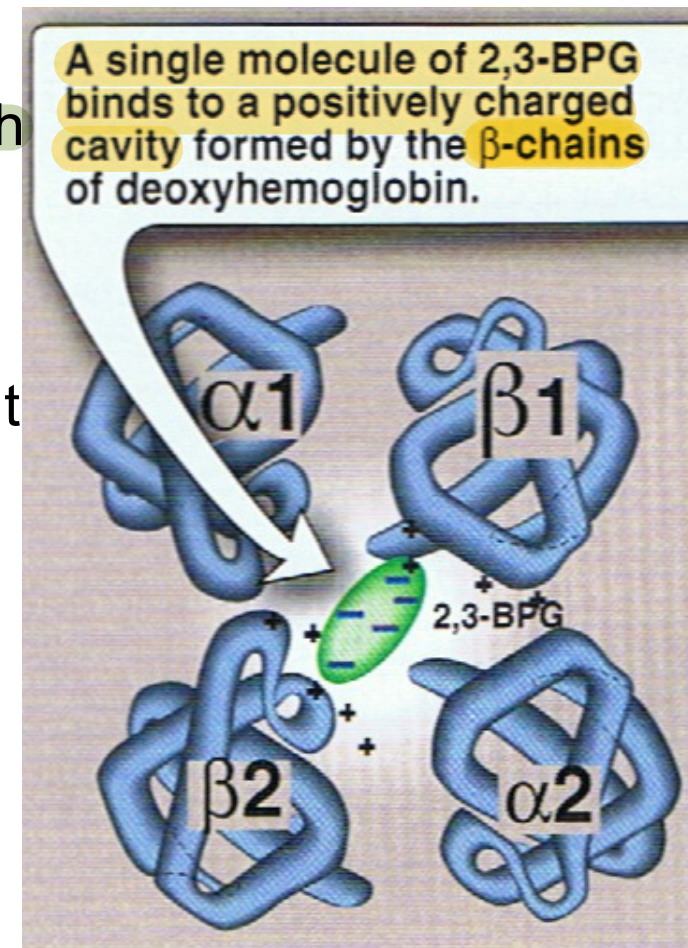
30. Carbaminohemoglobin forms when:

- A. CO₂ binds iron
- B. CO₂ binds amino groups
- C. CO₂ binds heme
- D. None of the choices
- E. All of the choices



Effect of 2,3-BPG

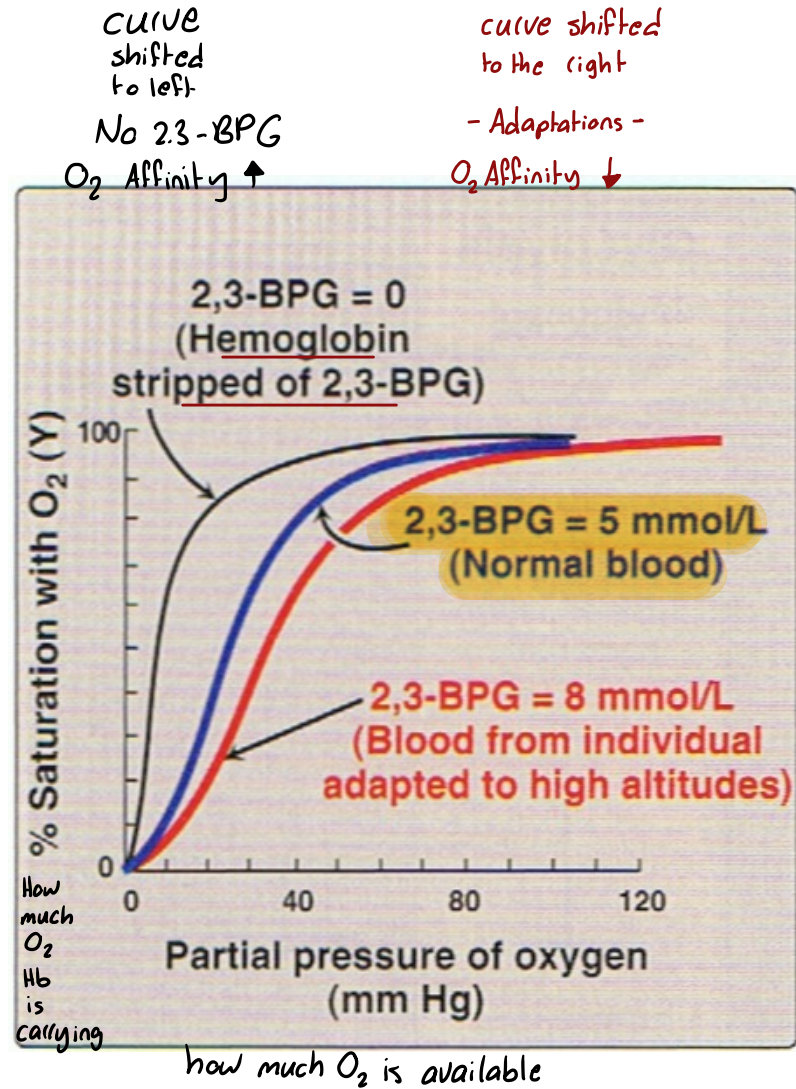
- One molecule of 2,3-BPG binds to a pocket, formed by the two β -globin chains, in the center of the deoxyhemoglobin tetramer.
- This pocket contains several positively charged amino acids that form ionic bonds with the negatively charged phosphate groups of 2,3-BPG.
- A mutation of one of these residues can result in hemoglobin variants with abnormally high oxygen affinity.
- 2,3-BPG is ^{Je}expelled on oxygenation of the hemoglobin.



Effect of 2,3-BPG

- In RBC's, the presence of 2,3- BPG significantly reduces the affinity of hemoglobin for oxygen, shifting the oxygen-dissociation curve to the right.
- This reduced affinity enables hemoglobin to release oxygen efficiently at the partial pressures found in the tissues.
- The concentration of 2,3-BPG in the red blood cell increases in response to chronic hypoxia (obstructive pulmonary emphysema, or at high altitudes), where circulating hemoglobin may have difficulty receiving sufficient oxygen

2,3 - BPG conc ↑ 8 - chronic hypoxia
 - obstructive pulmonary emphysema
 - high altitudes



9. 2,3-BPG binds:

A. Oxyhemoglobin

B. Deoxyhemoglobin

C. α chains

D. None of the choices

E. Two of the choices

B

14. Absence of 2,3-BPG causes:

A. Right shift

B. Left shift

C. No change

D. Two of the choices

E. None of the choices

B

2,3-BPG in transfused blood

- storing blood in acid-citrate-dextrose, leads to a decrease of 2,3-BPG in the red cells. Such blood displays an abnormally high oxygen affinity, and fails to unload its bound oxygen properly in the tissues. Hemoglobin deficient in 2,3-BPG thus acts as an oxygen “trap” rather than as an oxygen transport system. ✓
- Transfused red blood cells are able to restore their depleted supplies of 2,3-BPG in 24 to 48 hours. However, severely ill patients may be seriously compromised if transfused with large quantities of such 2,3-BPG-”stripped” blood. The decrease in 2,3-BPG can be prevented by adding substrates such as inosine to the storage medium.
- Inosine, an uncharged molecule, can enter the red blood cell, where its ribose moiety is released, phosphorylated, and enters the hexose monophosphate pathway eventually being converted to 2,3-BPG.

[1] Inosine (uncharged) enters the RBC

[2] It provides ribose

[3] Ribose is phosphorylated

[4] enter (hexose monophosphate pathway)

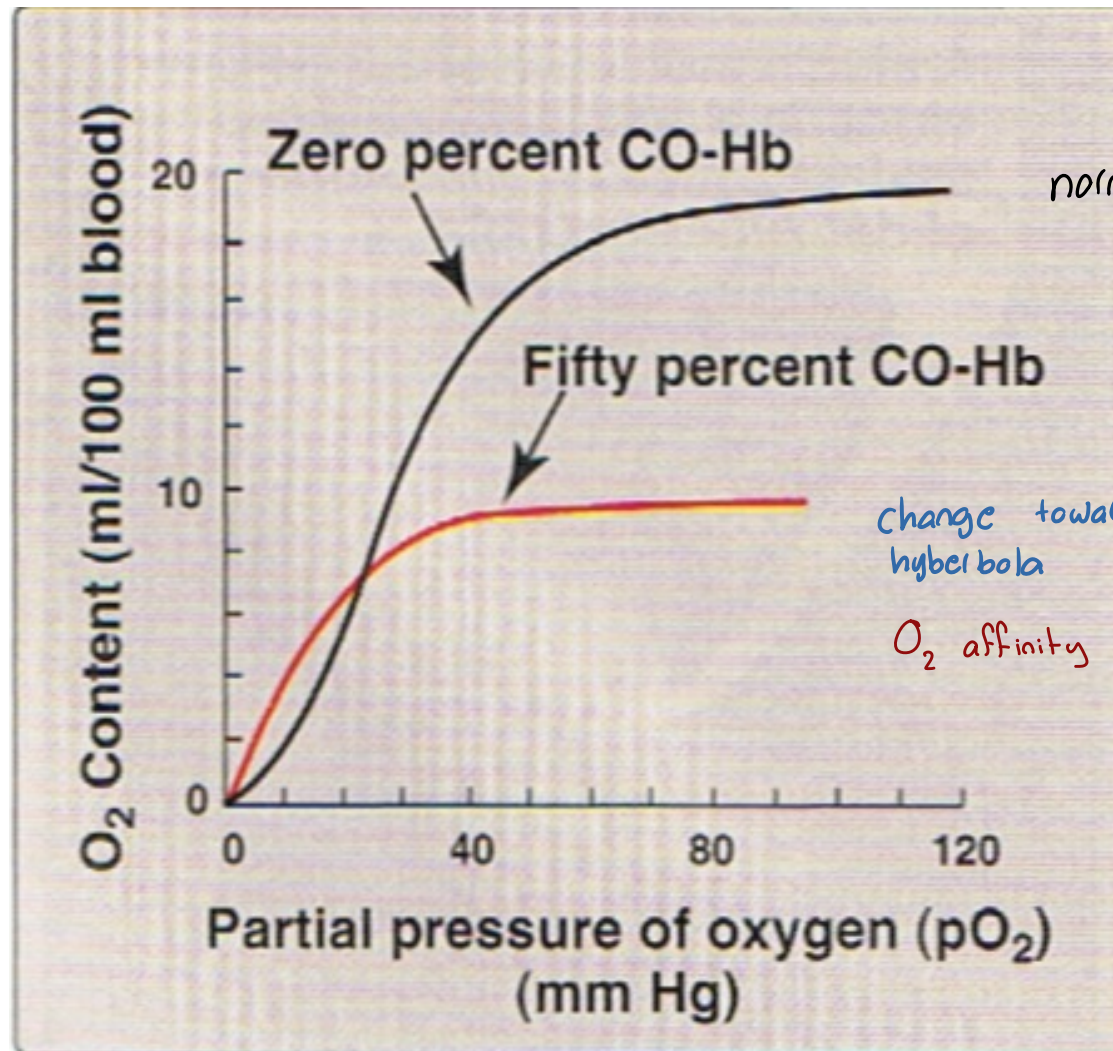
[5] converted to 2,3-BPG

Binding of CO

O₂ Affinity ↑

- Carbon monoxide (CO) binds tightly (but reversibly) to the hemoglobin iron (HbCO) with affinity 220 times more than O₂.
- When carbon monoxide binds to one or more of the four heme sites, hemoglobin shifts to the relaxed conformation^R, causing the remaining heme sites to bind oxygen with high affinity.
- This shifts the oxygen saturation curve to the left, and changes the normal sigmoidal shape toward a hyperbola makes hemoglobin unable to release oxygen to the tissues
- Carbon monoxide toxicity appears to result from a combination of tissue hypoxia and direct CO-mediated damage at the cellular level which is treated with 100 percent oxygen therapy (facilitates the dissociation of CO from the hemoglobin).

Effect of CO



normal sigmoidal shape

change towards hyperbola

O₂ affinity ↑

6. Which shifts curve to the RIGHT?

A. ↓ pH

B. ↑ CO₂

C. ↑ 2,3-BPG

D. All of the choices

E. None of the choices

D

8. CO poisoning causes:

A. Left shift

B. Increased O₂ release

C. Hyperbolic-like curve

D. Two of the choices

E. None of the choices

D

12. Right shift graph indicates:

- A. Increased affinity
- B. Decreased O₂ release
- C. Decreased affinity
- D. Two of the choices
- E. None of the choices

C

اجا سوأل

myoglobin Affinity ↑

اي واحد من الآتي ما يكون شكلة hyperbolic

جوابه OHb with increase number of 2,3BPG

13. CO effect on graph:

Code

```
Shift ← Left + curve becomes more hyperbolic
```

This means:

- A. Better oxygen delivery
- B. Poor tissue oxygenation
- C. Increased unloading
- D. None of the choices
- E. Two of the choices

Minor Hemoglobins

Setus

➤ **HbF:** in infants

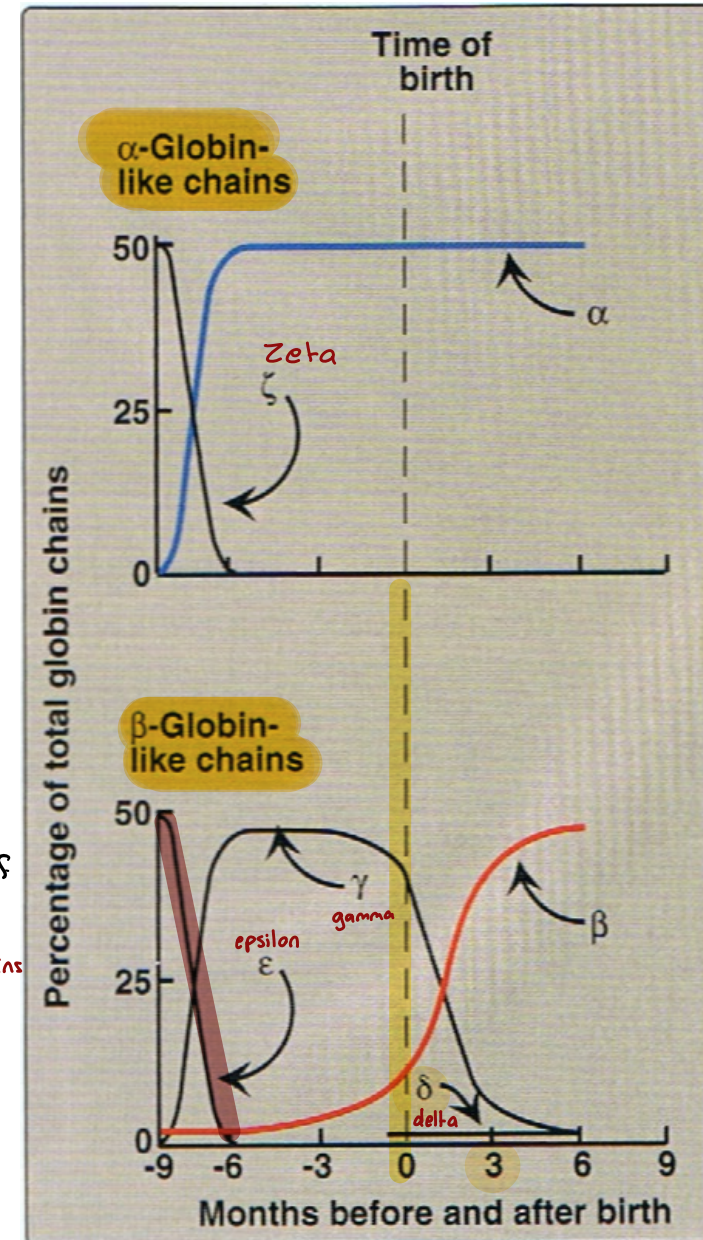
3 months

➤ **HbA2:** 12 weeks after birth

➤ **HbA1c:** under unphysiologic conditions
(glycosylated)

Form	Chain composition	Fraction of total hemoglobin
HbA <i>normal</i>	$\alpha_2\beta_2$	90%
HbF	$\alpha_2\gamma_2$ <i>gamma</i>	<2%
HbA ₂	$\alpha_2\delta_2$ <i>delta</i>	2-5%
HbA _{1c}	$\alpha_2\beta_2$ -glucose	3-9%

$\zeta_2\epsilon_2$ **golvel 1**
First 3 months of conception
2 zeta chains 2 epsilon chains



ال HBF عبارة عن

2 alpha 2 gama

جابت كيرف وكاتبه هاد shift to the left فشو

O_2 affinity ↑

الصح؟

كانت

O_2 affinity ↑

1) Hbf for o2

2) HbA1 for o2 when shifted to left O_2 affinity ↑

3) co

O_2 affinity ↑

4) اشي without 2,3- BPG

5) all of the above وطبعاً هاد الجواب O_2 affinity ↑

α_2 δ_2

صيغة hba2

HbF O_2 affinity is higher than HbA

↳ HbF doesn't bind well to 2,3-BPG

عند الولادة O_2 عند 0
HbF $\alpha_2 \gamma_2$
HbA $\alpha_2 \beta_2$

After 6 months
mainly HbA
 $\alpha_2 \beta_2$

Fetal hemoglobin (HbF)

(hyperbolic)
curve

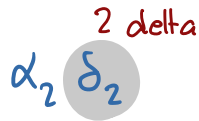
$\alpha_2 \gamma_2$

- HbF is a tetramer consisting of two α chains identical to those found in HbA, plus two gamma (γ) chains ($\alpha\gamma_2$). The γ chains are members of the globin gene family
- HbF synthesis during development: In the first few weeks after conception, embryonic hemoglobin composed of two zeta chains and two epsilon chains ($\zeta_2\epsilon_2$), is synthesized by the embryonic yolk sac.
- Within a few weeks, the fetal liver begins to synthesize HbF in the developing bone marrow. HbF is the major hemoglobin found in the fetus and newborn, accounts for about 60% of the total Hb in the erythrocytes during the last months of fetal life.
- HbA synthesis starts in the bone marrow at about the eighth month of pregnancy and gradually replaces HbF
- Under physiologic conditions, HbF has a higher affinity for oxygen than does HbA, so HbF's binding only weakly to 2,3-BPG.
- In contrast, if both HbA and HbF are stripped of their 2,3-BPG, they then have a similar affinity for oxygen. The higher oxygen affinity of HbF facilitates the transfer of oxygen from the maternal circulation across the placenta to the red blood cells of the fetus.



الأم

- HbF = high O₂ affinity
- Reason = weak binding to 2,3-BPG
- Purpose = helps fetus "steal" oxygen from mother



Hemoglobin A2 (HbA2)

appear after 3 months of birth

- HbA2 is a minor component of normal adult hemoglobin, first appearing about twelve weeks after birth and, ultimately, constituting about two percent of the total hemoglobin.

2%

- It is composed of two α -globin chains and two delta- (δ) globin chains ($\alpha_2\delta_2$)

28. HbF advantage in fetus:

A. Lower affinity

B. Competes poorly with maternal Hb

C. Extracts oxygen from mother

D. None of the choices

E. Two of the choices

C

15. Match correctly:

Column A

Column B

1. Myoglobin | A. Cooperative binding
2. Hemoglobin | B. Oxygen storage
3. HbF | C. Weak 2,3-BPG binding

Options:

- A. 1-B, 2-A, 3-C
- B. 1-A, 2-B, 3-C
- C. 1-B, 2-C, 3-A
- D. None of the choices
- E. All of the choices

10. HbF has higher affinity because:

A. Stronger 2,3-BPG binding

B. Weaker 2,3-BPG binding

C. More β chains

D. None of the choices

E. All of the choices

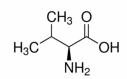
B

Hemoglobin A1c

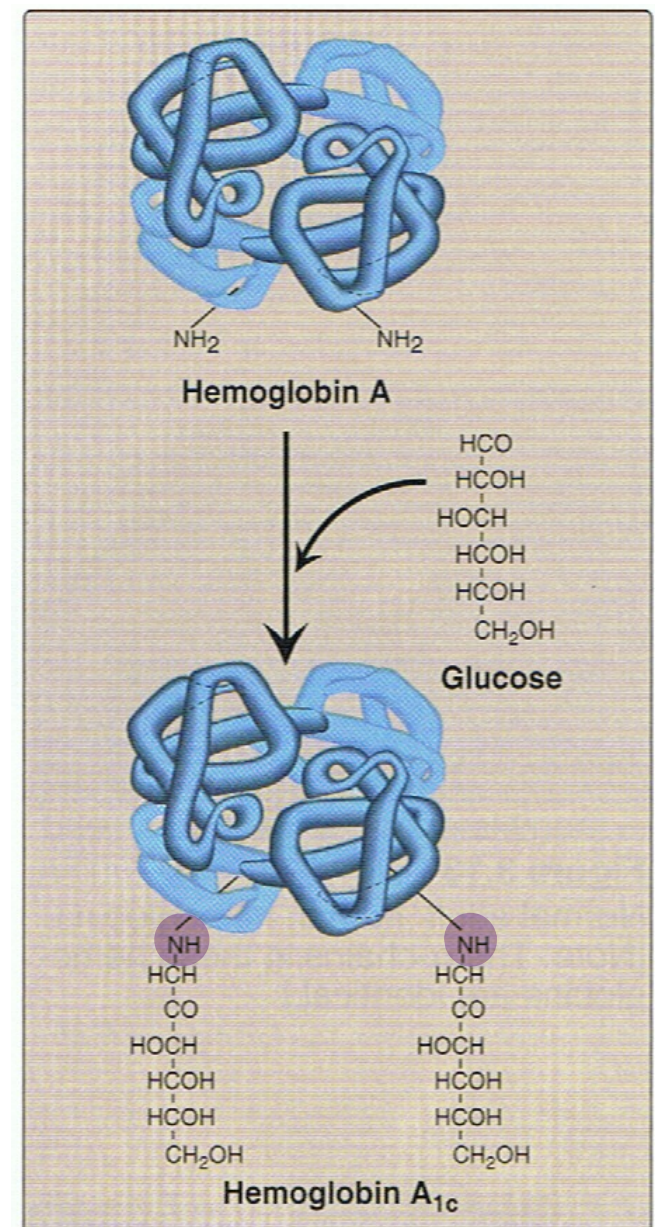
$\alpha_2 \beta_2$ -glucose

➤ Under physiologic conditions, HbA is slowly and nonenzymatically glycosylated, the extent of glycosylation being dependent on the plasma concentration of a particular hexose. The most abundant form of glycosylated hemoglobin is HbA1.

➤ It has glucose residues attached predominantly to the NH₂ groups of the N-terminal valines of the β -globin chains



➤ HbA1c are found in red blood cells of patients with diabetes mellitus



23. HbA1c indicates:

A. Oxygen affinity

B. Blood glucose levels

C. Iron levels

D. None of the choices

E. All of the choices

B

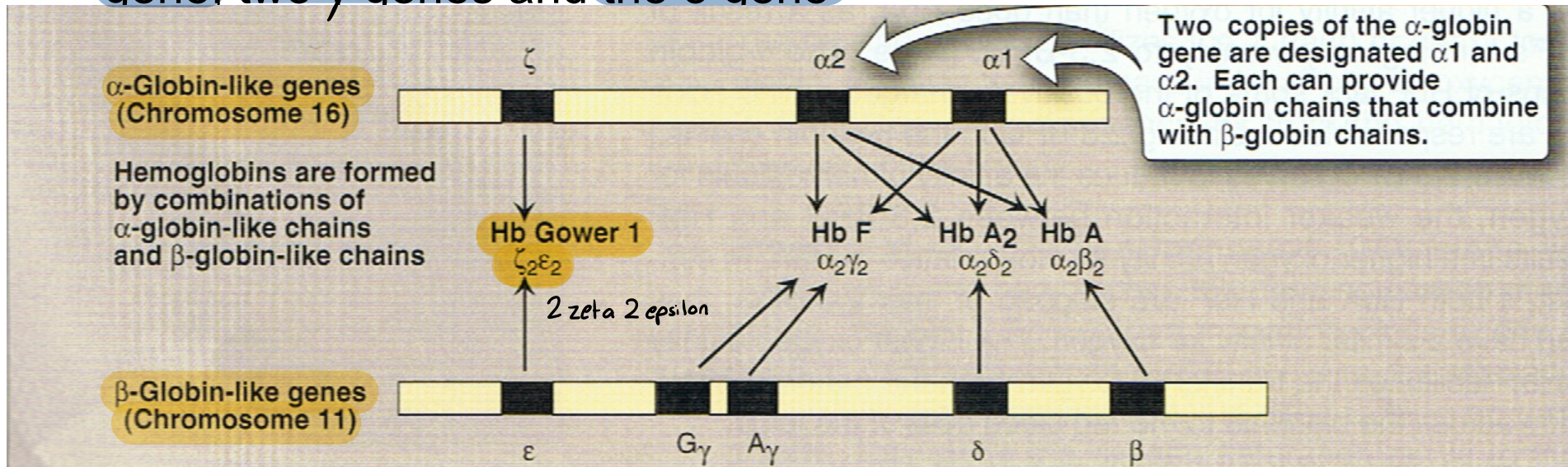
كان في سؤال عن Ha1C لأي مرض

Diabetes

Organization of the globin genes

Gene family

- The genes coding for the α -globin-like and β -globin-like subunits of the hemoglobin chains occur in two separate gene clusters (or families) located on two different chromosomes
- The α -gene cluster on chromosome 16 contains two genes for the α -globin chains. It also contains the zeta (ζ) gene *2 mum 2 dad*
- *1 mum 1 dad* A single gene for the β -globin chain is located on chromosome 11. There are an additional four β -globin-like genes: the epsilon (ϵ) gene, two γ genes and the δ gene



◆ A. α -like gene family (Chromosome 16)

Contains genes that produce alpha-type chains:

- α (alpha) → used in fetal + adult Hb
- ζ (zeta) → used in embryonic Hb only

👉 Important detail:

- There are 2 α genes ($\alpha 1$ and $\alpha 2$) → this increases α -chain production (important for balance)

◆ B. β -like gene family (Chromosome 11)

Contains genes that produce **beta-type chains**:

- ϵ (epsilon) → embryonic stage
- γ (gamma) → fetal stage (HbF)
- δ (delta) → minor adult Hb
- β (beta) → main adult Hb (HbA)

Steps in globin chain synthesis

- Expression of a globin gene **begins in the nucleus** of red cell precursors, where the DNA sequence encoding the gene is transcribed. RBC
- The RNA produced by transcription is actually a precursor of the messenger RNA (mRNA) that is used as a template for the synthesis of a globin chain.
- Before it can serve this function, **two noncoding stretches of RNA (introns) must be removed from the mRNA precursor sequence**, and the remaining three fragments (exons) reattached in a linear manner
- The resulting **mature mRNA** enters the cytosol, where its genetic information is translated, producing a globin chain

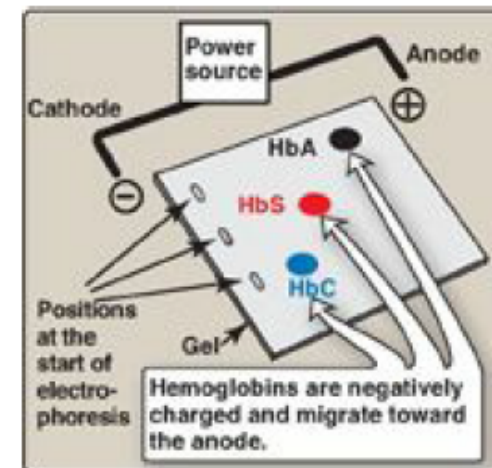
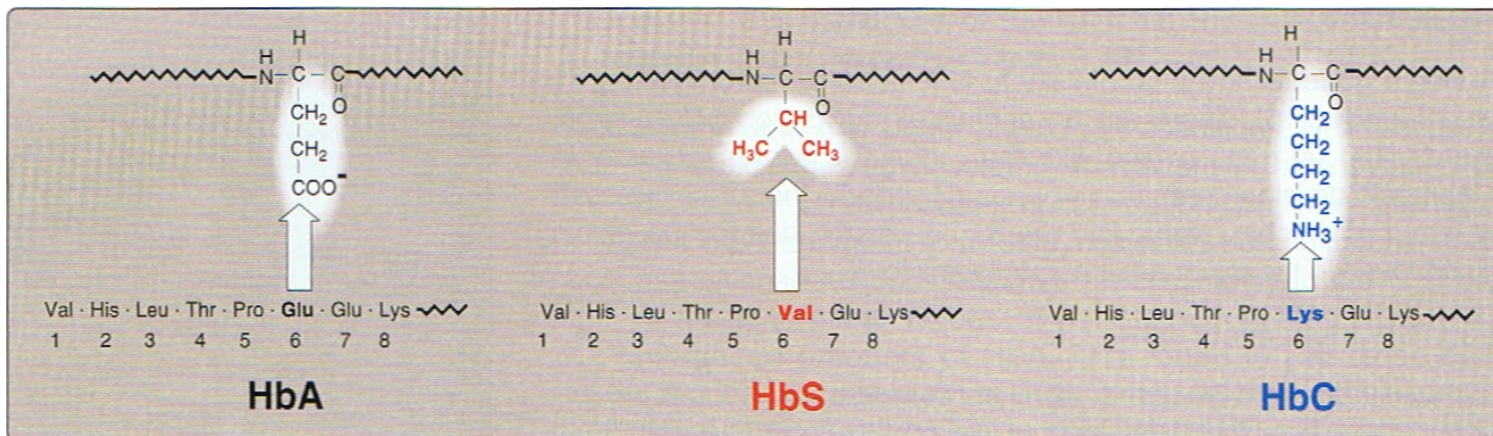
genetic disorders

hemoglobinopathies

- Hemoglobinopathies are disorders caused by:
- Production of a structurally abnormal hemoglobin molecule
- Synthesis of insufficient quantities of normal hemoglobin subunits
- or, rarely, both.

Examples:

- Sickle cell disease (HbS disease) point mutation in β chain (E6V) *glutamic acid* → *valine*
- hemoglobin C disease (HbC disease) mutation in β chain (E6K) *glutamic acid* → *lysine*
- thalassemia syndromes (α and β thalassemia)
- methemoglobinemia



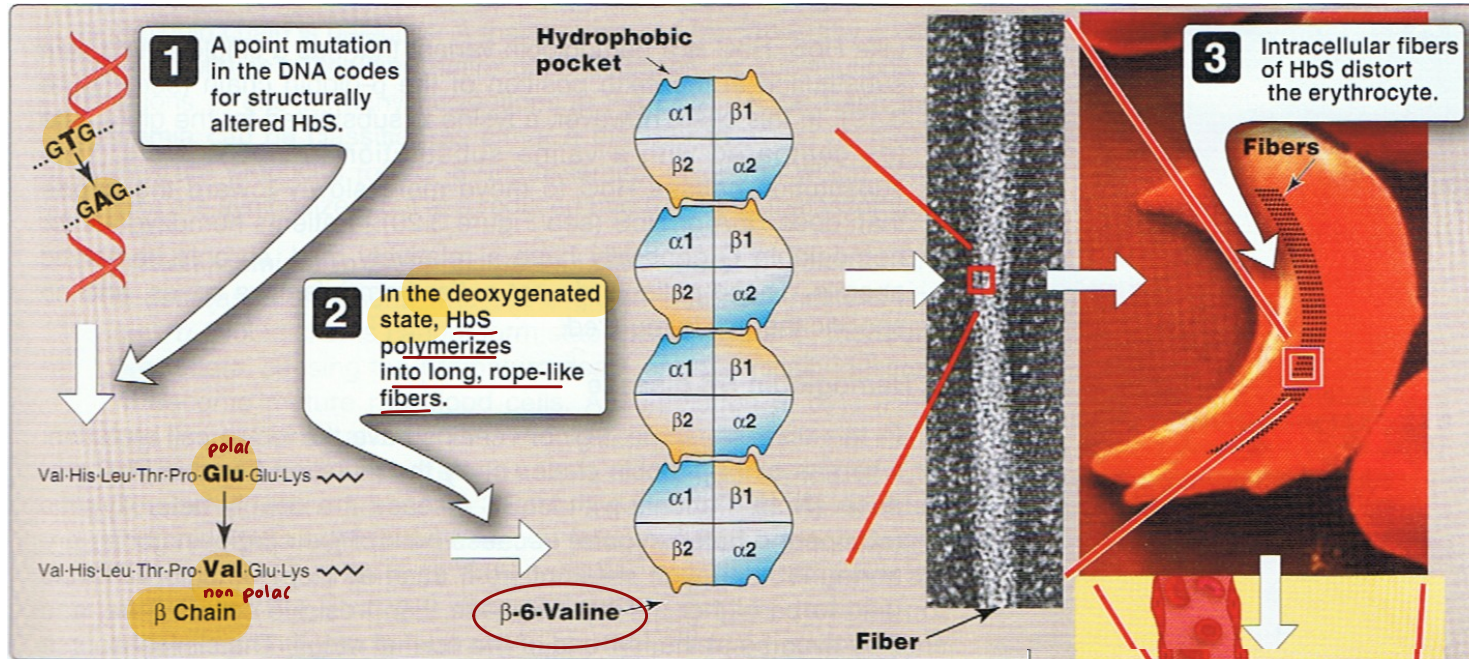


Sickle cell anemia

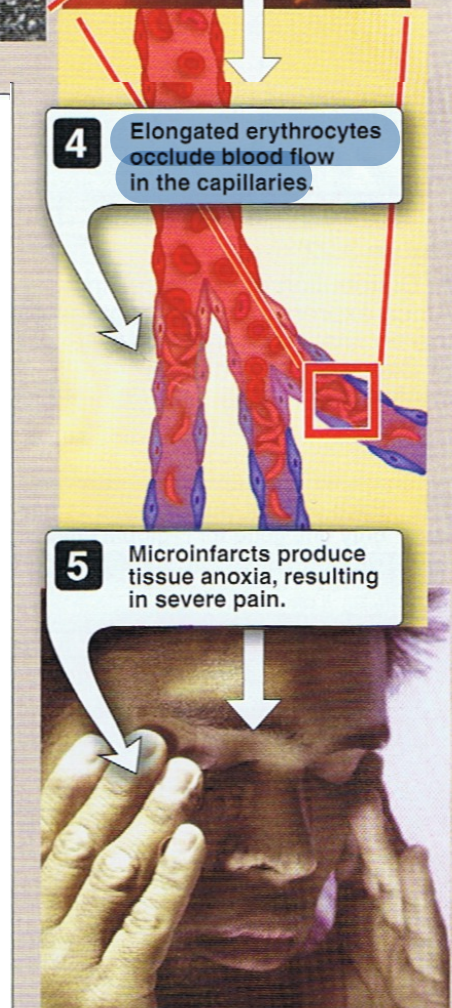
- The substitution of the nonpolar valine for a charged glutamate residue forms a protrusion on the β -globin
- At low oxygen tension, HbS polymerizes inside the red blood cells, first forming a gel, which assembled later to fibrous polymers producing rigid, misshapen erythrocytes. RBCs
- Sickled cells block the flow of blood in the narrow capillaries leading to localized anoxia (oxygen deprivation) in the tissue, causing pain and eventually death (infarction) of cells in the vicinity of the blockage.

حجرات

حجرات



- 1 mutation in DNA (E6V)
- 2 low O_2 (Hb sticks together)
HbS polymerizes into "long rope like fibers"
- 3 fibers deform the RBCs
RBCs becomes rigid + sickle-shaped
- 4 sickled cells block capillaries
Normal RBC = flexible → passes easily
Sickled RBC = rigid → gets stuck
- 5 Causes Anoxia (oxygen deprivation)
severe pain (crisis)



factors increase sickling

➤ Sickling and the severity of disease is enhanced by:

How much O_2 is available in environment/blood

➤ decreased (oxygen tension) as a result of high altitudes or flying in a nonpressurized plane *increase O_2 release bc tissues need O_2*

➤ increased pCO₂

) acidosis → O_2 release ↑

➤ decreased pH

➤ An increased concentration of 2,3-BPG in erythrocytes.

O_2 release ↑

Treatment

1. Adequate hydration
2. Analgesics *درد کشنده*
3. Aggressive antibiotic therapy if infection is present
4. transfusions in patients at high risk for fatal vasocclusions.
Intermittent transfusions with packed red cells reduce the risk of stroke
5. Hydroxyurea (an anti-^{تسر}tumor drug) decreases the frequency of painful crises and reduces mortality. The mechanism of action is not understood, but it may increase HbF that decreases sickling

O_2 Affinity ↑
oxyform

Sickle cell anemia


- The high frequency of the HbS gene among black Africans, despite its damaging effects in the homozygous state
- heterozygotes for the sickle cell gene are less susceptible to malaria, caused by the parasite *Plasmodium falciparum*.
- This organism spends an obligatory part of its life cycle in the red blood cell. Because these cells have a shorter life span than normal, the parasite cannot complete the intracellular stage of its development
- This fact may provide a selective advantage to heterozygotes living in regions where malaria is a major cause of death.

مُعرف

20. In sickle cell disease, mutation is:

- A. Glu → Val
- B. Val → Glu
- C. Glu → Lys
- D. None of the choices
- E. Two of the choices

A

21. Sickling increases with:  anything that increases
the deoxyform

- A. High O₂
- B. Low pH
- C. Low CO₂
- D. None of the choices
- E. Two of the choices

B

E6K

⁻
glutamic acid
polar

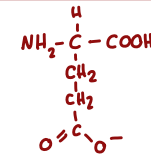
⁺
lysine
polar (Basic)

Hemoglobin C disease

➤ Like HbS, HbC is a hemoglobin variant that has a single amino acid substitution in the sixth position of the β -globin chain

➤ In this case, however, a lysine is substituted for the glutamate (as compared with a valine substitution in HbS)

ionized form of glutamic acid



➤ Patients homozygous for hemoglobin C generally have a relatively mild, chronic hemolytic anemia. These patients do not suffer from infarctive crises, and no specific therapy is required.

تحليل الدم

Hemoglobin SC disease

E6V

- In this disease, some β -globin chains have the sickle cell mutation, whereas other β -globin chains carry the mutation found in HbC disease

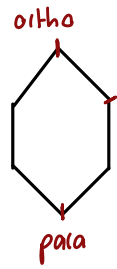
E6K

- Patients with HbSC disease have both of their β -globin genes abnormal, although different from each other
- Compared to sickle cell disease, hemoglobin levels tend to be higher in HbSC disease (may be at the low end of the normal range)
- Patients with HbSC disease to remain well (and undiagnosed) until they suffer an infarctive crisis (beginning in childhood)
- This crisis often follows childbirth or surgery and may be fatal.

وسألت عن نوع الطفرة

E6V

E6K



meta mean change!

contains heme

- Fe⁺²

- protoporphyrin

protein

Methemoglobinemias

Hb



globular

➤ Oxidation of the heme component of hemoglobin to the ferric (Fe+3) state forms methemoglobin, which cannot bind oxygen.

➤ caused by:

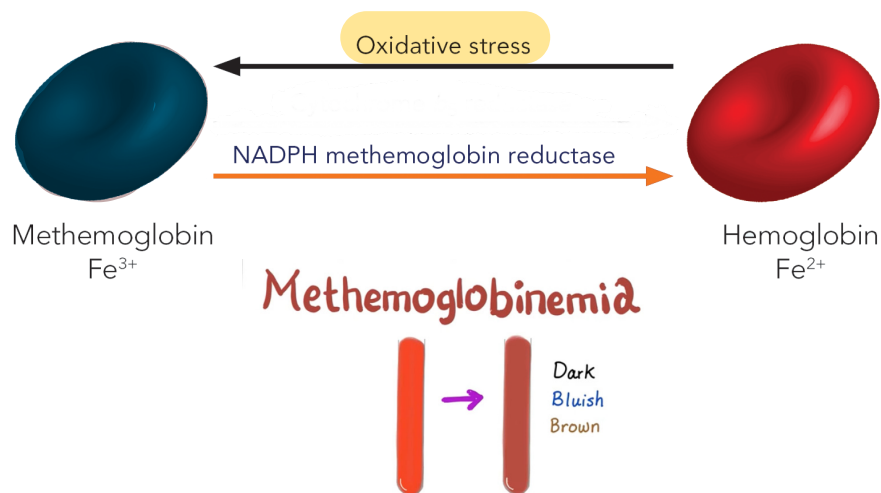
- The action of certain drugs, such as nitrates
- Endogenous products, such as reactive oxygen intermediates
- Inherited defects, for example, certain mutations in the α- or β-globin chain promote the formation of methemoglobin (HbM)
- Deficiency of NADH-cytochrome b5 reductase which is responsible for the conversion of methemoglobin (Fe+3) to hemoglobin (Fe+2), leads to the accumulation of methemoglobin

reduction

➤ newborns are particularly susceptible to the effects of methemoglobin-producing compounds

Methemoglobinemias

- The methemoglobinemias are characterized by “chocolate cyanosis” (a brownish-blue coloration of the skin and membranes) and chocolate colored-blood, as a result of the dark-colored methemoglobin
- Symptoms are related to tissue hypoxia, and include anxiety, headache, and dyspnea. In rare cases, coma and death can occur.



- hypoxia O₂ ↓
- dyspnea (shortness of breath)
- headache
- anxiety
- coma

22. Methemoglobin contains:

A. Fe^{2+}

B. Fe^{3+}

C. Cannot bind O_2

D. Two of the choices

E. None of the choices

D

Chocolate cyanosis and chocolate colored-blood as result of:

الجواب Methemoglobinemias

Thalassemia

- The thalassemias are hereditary hemolytic diseases in which an imbalance occurs in the synthesis of globin chains (either the α - or β -globin is defective)
 β -thalassemia *α -thalassemia*
- As a group, they are the most common single gene disorders in humans
- Normally, synthesis of the α - and β -globin chains are coordinated, so that each α -globin chain has a β -globin chain (formation of $\alpha_2\beta_2$ (HbA))
- A thalassemia can be caused by a variety of mutations, including entire gene deletions, or substitutions or deletions of one to many nucleotides in the DNA.
- It can be classified as either a disorder in which no globin chains are produced (α^0 - or β^0 -thalassemia), or one in which some chains are synthesized, but at a reduced rate (α^{+} - or β^{+} -thalassemia)

اكتب ردا...

جابت عن مسببات التلاسيميا اي وحده منهم

16. Match disease with cause:

1. Sickle cell | A. β -chain mutation E6V
2. HbC | B. β -chain mutation E6K
3. Thalassemia | C. Decreased synthesis

Options:

- A. Correct match all
- B. Only 1 & 2 correct
- C. Only 2 & 3 correct
- D. None of the choices
- E. Two of the choices

A

norma HbA
 $\alpha_2\beta_2$

No β -globin production

β -Thalasseмииas

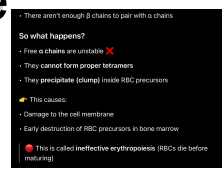
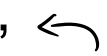
heterozygous \rightarrow minor
homozygous \rightarrow major

Hb Bart's \uparrow γ_4
HbF \uparrow $\alpha_2\gamma_2$
HbA₂ $\uparrow\uparrow$ $\alpha_2\delta_2$
Hb electrophoresis (Abnormal)

➤ In these disorders, synthesis of β -globin chains is decreased or absent, whereas α -globin chain synthesis is normal

2

➤ α -Globin chains cannot form stable tetramers which precipitate, causing the premature death of cells initially destined to become mature red blood cells



➤ Accumulation of $\alpha_2\gamma_2$ (HbF) and γ_4 (Hb Bart's) also occurs. There are only two copies of the β -globin gene in each cell (one on each chromosome 11)

one from mother
one from father

Hb Bart's \uparrow γ_4


II

➤ Individuals with β -globin gene defects have either β -thalassemia trait (β -thalassemia minor) if they have only one defective β -globin gene, or β -thalassemia major if both genes are defective

2

β -Thalassemias

- ^{فترة حمل} Because the β -globin gene is not expressed until late in fetal gestation, the physical manifestations of β -thalassemias appear only after birth. Those individuals with β -thalassemia minor make some β -chains, and usually do not require specific treatment
- Infants born with thalassemia major have the sad fate of being seemingly healthy at birth, but becoming severely anemic during the first or second year of life (require regular transfusions of blood)
- Although this treatment is lifesaving, the cumulative effect of the transfusions is iron overload (a syndrome known as hemosiderosis), which typically causes death between the ages of 15 and 25 years
- The increasing use of bone marrow replacement therapy has been a boon to these patients

➤ 

المرضى الي يعانون من B-thalassemia عندهم
كل أنواع ال Hb ما عدا :

-HbA $\alpha_2 \beta_2$

-HbF $\alpha_2 \gamma_2$ ✓

-Hb bart's γ_4 ✓

HbA2... عرض المزيد

$\alpha_2 \beta_2$ ✓

١٦ أعجبنى رد

سؤال شو نوع الهيموغلوبين الي مش موجود عند الي عندهم بيتا ثلاسيميا

1y Like Reply

HbA $\alpha_2\beta_2$

β -thalassemia

α chains production ↓

β/γ normal

α -Thalassemia

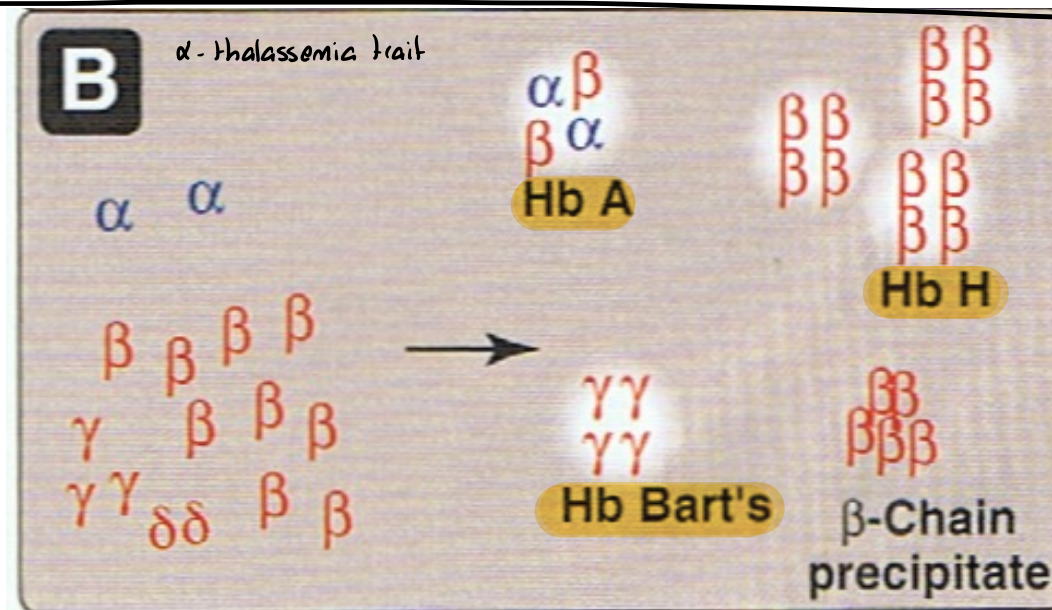
- These are defects in which the synthesis of α -globin chains is decreased or absent.
- Because each individual's genome contains four copies of the α -globin gene (two on each chromosome 16), there are several levels of α -globin chain deficiencies:
 - If one is defective, the individual is termed a silent carrier of α -thalassemia (no physical manifestations of the disease)
 - If two are defective, the individual is designated as having α -thalassemia trait
 - If three α -globin genes are defective, the individual has hemoglobin H (HbH) disease, a mildly to moderately severe hemolytic anemia
- The synthesis of unaffected γ - and then β -globin chains continues, resulting in the accumulation of γ tetramers in the newborn (γ_4 , Hb Bart's) or β tetramers (β_4 , HbH)

After birth

before birth

α -Thalassemia

- Although these tetramers are fairly soluble, the subunits show no heme-heme interaction.
- Their oxygen dissociation curves are almost hyperbolic, indicating that these tetramers have very high oxygen affinities (useless as oxygen delivers to the tissues) O_2 affinity \uparrow
- If all four α -globin genes are defective, fetal death result, because α -globin chains are required for the synthesis of HbF. $\alpha_2 \delta_2$



1 gene defective

- silent carrier -

2 genes defective

α -thalassemia
trait

3 genes defective

HbH disease

↳ excess β

β_4 tetramers = HbH

γ_4 Bart's

4 genes defective

★ fetal death

No $\text{HbA } \alpha_2\beta_2$
 $\text{HbF } \alpha_2\gamma_2$

γ_4 Hb bart's form

24. β -thalassemia leads to:

A. Excess β chains

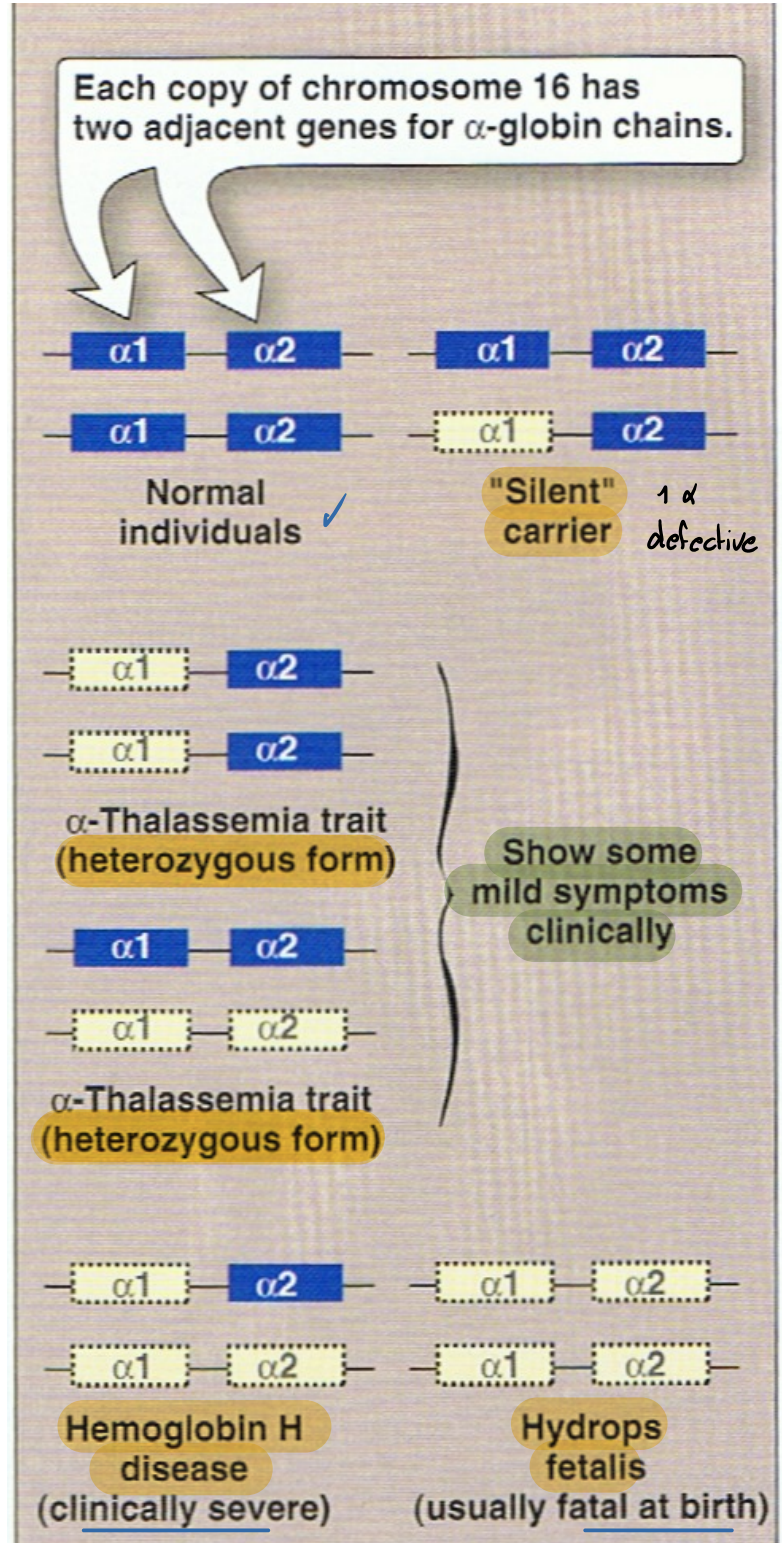
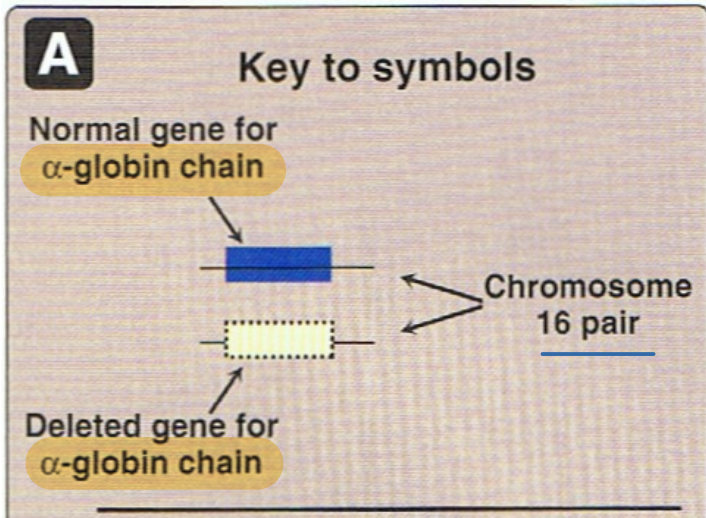
B. Excess α chains

C. Balanced chains

D. None of the choices

E. Two of the choices

B



Hemoglobinopathies

Synthesis of structurally abnormal hemoglobins

for example

Hb S E6V

caused by

Point mutation in both genes coding for β chain

composed of

β_6 Glu \rightarrow Val

leads to

Decreased solubility in deoxy form

leads to

Polymer formation

leads to

Vascular occlusion

leads to

Pain ("crises")

for example

Hb C E6K

caused by

Point mutation in both genes coding for β chain

composed of

β_6 Glu \rightarrow Lys

leads to

Hemolytic anemia

for example

Hb SC

caused by

Different point mutations in each gene coding for β chain

composed of

β_6 Glu \rightarrow Val

β_6 Glu \rightarrow Lys

leads to

Often asymptomatic

occasional episodes of

Decreased solubility in deoxy form

leads to

Polymer formation

leads to

Vascular occlusion

leads to

Pain ("crises")

polymerization = rigid + sickle shaped

Synthesis of insufficient quantities of normal hemoglobin

for example

α -thalassemias

caused by

Decreased synthesis of α chains

leads to

Anemia

leads to

Accumulation of γ_4 (Hb Bart's) and β_4 (Hb H), and β -chain precipitation

1- γ_4 Hb Bart's

2- β_4 HbH

3- β -chain precipitation

for example

β -thalassemias

caused by

Decreased synthesis of β chains

leads to

Anemia

leads to

Accumulation of γ_4 (Hb Bart's) and α -chain precipitation

Methemoglobinemia

characterized by

oxidation

$Fe^{++} \rightarrow Fe^{+++}$

leads to

Inability to bind O_2

leads to

Chocolate cyanosis

Other

for example

Methemoglobinemia