PASSION ACADEMIC TEAM

YU - MEDICINE

Sheet#

Lec. Date : 17-2-2020

Lec. Title : Hemoglobin

Written By :

If you come by any mistake , please kindly report it to shaghafbatch@gmail.com

RESPIRATORY SYSTEM

Hemoglobin

Dr. Mazhar Al Zoubi

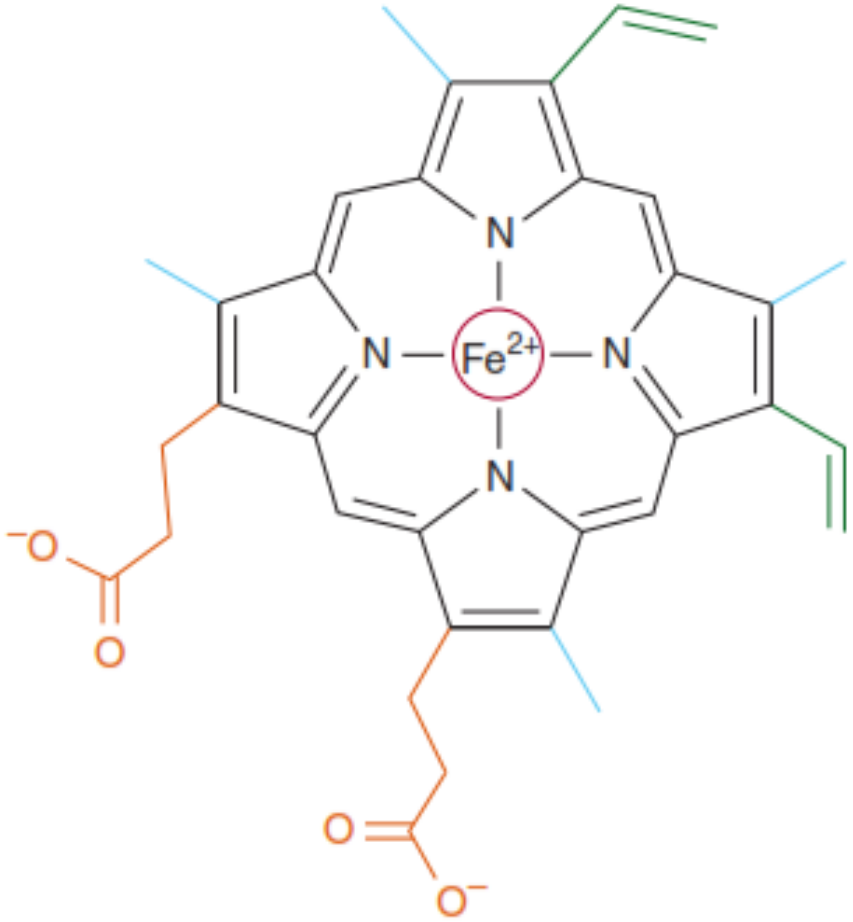
Hb Structure

- Normal level 14-16 g/dL (male)
- Around 67,000 Dalton
- Many types: A1 (most common), A2, F, D and Gowers
- Two family genes:
  - alpha 141 a.a (Chromosome 16)
  - beta 146 a.a. (Chromosome 11)
- 36 His residues/Hb
- 4% of total mass is heme

Table 22.1. Amino acid sequence of globin

Hb chain	Amino acid sequence number							
	1	58	63	87	92	141	145	146
Alpha	Val	Distal His	-	Proximal His	-	Last Arg	Nil	Nil
Beta	Val	-	Distal His	-	Proximal His	-	Tyr	Last His
Gamma	Gly	-	Distal His		Proximal His	-	Tyr	Last His
Delta	Val	-	Distal His	-	Proximal His	-	Tyr	Last His

مش حفظ هدول يجماعة ☺



Ring structure with the centre of iron.
Why we choose iron to be in this structure?
because it's able to form 6 bonds,4 of them are bind with heme.

Oxygenation and Oxidation

- When hemoglobin carries oxygen, the Hb is **oxygenated. The iron atom in Hb is still in the** ferrous state.
- **Oxidized Hemoglobin is called** Met-Hb;(oxidized Hb without oxygen) then iron is in ferric state and the oxygen carrying capacity is lost.
- We have normal concentration of met-Hb if it's access, it should be returned by certain treatments, to return it back to its normal concentration, in order to be able to bind oxygen again.

TRANSPORT OF OXYGEN BY HEMOGLOBIN

- **Oxygen Dissociation Curve (ODC)**

In fact, it is association of oxygen, (increase the concentration of oxygen and notice the saturation)

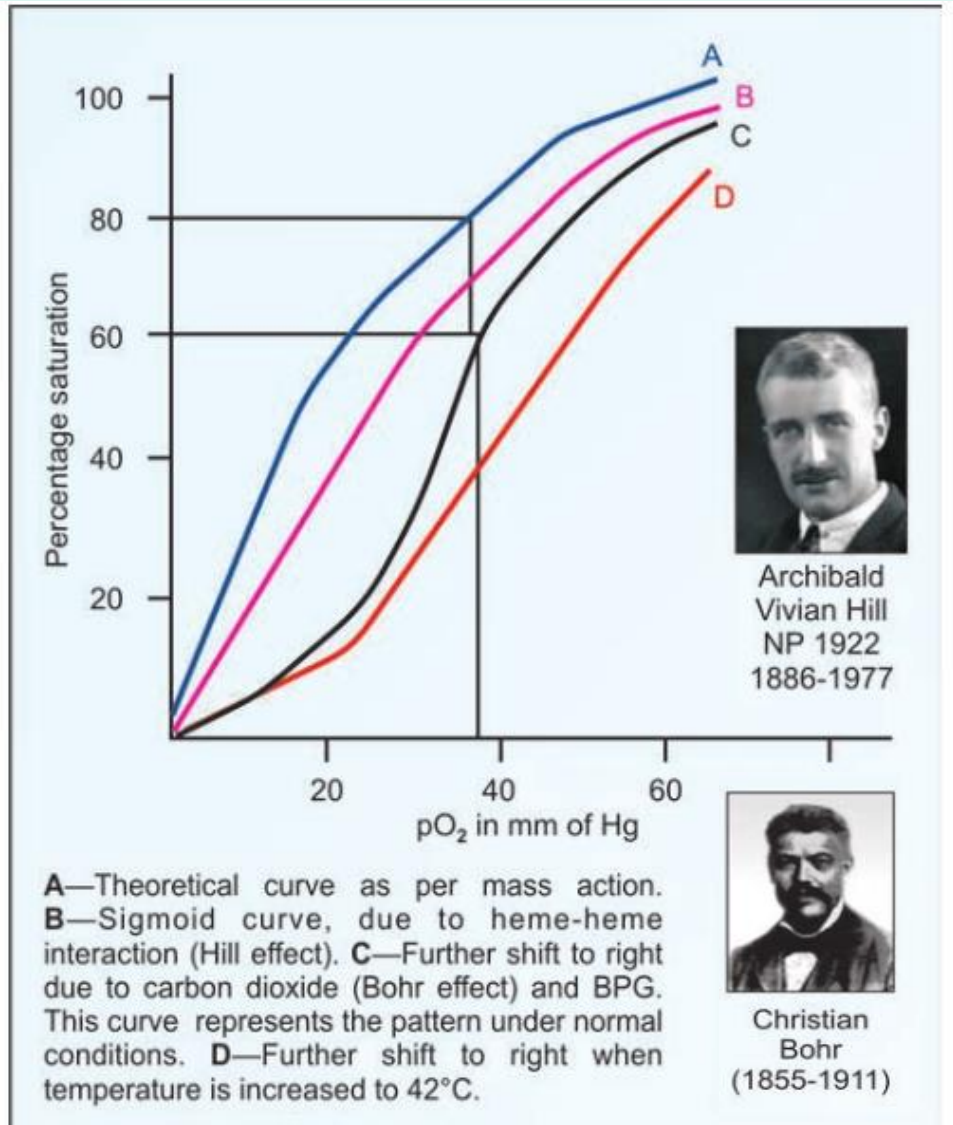
* The Hb behavior is by 4 sections:

A- the theortical how is the Hb will behave if you increase the oxygen concentration

B- the sigmoidal curve: almost similar to the normal one

C-shift to the right

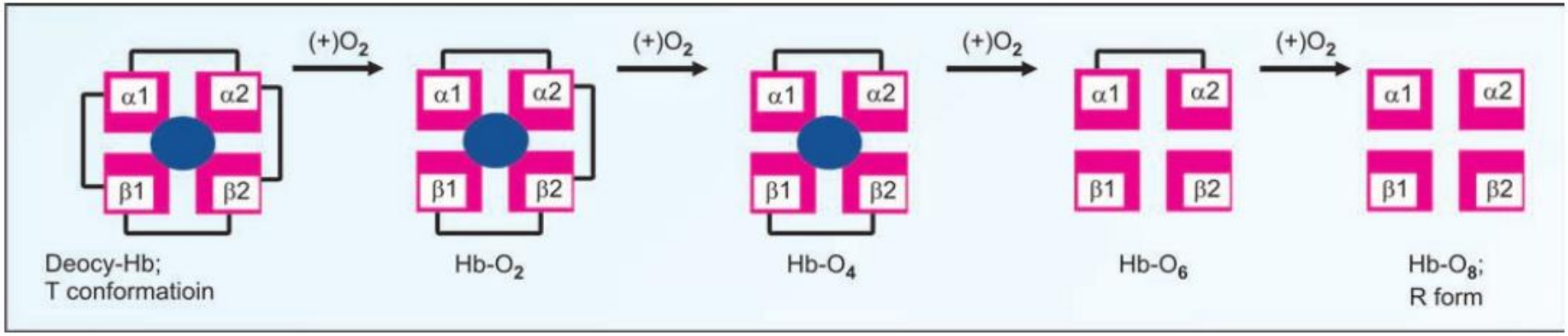
D- more shifting



A—Theoretical curve as per mass action. **B**—Sigmoid curve, due to heme-heme interaction (Hill effect). **C**—Further shift to right due to carbon dioxide (Bohr effect) and BPG. This curve represents the pattern under normal conditions. **D**—Further shift to right when temperature is increased to 42°C.

Heme-heme Interaction and Cooperativity

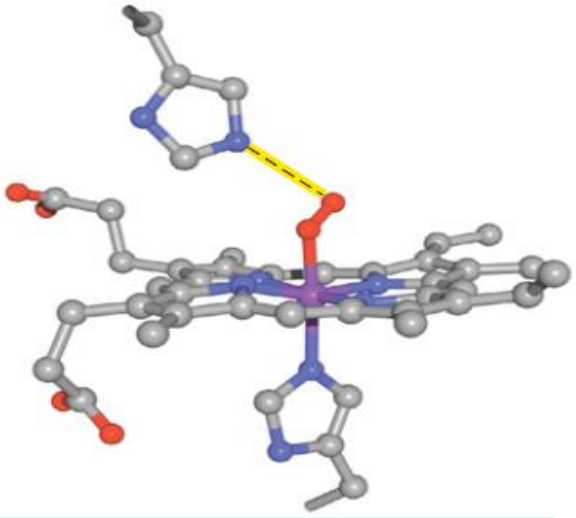
- Homotropic interaction (positive cooperativity)
- **97% saturated with oxygen at lung**
- Hb saturation is **60% saturated** in the tissue capillaries



Affinity 1 time	Affinity 2 times	Affinity 4 times	Affinity 18 times
$Hb \xrightarrow[(+)O_2]{} HbO_2$	$HbO_2 \xrightarrow[(+)O_2]{} HbO_4$	$HbO_4 \xrightarrow[(+)O_2]{} HbO_6$	$HbO_6 \xrightarrow[(+)O_2]{} HbO_8$

Highest affinity

Apomyoglobin Provides a Hindered Environment for the Heme Iron



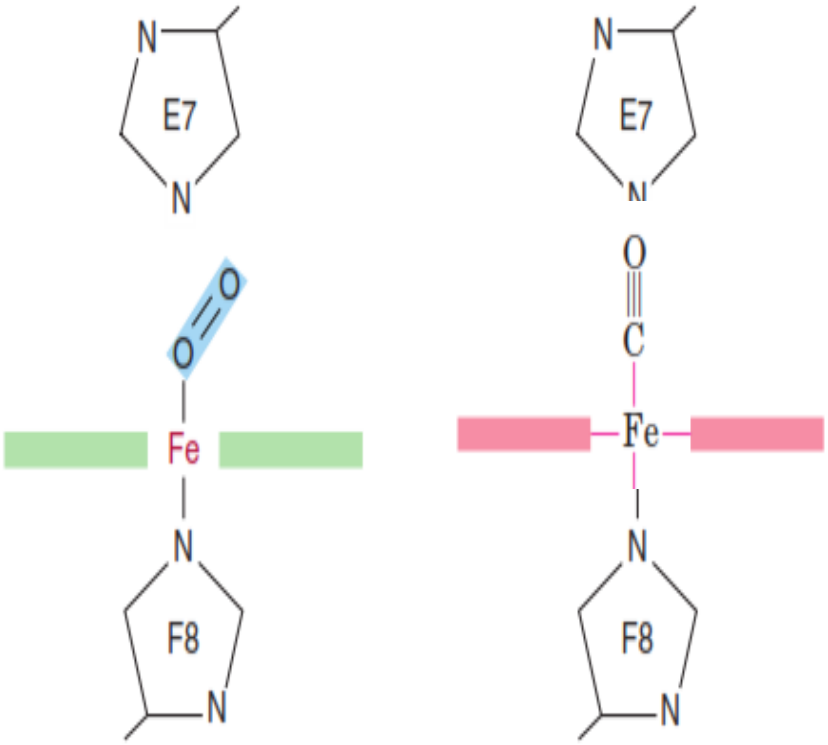


FIGURE 6–3 Angles for bonding of oxygen and carbon monoxide (CO) to the heme iron of myoglobin. The distal E7 histidine hinders bonding of CO at the preferred (90°) angle to the plane of the heme ring.

*Once you have something in the middle, it will pulled up the heme to be more planer , this change will lead all of the subunits to move, this movement will do conformational change, so the next subunite will be accessible to the oxygen.
*This we called allosteric effects: (you are making something in one side and its effect the other side)

Why is the carbon monoxide more toxicity than other molecules?
because it is more stable, we have high affinity to bind carbon monoxide than oxygen. So the dissociation of carbon monoxide is harder. We need 250 molecule of oxygen to dissociate one carbon monoxide.

Isolated heme binds carbon monoxide (CO) 25,000 times more strongly than oxygen.

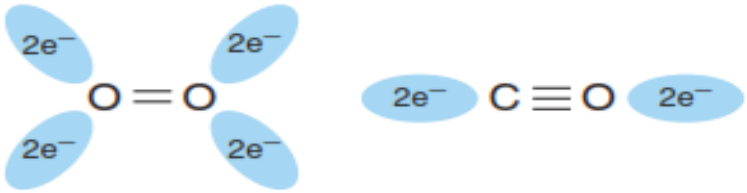


FIGURE 6–4 Orientation of the lone pairs of electrons relative to the O = O and C ≡ O bonds of oxygen and carbon monoxide. In molecular oxygen, formation of the double bond between the two oxygen atoms is facilitated by the adoption of an sp^2 hybridization state by the valence electron of each oxygen atom. As a consequence, the two atoms of the oxygen molecule and each lone pair of electrons are coplanar and separated by an angle of roughly 120° (**left**). By contrast, the two atoms of carbon monoxide are joined by a triple bond, which requires that the carbon and oxygen atoms adopt an sp hybridization state. In this state the lone pairs of electrons and triple bonds are arranged in a linear fashion, where they are separated by an angle of 180° (**right**).

The affinity of CO to Hb is 200 times more than that of oxygen.

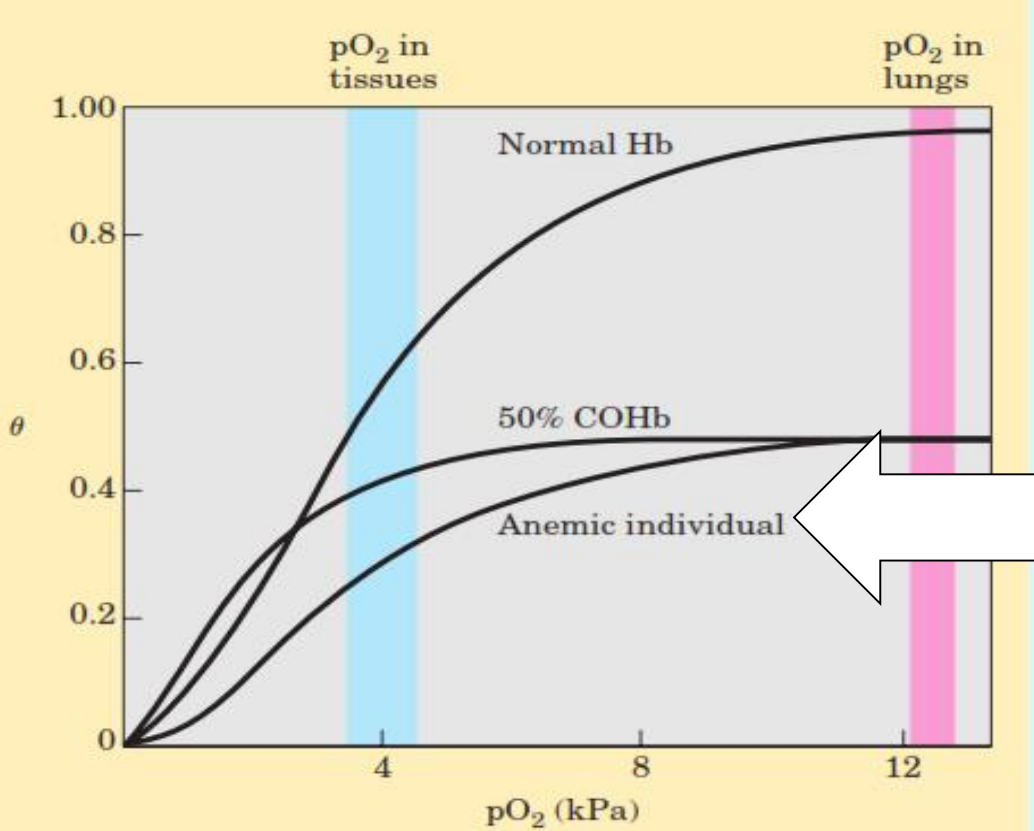


FIGURE 2 Several oxygen-binding curves: for normal hemoglobin, hemoglobin from an anemic individual with only 50% of her hemoglobin functional, and hemoglobin from an individual with 50% of his hemoglobin subunits complexed with CO. The pO_2 in human lungs and tissues is indicated.

means that carbon monoxide has the same effect of anemia. (low supply)

CLINICAL CORRELATES

Hemoglobin has about 250 times the affinity for carbon monoxide than it does for oxygen. Prolonged or heavy exposure to carbon monoxide results in disorientation, headache, and **potentially fatal asphyxiation.** Patients may have "**cherry-red mucous membranes**" due to the accumulation of **carboxyhemoglobin.**

→50% COHb: toxicity with carbon monoxide→ the curve is in depletion to the half, means as you increase the oxygen concentration in hospital, there will be no saturation, but you have to keep the patient and the oxygen, but it is not treatment to recover (as you will not affect the affinity).

* you have to wait until carbon monoxide release itself, depend on partial pressure, (partial pressure of carbon monoxide in the environment is less carbon monoxide release)

THE OXYGEN DISSOCIATION CURVES FOR MYOGLOBIN & HEMOGLOBIN SUIT THEIR PHYSIOLOGIC ROLES

*hemoglobin:
-sigmoidal
-4 subunits
-has allosteric cooberative.

*myoglobin:
-hyperpolic.
-one unit
-has no allosteric cooberative. (saturation is faster).

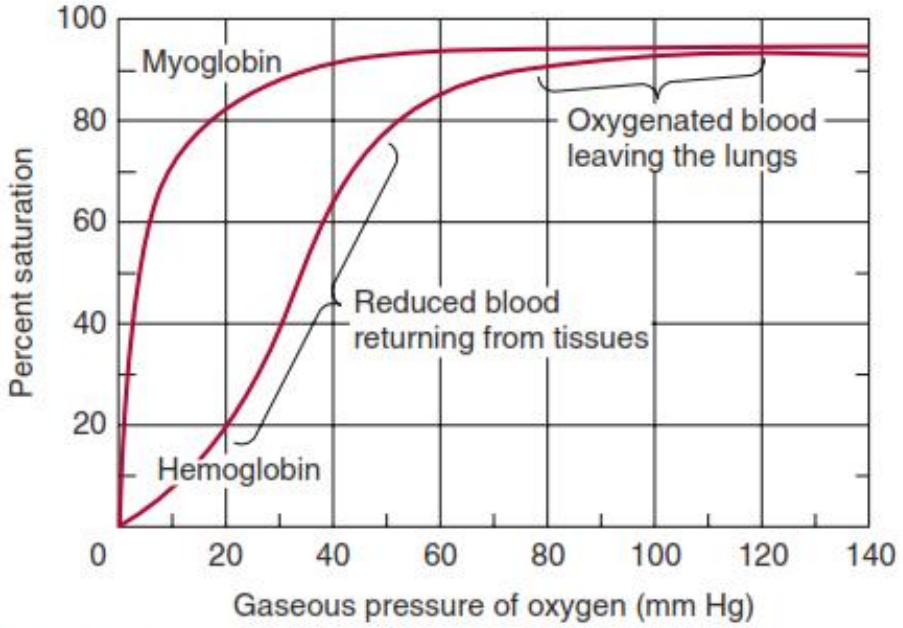


FIGURE 6–5 Oxygen-binding curves of both hemoglobin and myoglobin. Arterial oxygen tension is about 100 mm Hg; mixed venous oxygen tension is about 40 mm Hg; capillary (active muscle) oxygen tension is about 20 mm Hg; and the minimum oxygen tension required for cytochrome oxidase is about 5 mm Hg. Association of chains into a tetrameric structure (hemoglobin) results in much greater oxygen delivery than would be possible with single chains. (Modified, with permission, from Scriver CR, et al (editors): *The Molecular and Metabolic Bases of Inherited Disease,* 7th ed. McGraw-Hill, 1995.)

Why we have other types o Hb(F,D,…)?
They are doing certain oxygen transportation mech. to certain tissue (depending on the need).
***F has more affinity than A.

Oxygenation of Hemoglobin Triggers Conformational Changes in the Apoprotein

Apoprptein: الجزء البروتيني بدون الهيم

P_{50} Expresses the Relative Affinities of Different Hemoglobins for Oxygen

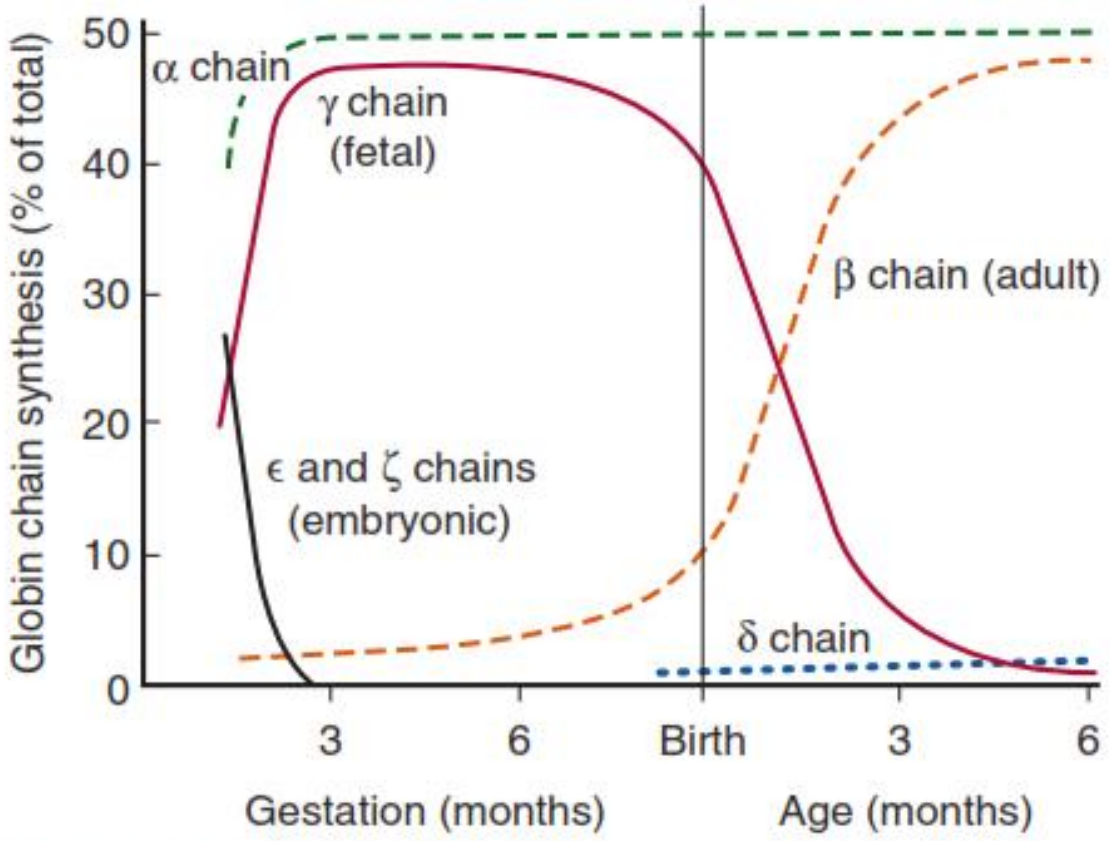


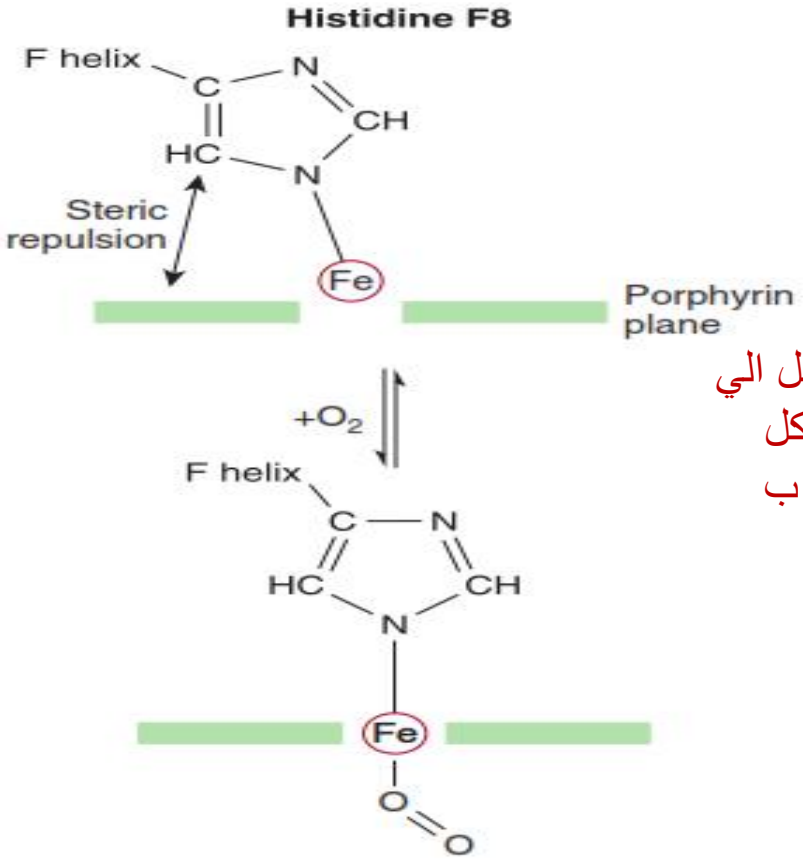
FIGURE 6–7 Developmental pattern of the quaternary structure of fetal and newborn hemoglobins. (Reproduced, with permission, from Ganong WF: *Review of Medical Physiology,* 20th ed. McGraw-Hill, 2001.)

الفا هي شغلة من الشغلات ال ما بتكون شغالة في بداية الحمل لحد ال3 شهور ولقدام بتتكون.

*Hb F (2alpha, 2gamma)

At the end we will have A, F, D, A2(A1C).

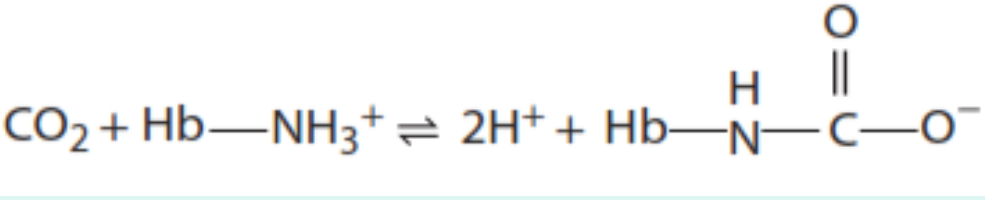
Oxygenation of Hemoglobin Is Accompanied by Large Conformational Changes

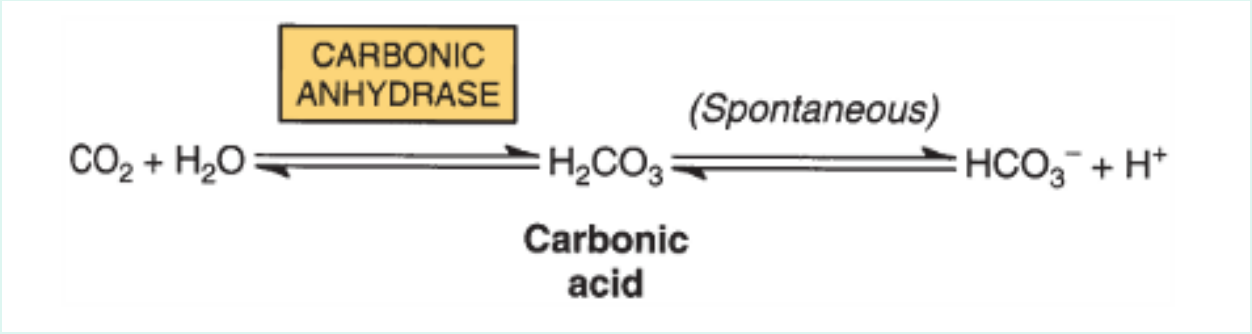


كل هاد حكيناه من قبل الي هو موضوع تغير شكل الهستدين لمن يرتبط ب الاكسجين

FIGURE 6–8 **On oxygenation of hemoglobin the iron atom moves into the plane of the heme.** Histidine F8 and its associated aminoacyl residues are pulled along with the iron atom. For a representation of this motion, see http://www.rcsb.org/pdb/101/motm.do?momID=41. (Slightly modified and reproduced, with permission, from Stryer L: *Biochemistry*, 4th ed. Freeman, 1995. Copyright © 1995 W. H. Freeman and Company.)

After Releasing O_2 at the Tissues, Hemoglobin Transports CO_2 & Protons to the Lungs





O2, CO → bind with heme

CO2 → bind to unterminal of alpha chain.

*Hb can carry 4 O2, 2 CO2.

Effect of pH and pCO2, Bohr Effect and Chloride Shift (Hamburger effect)

Bohr Effect: formation of H+ from H2CO3, the H will bind with Hb at certain histidine other than the distal and proximal one.

الزبدة من الموضوع بس انه الهيدروجين ما بنافس الاكسجين ولا بحل محله (وهالمعلومة ركز عليها الدكتور)

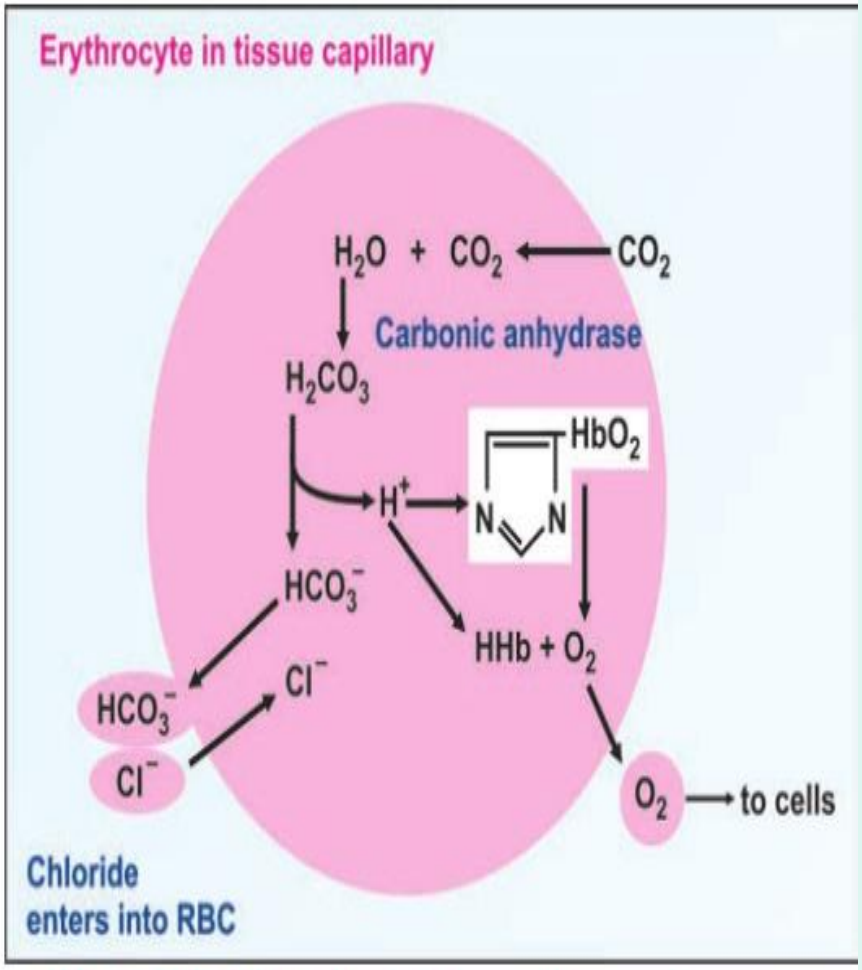


Fig. 22.5. Chloride shift; reactions in tissues

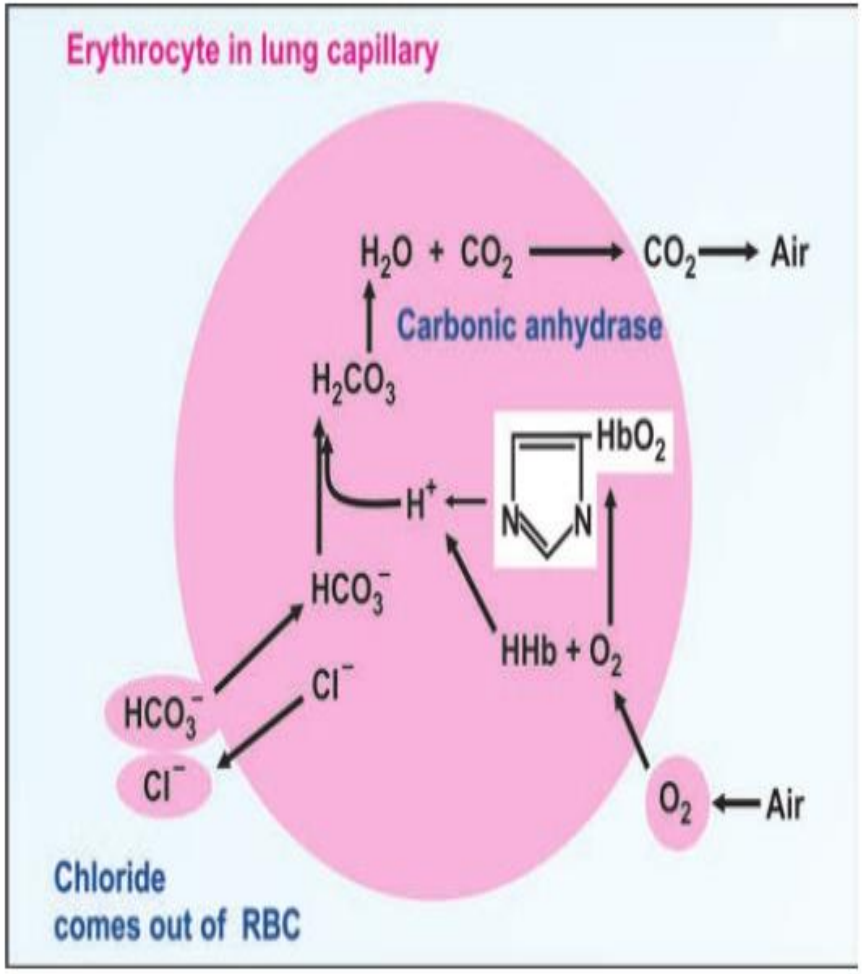


Fig. 22.6. Chloride shift; reactions in lungs

2,3-BPG Stabilizes the T Structure of Hemoglobin

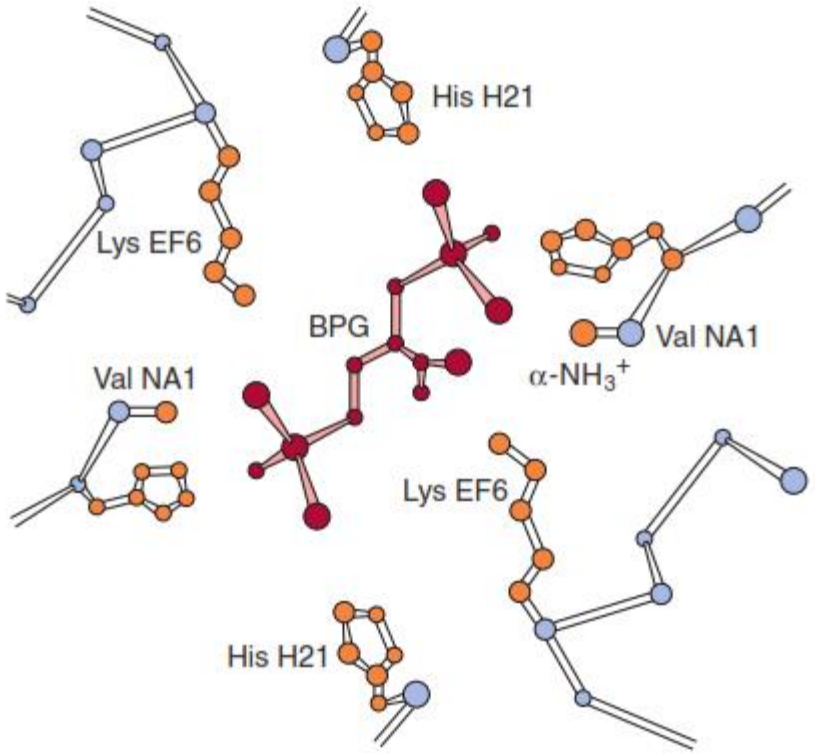
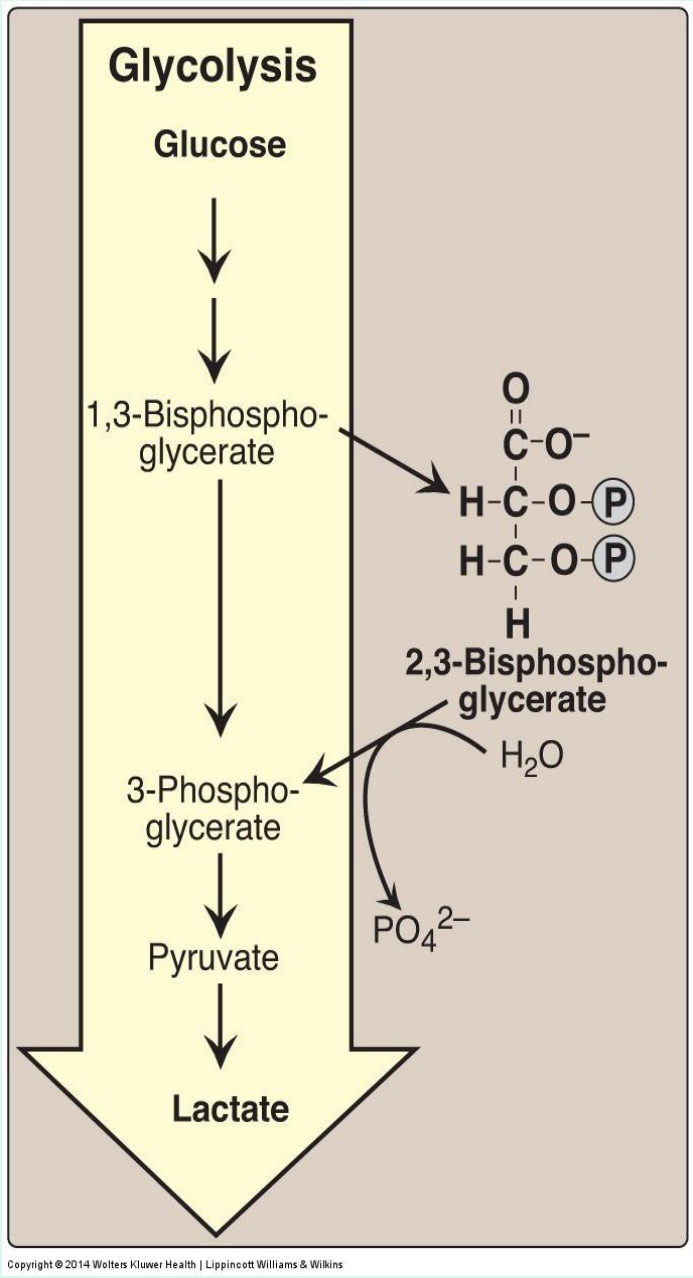


FIGURE 6–12 Mode of binding of 2,3-bisphosphoglycerate (BPG) to human deoxyhemoglobin. BPG interacts with three positively charged groups on each β chain. (Based on Arnone A: X-ray diffraction study of binding of 2,3-diphosphoglycerate to human deoxyhemoglobin. Nature 1972;237:146. Copyright © 1972. Adapted by permission from Macmillan Publishers Ltd.)

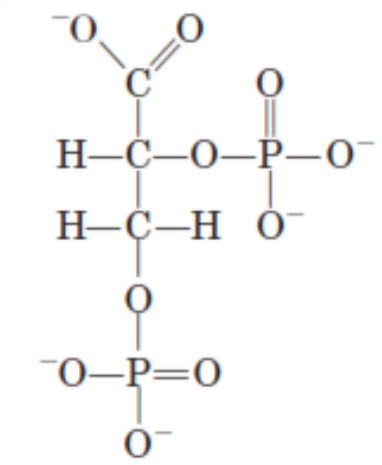


*At the site of the tissue:
-acidic conditions
-high CO2
-high 2,3-BPG
→decreasing the affinity of Hb to oxygen

*At the site of lungs:
-less acidity
-less CO2
-less 2,3-BPG
→increasing the affinity of Hb to oxygen.

Oxygen Binding to Hemoglobin Is Regulated by 2,3-Bisphosphoglycerate

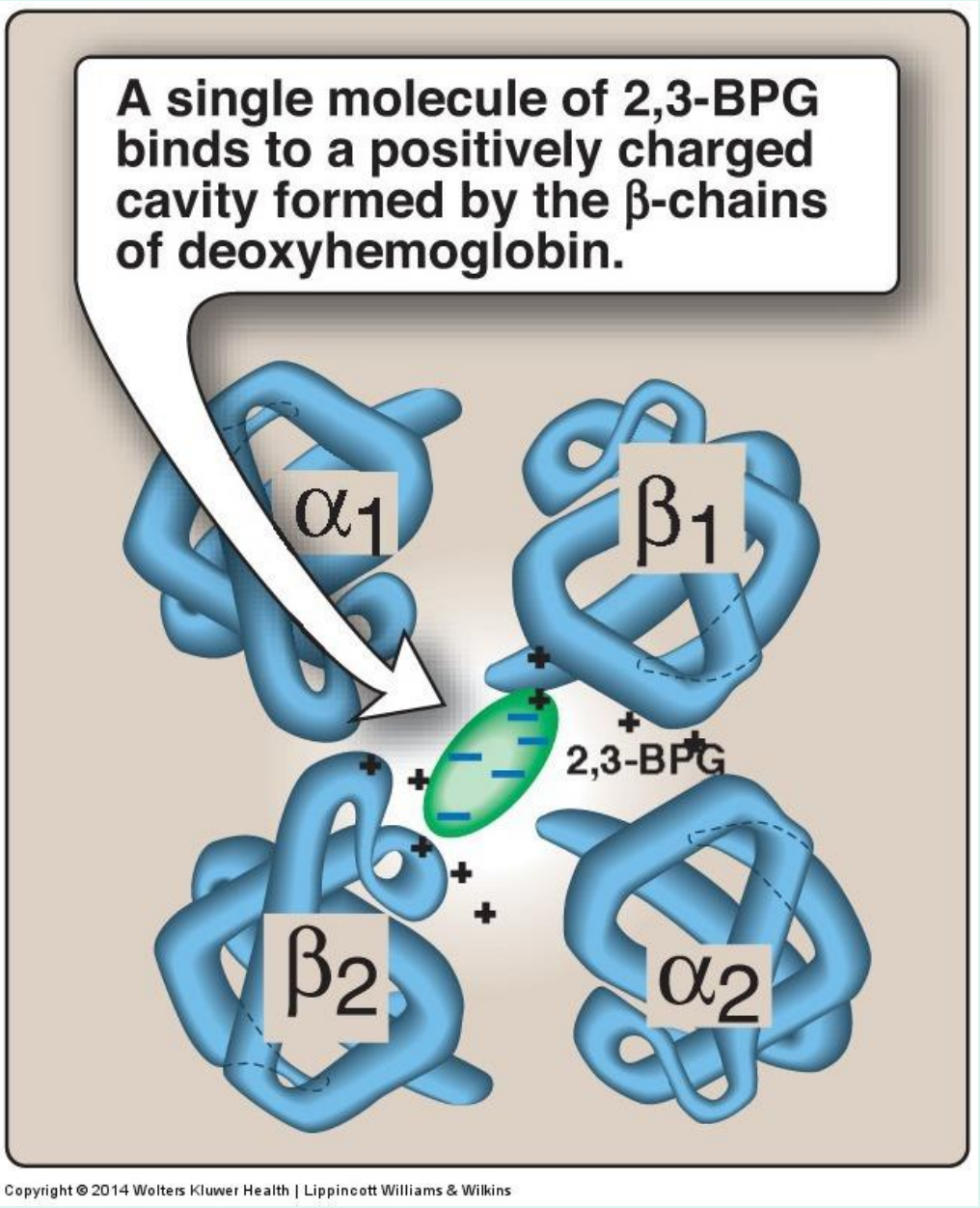
The interaction of **2,3-bisphosphoglycerate (BPG)** with hemoglobin provides an example of heterotropic allosteric modulation.



2,3-Bisphosphoglycerate

$$HbBPG + O_2 \rightleftharpoons HbO_2 + BPG$$

All of this in order to the main factor which is partial pressure of oxygen.



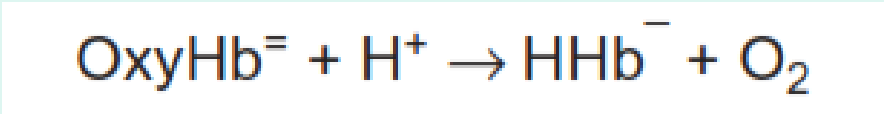
Adaptation to High Altitude

Physiologic changes that accompany prolonged exposure to high altitude include increases in the number of erythrocytes, the concentration of hemoglobin within them, and the synthesis of BPG. Elevated BPG lowers the affinity of HbA for O_2 (increases P_{50}), which enhances the release of O_2 at peripheral tissues.

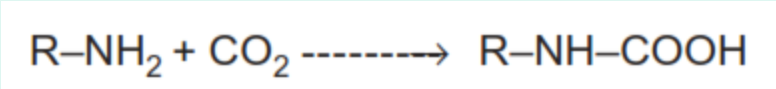
1. Increase in the number of RBCs
2. Increase in concentration of Hb inside RBCs
3. Increase in BPG.

TRANSPORT OF CARBON DIOXIDE

1. **Dissolved Form**
   - 10% of CO2
2. **Isohydric Transport**
   - 75%
   - **Haldane effect (Hb buffering of H ions)**
   - **Oxy-Hb is More Negatively Charged Than Deoxy-Hb**



3. **Carriage as Carbamino-Hemoglobin**
   - **15 %**



Methemoglobin & Hemoglobin M

- The heme iron is ferric (Fe^{3+}) rather than ferrous (Fe^{2+})
- Normal blood has only less than 1%
- Thus can neither bind nor transport O_2
- Corrected by **methemoglobin reductase**
- In hemoglobin M, **histidine** F8 (His F8) has been replaced by **tyrosine**. Congenital Met-Hb
- Can be treated by oral administration of methylene blue(will reduce the met-Hb), or ascorbic acid
- **Acquired or Toxic Methemoglobinemia**
  - Nitrates.
  - Aniline dyes
  - Cetaminophen, phenacetin, sulphanilamide, amyl nitrite, and sodium nitroprusside

Hb M

Methaemoglobin

Methaemoglobin is haemoglobin in which iron is in the ferric (Fe^{3+}) form (haemin); therefore, it cannot carry oxygen. It is brown and is normally present in very low plasma concentrations; drugs such as sulphonamides or nitrites/nitrates may increase methaemoglobin. The symptoms of methaemoglobinaemia are due to hypoxia, which causes cyanosis and an increased respiratory rate and, if methaemoglobin is greater than 70 per cent of the total haemoglobin, can be fatal. Methemoglobin may cause a pulse oximeter to read about 85 per cent regardless of the actual amount of oxygen saturation. Methaemoglobinaemia is associated with glucose-6-phosphate dehydrogenase (G6PD) deficiency (see

Hemoglobin S

Due to the mutation in amino acid 6 in ß chain

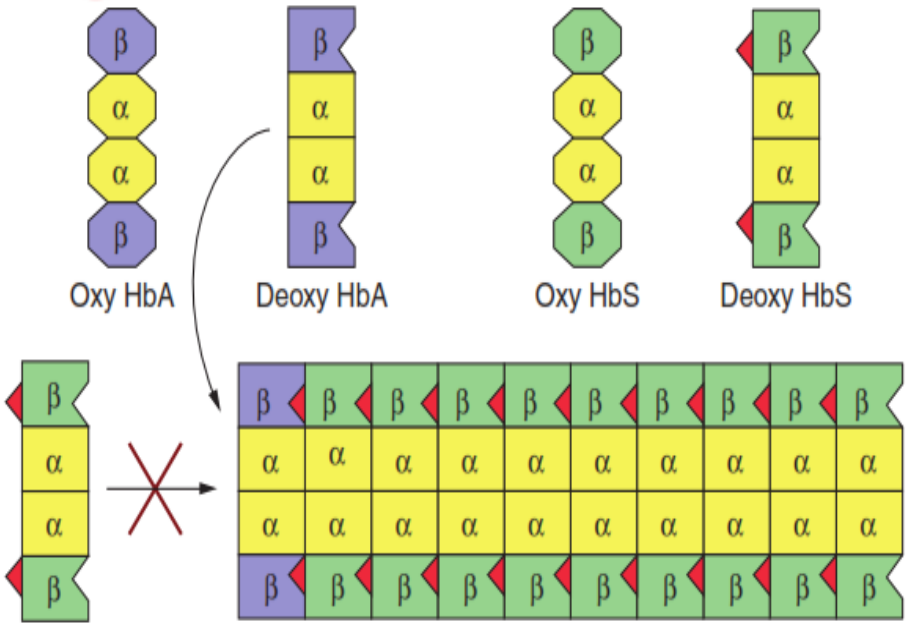


FIGURE 6–13 Polymerization of deoxyhemoglobin S. The dissociation ofoxygen from hemoglobin S (HbS) unmasks a sticky patch (red triangle) on thesurface of its β-subunits (green) that can adhere to a complementary site on the β-subunits of other molecules of deoxyHbS. Polymerization to a fibrouspolymer is interrupted deoxyHbA, whose β-subunits (lavender) lack the sticky patch required for binding additional HbS subunits. (Modified and reproduced, with permission, from Stryer L: *Biochemistry*, 4th ed. Freeman, 1995. Copyright © 1995 W. H. Freeman and Company.)

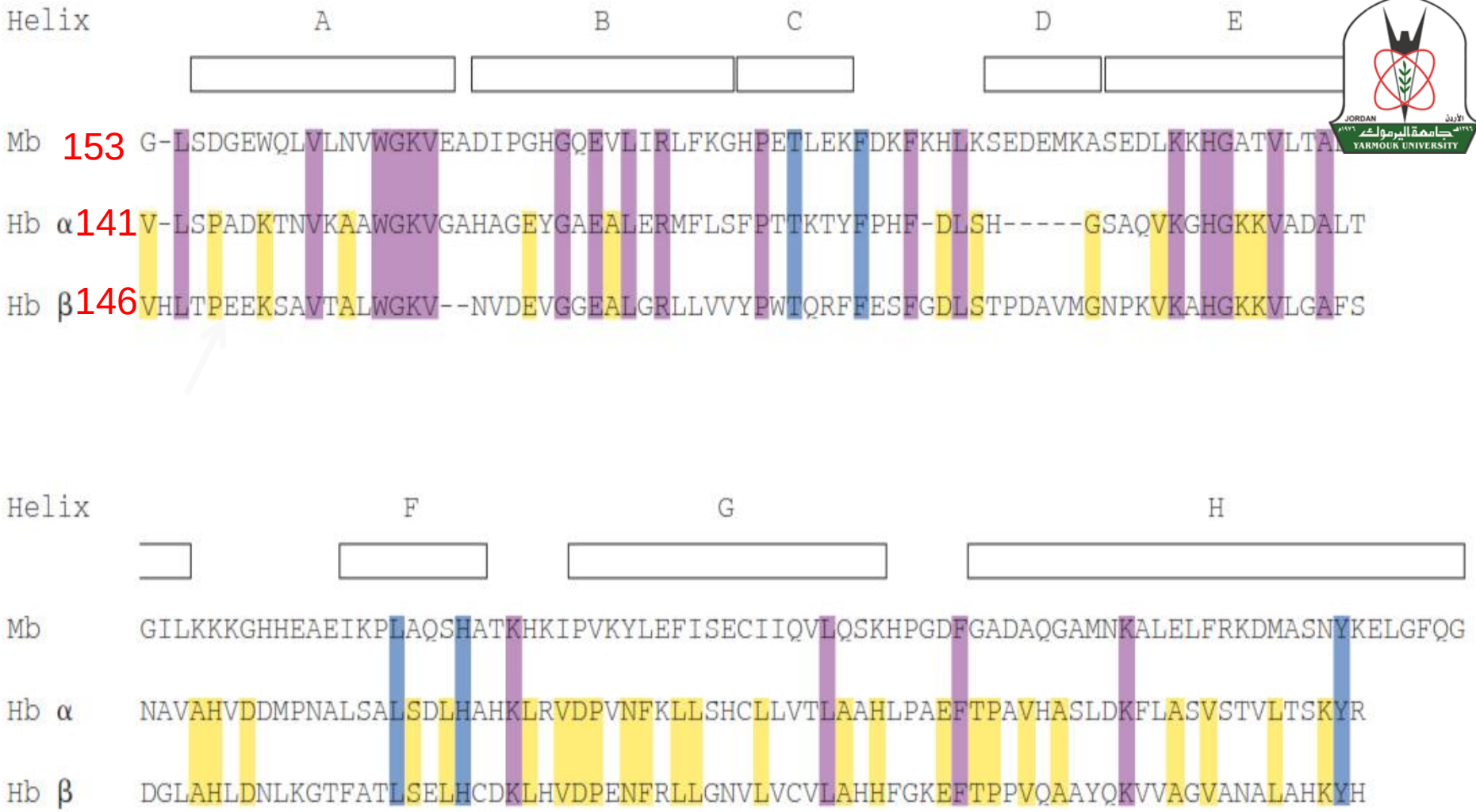
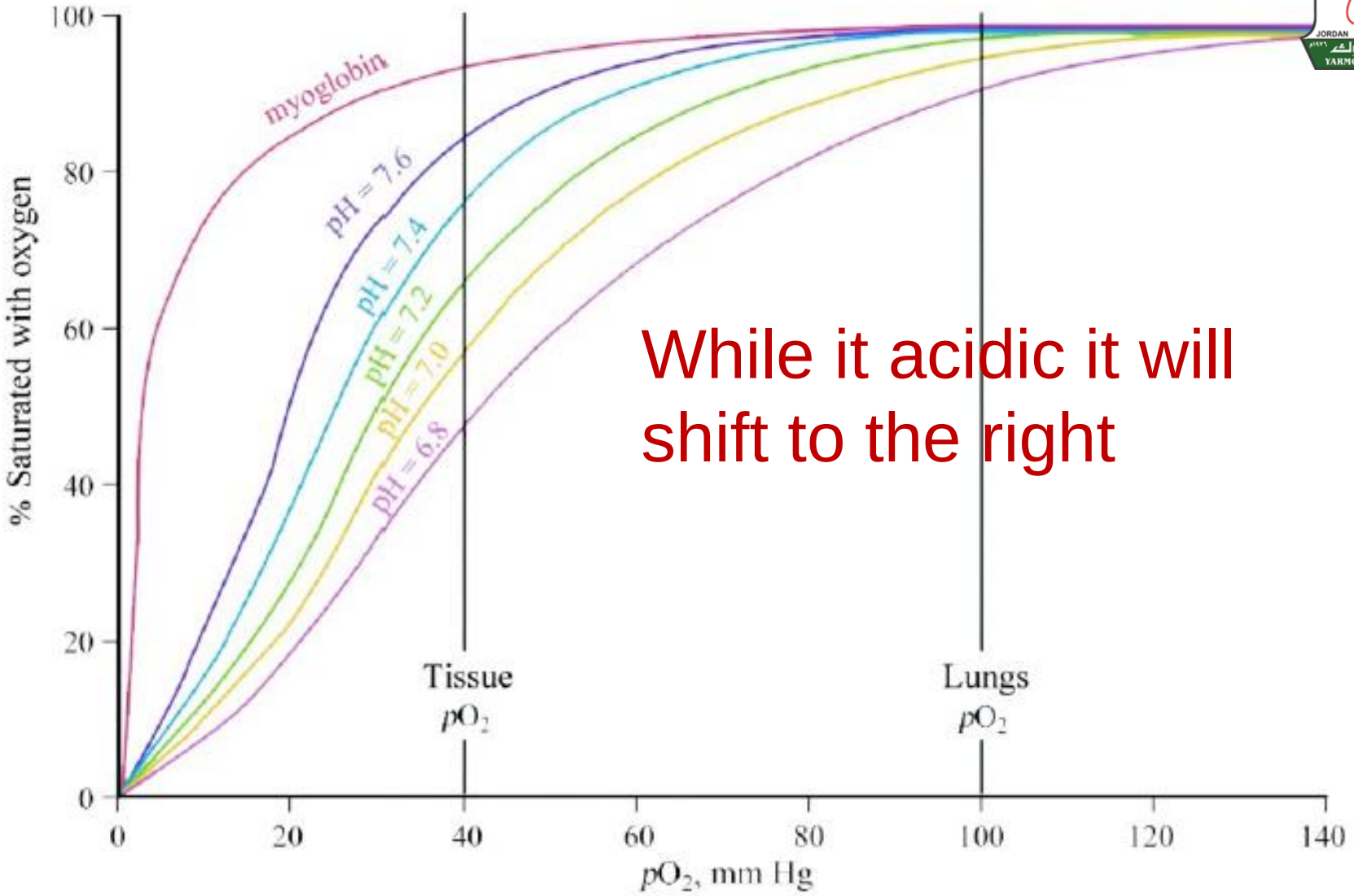


Figure 5-5 The amino acid sequences of myoglobin and the hemoglobin α and β chains. The sequence of human myoglobin (Mb) and the human hemoglobin (Hb) chains are written so that their helical segments (bars labeled A through H) are aligned. Residues that are identical in the α and β globins are shaded yellow; residues identical in myoglobin and the α and β globins are shaded blue, and residues that are invariant in all vertebrate myoglobin and hemoglobin chains are shaded purple. The one-letter abbreviations for amino acids are given in Figure 4-2. [After Dickerson, R. E., and Geis, I., *Hemoglobin*, pp. 68–69, Benjamin/Cummings (1983).]

? Can you identify positions occupied by structurally similar amino acids in all three globins?



While it acidic it will shift to the right

The Bohr Effect

Haemoglobin and related compounds

Carboxyhaemoglobin — **cherry red**

Methaemoglobin — **brown**

Methaemalbumin — **brown**

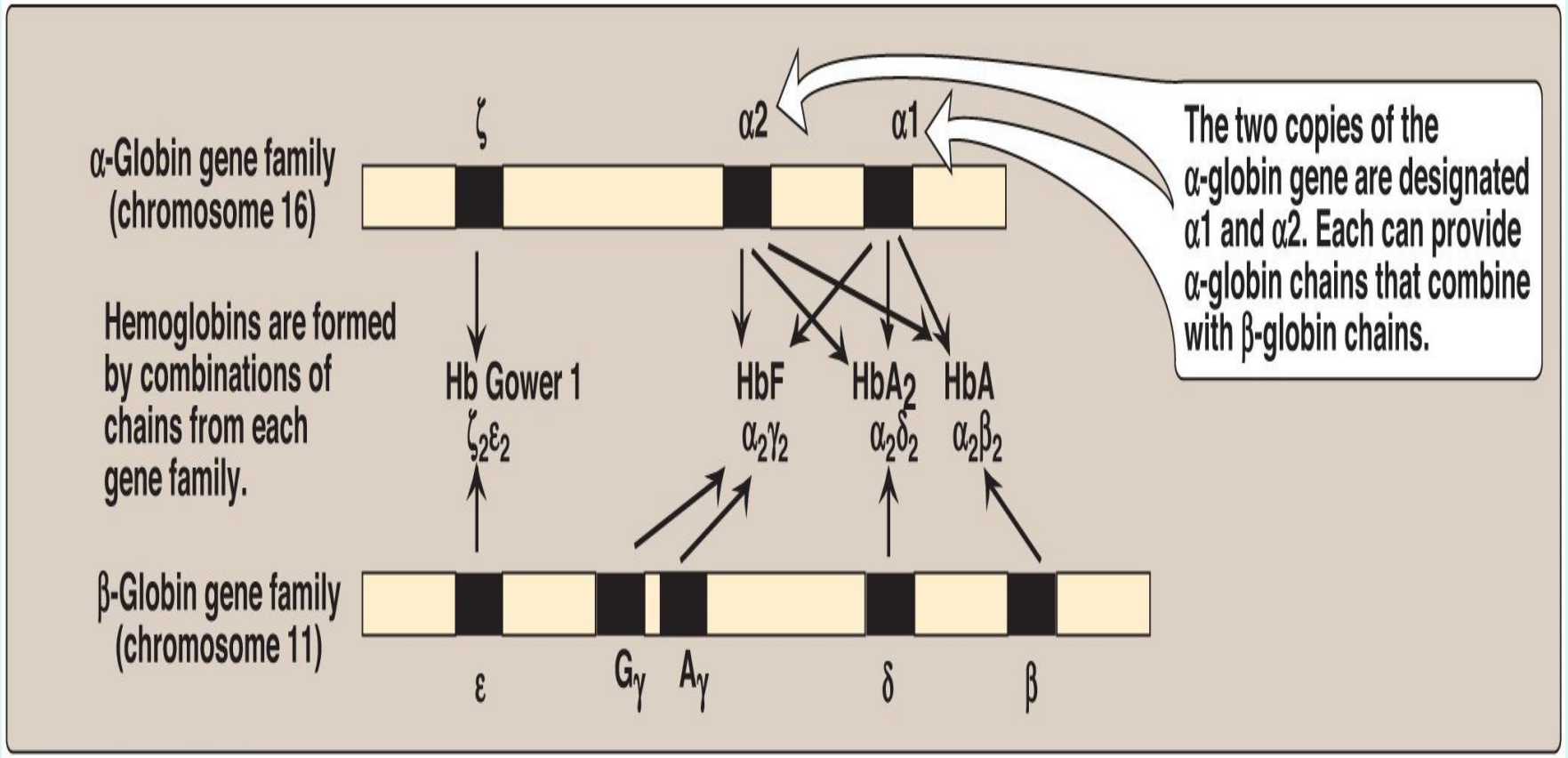
Sulphaemoglobin

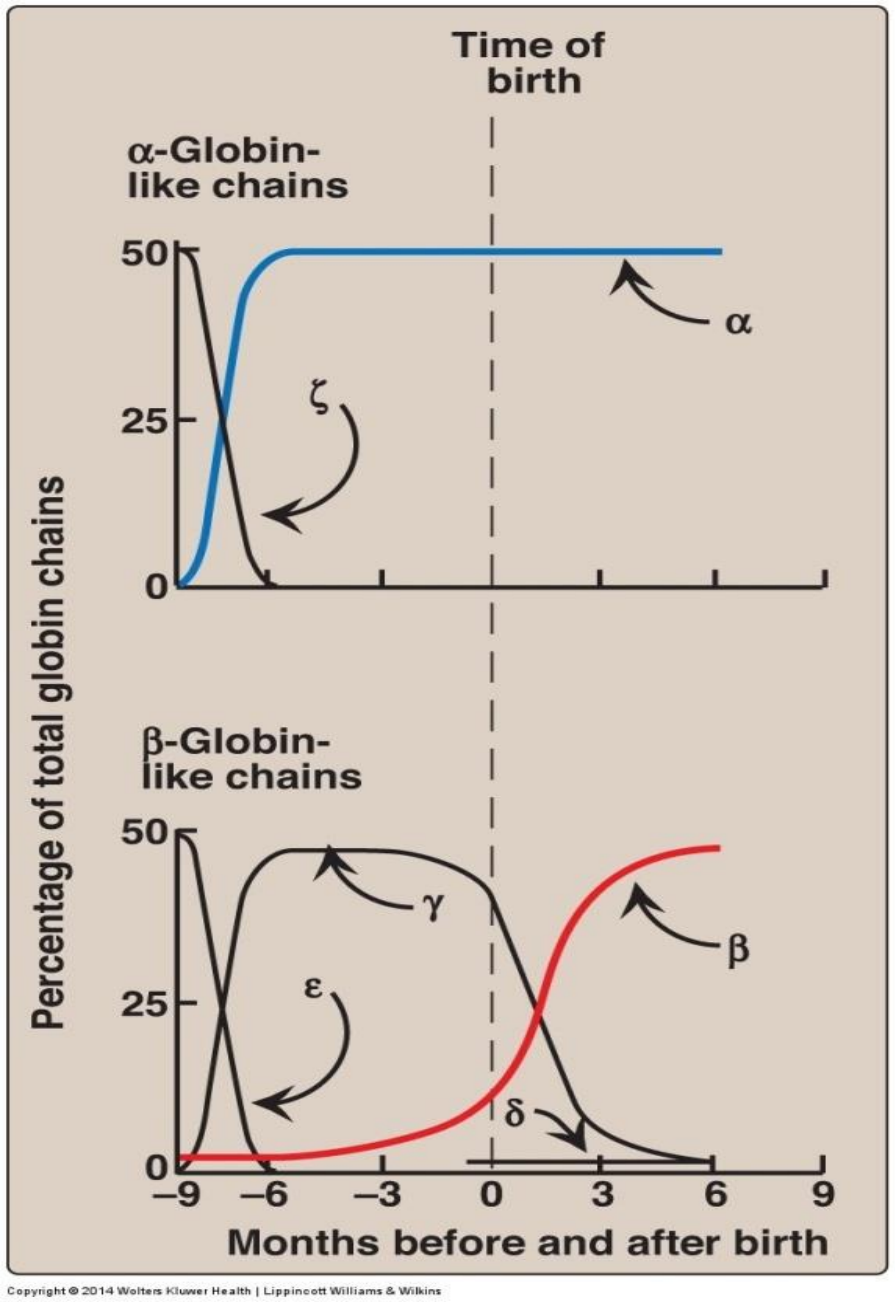
Sulphaemoglobin is similar to methaemoglobin but contains sulphur; unlike methaemoglobin, it cannot be reconverted to haemoglobin in vivo. It remains in intact

brown

Form	Chain composition	Fraction of total hemoglobin
HbA	$\alpha_2\beta_2$	90%
HbF	$\alpha_2\gamma_2$	<2%
HbA_2	$\alpha_2\delta_2$	2%–5%
HbA_{1c}	$\alpha_2\beta_2$-glucose	3%–9%

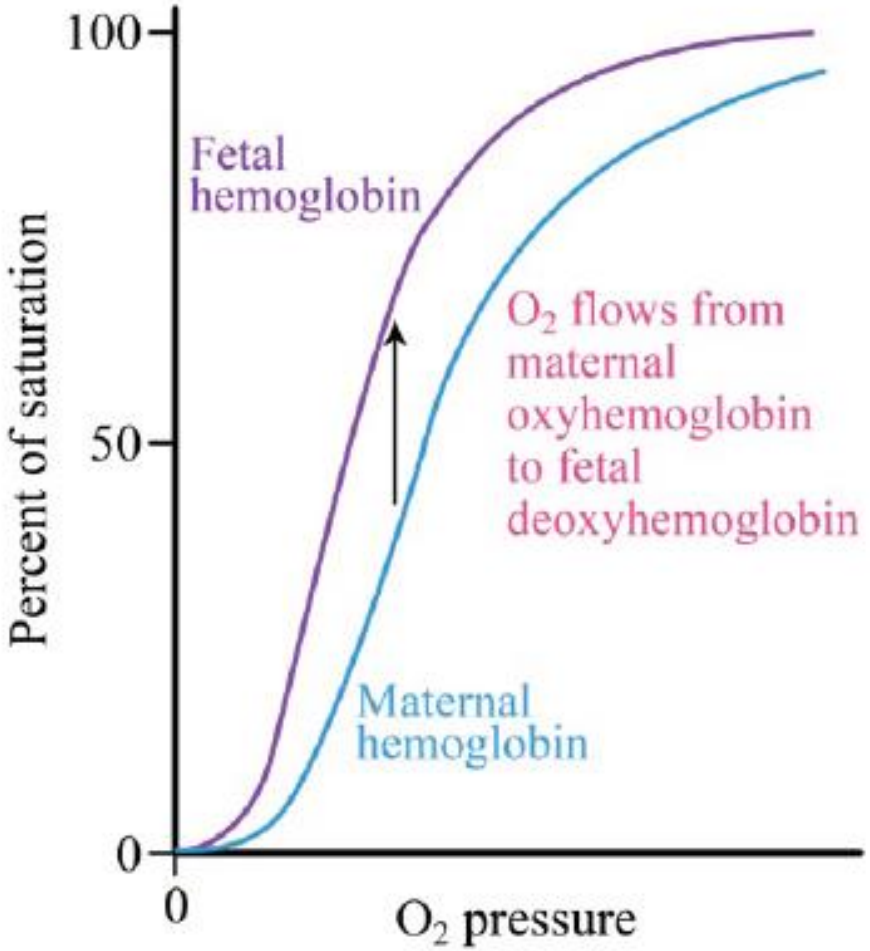
Glycated Hb



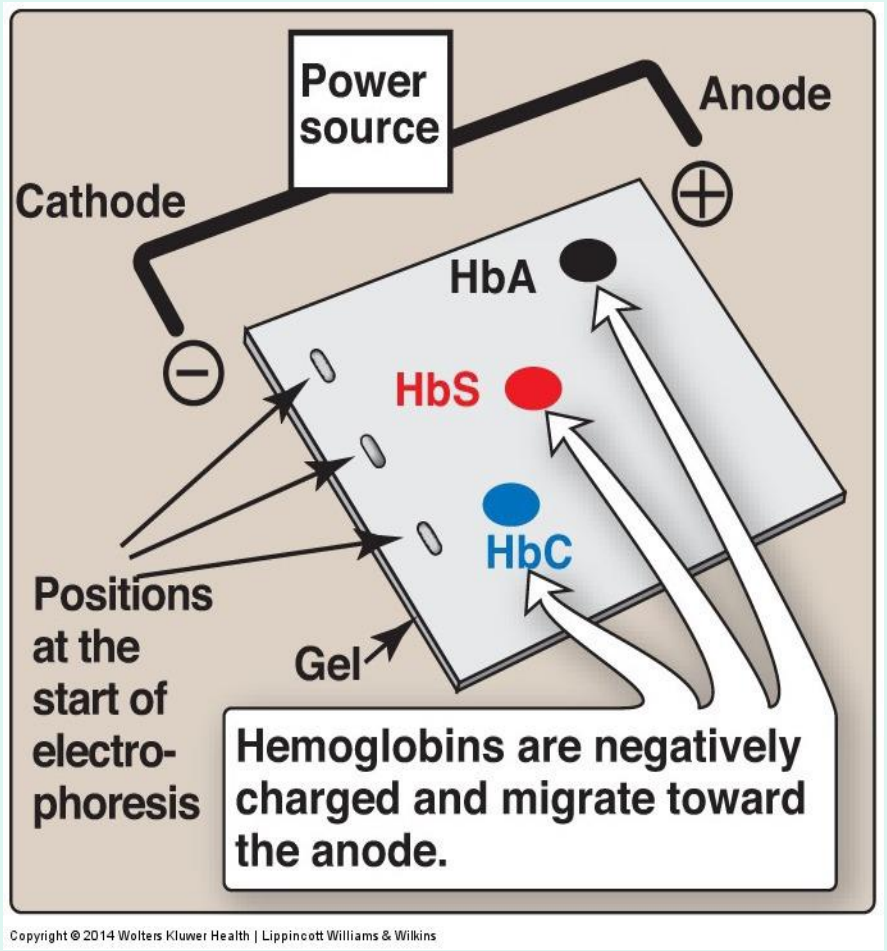


Fetal Hemoglobin

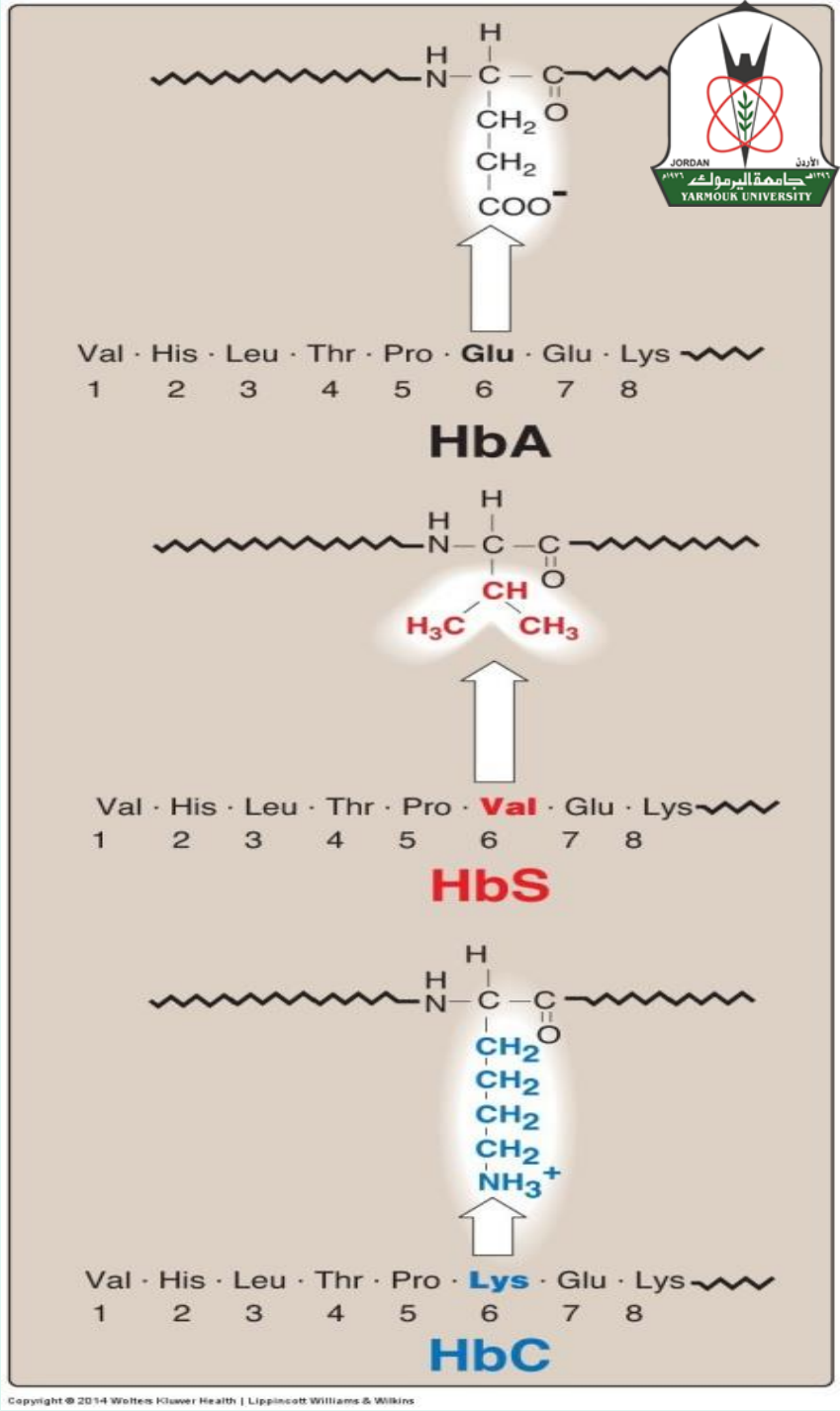
fetal hemoglobin's greater affinity for oxygen is that it doesn't bind 2,3 BPG.

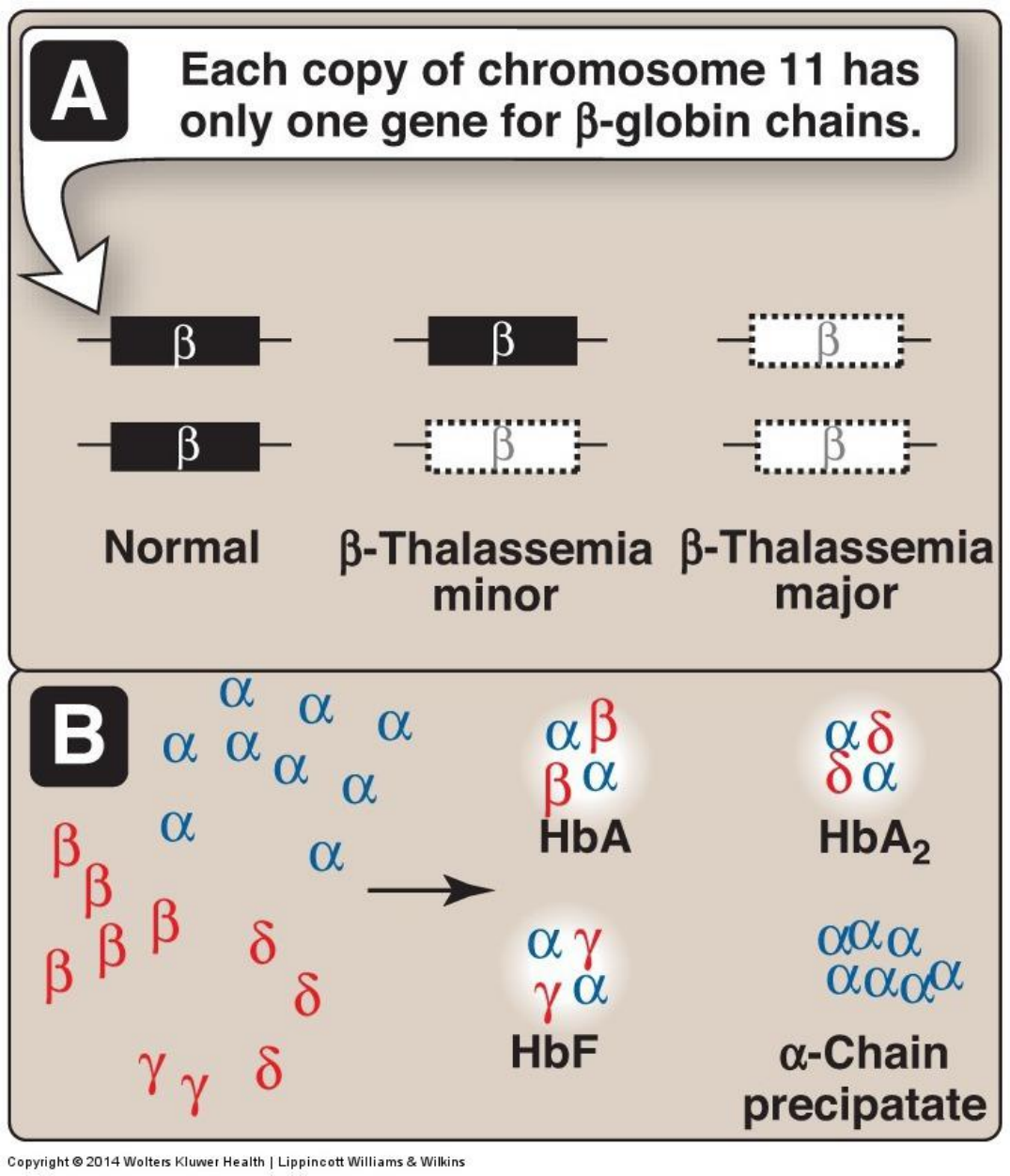


Fetal Hemoglobin Binding of O_2



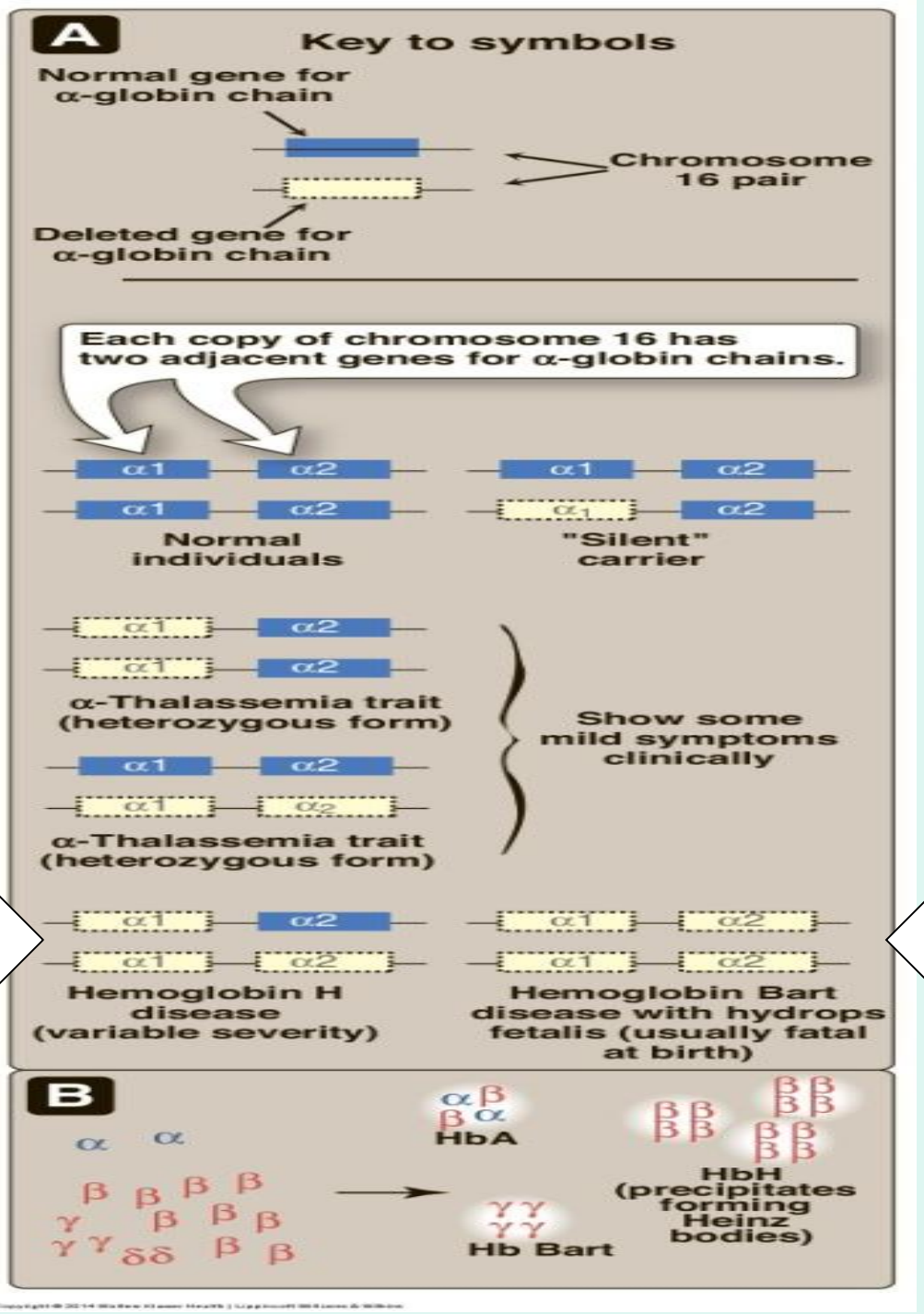
We can separate it by gel electrophoresis (from negative to the positive pole):
A is negative, so it is the faster.
B is neutral.
C is positive charge.



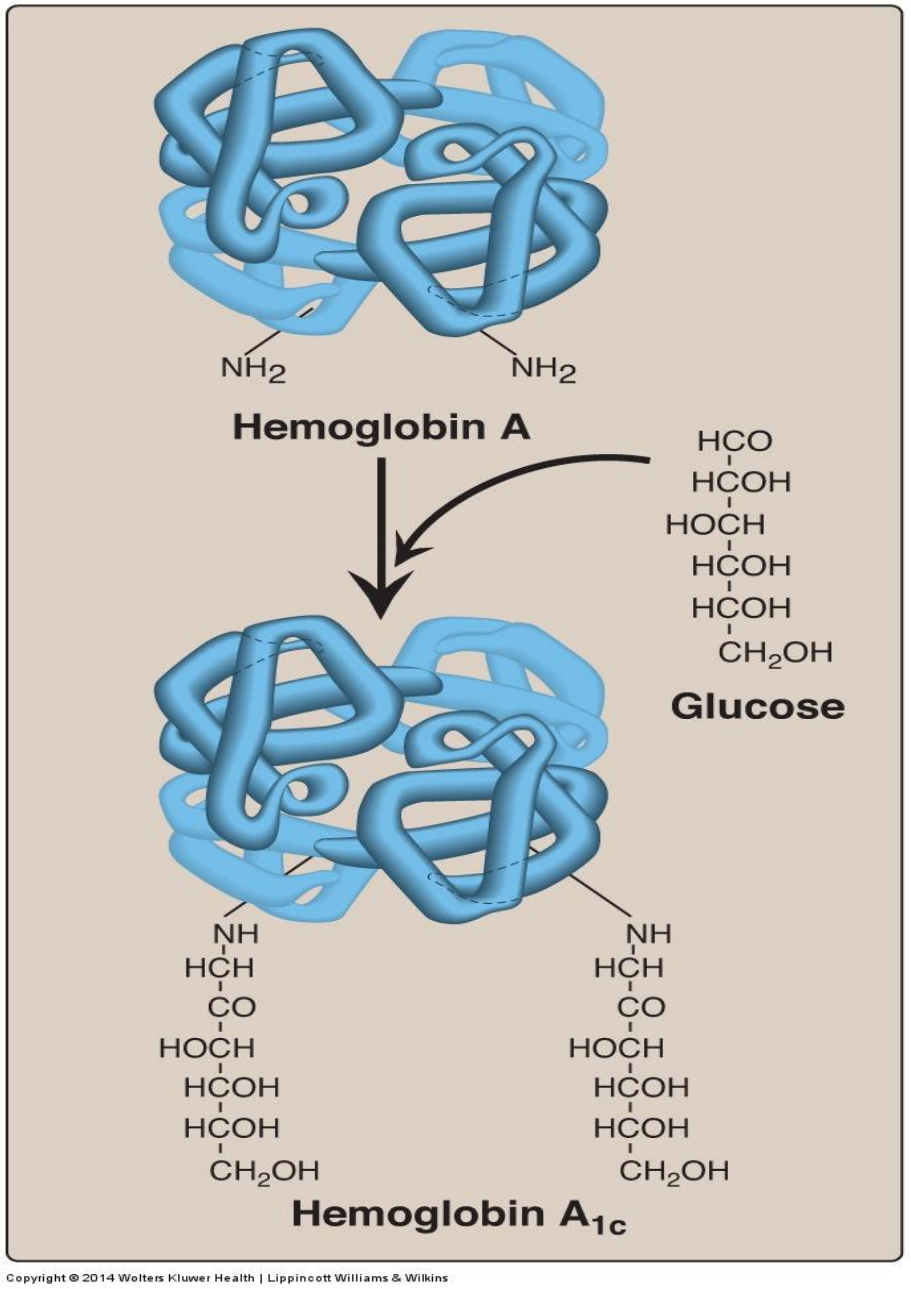


Population is more risk to have beta type , because it has2 alleles while alpha has 4.

You have very low concentration of alpha



You have no alpha



NUMEROUS MUTATIONS AFFECTING HUMAN HEMOGLOBINS HAVE BEEN IDENTIFIED

More than 1100

More than 7% of the globe's population

هيك بكون كملت معكم البيوكم لهاد السستم
سامحوني ع اي اخطاء
إن احسنت فمن الله وإن اخطأت فمن نفسي
+اذا في اي تعديلات خبرونا مشان نعدلها
(التعديلات للاخطاء العلمية, الاملائية لابد منها)
كل التوفيق للجميع
#دعواتكم