- Structure and function of hemoglobin-

Biochemistry Teamwork

Osamah Al-Jarallah	Al-Anood Asiri
Abdulaziz Al-Shamlan	Lama Mokhlis
Abdullah Al-Mazyad	Noha Khalil
Turki Al-Otaibi	Reem Al-Mansour
Khalid Al-Khamis	Hadeel Helmi
Saud Al-awad	Nuha Al-Furayh
Khaled Almohaimede	Jumana Al-Shammari
Meshal Al-Otaibi	Deema Jomar

By : Khaled Almohaimede , Abdulaziz Al-Shamlan & Noha Khalil

Structure and function of hemoglobin

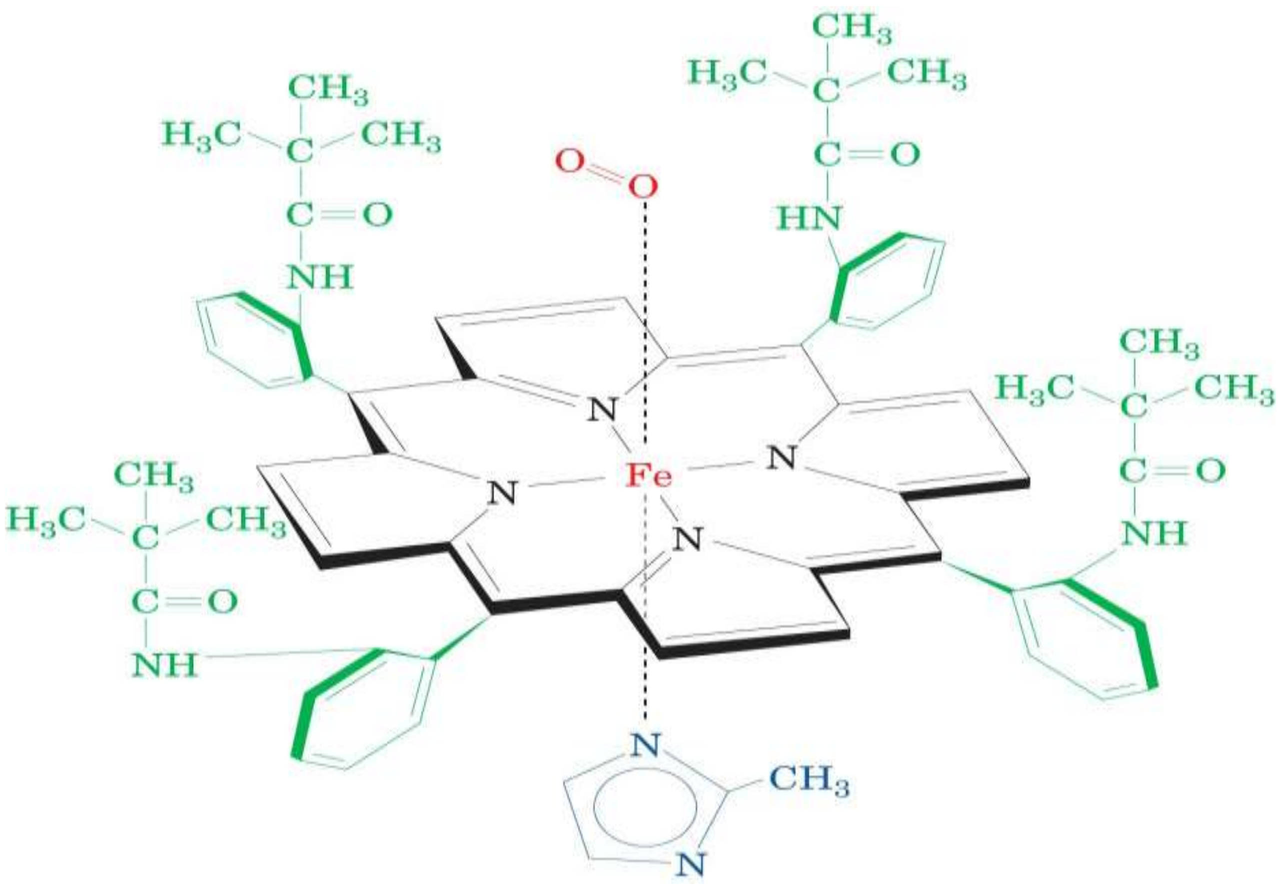
Hemoglobin (Hb)

- A hemeprotein found only in red blood cells
- Oxygen transport function
- Contains heme as prosthetic group
- Heme reversibly binds to oxygen (the point of reversible binding is whenever the oxygen is high it takes it and whenever it is low it releases it)

Prosthetic group: Helper molecule that is bound to a protein

The heme group

- A complex of protoporphyrin IX and ferrous iron (Fe^{+2})
- Fe^{+2} is present in the center of the heme
- Fe^{+2} binds to four nitrogen atoms of the porphyrin ring
- Forms two additional bonds with:
  - Histidine residue of globin chain
  - Oxygen



The heme group: Fe^{+2} – porphyrin complex with bound O_2

Types of Hb

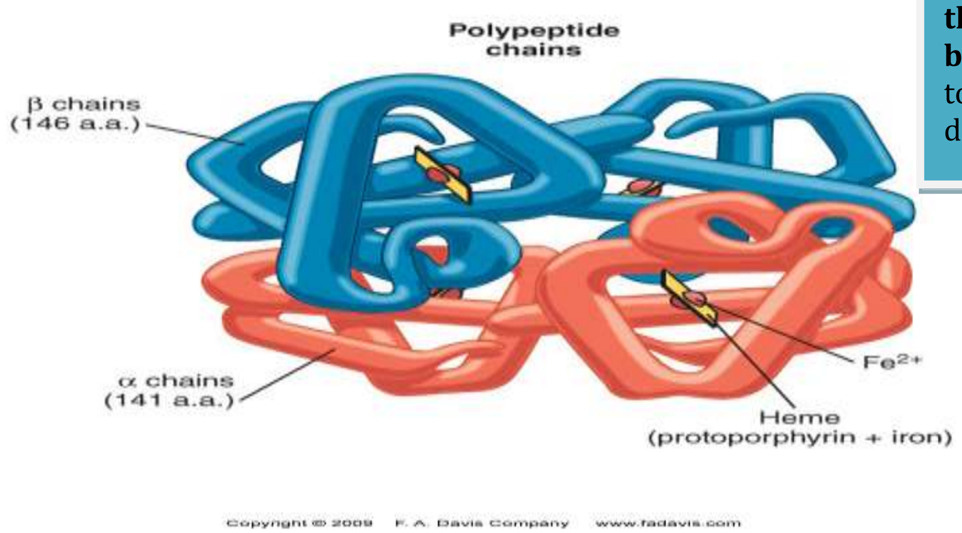
Normal:	**HbA (97%)**
	HbA_2 (2%)
	HbF (1%)
	HbA_{1c} **Levels are high in diabetic patient.**
Abnormal:	**Carboxy Hb**
	Met Hb
	Sulf Hb

Hemoglobin A (HbA)

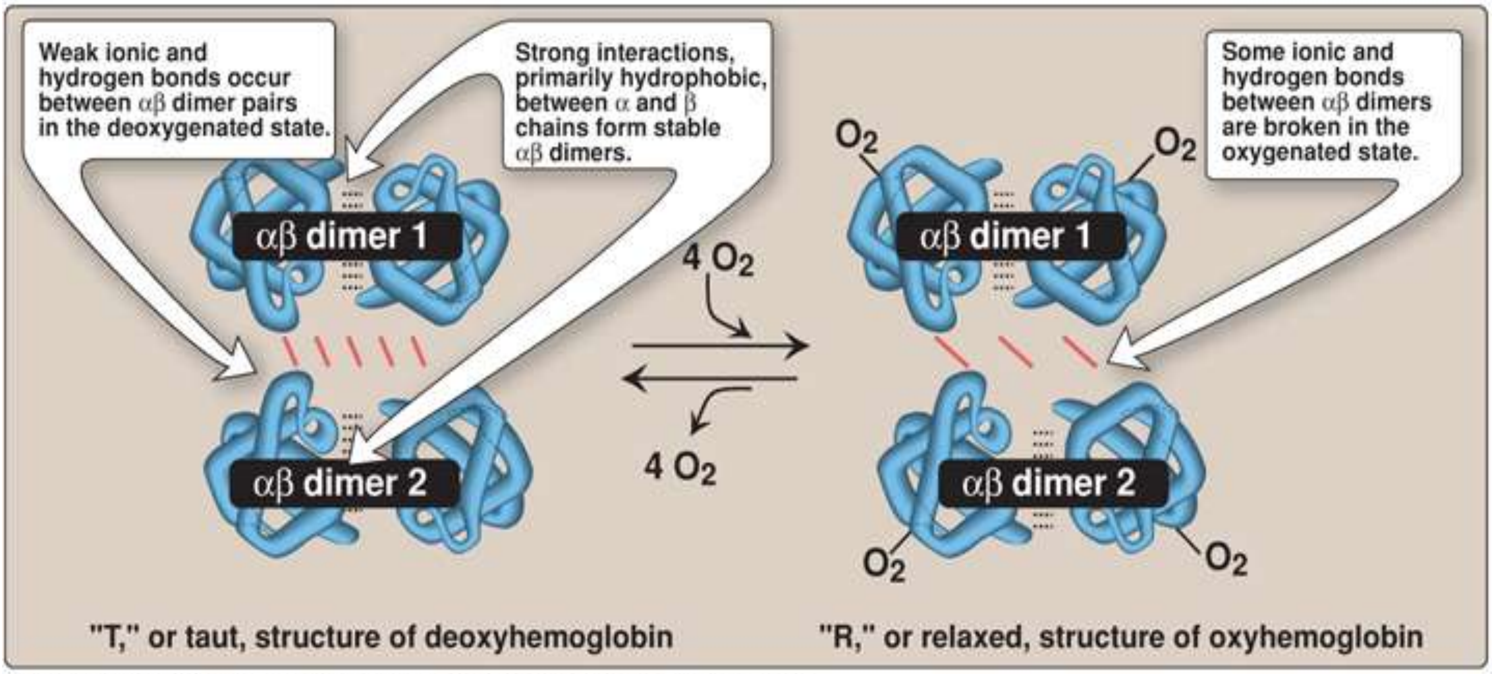
- Major Hb in adults
- Composed of four polypeptide chains:
    - Two α and two β chains
- Contains two dimers of αβ subunits
- The dimers are held together by non-covalent interactions
- Each chain is a subunit with a heme group in the center that carries oxygen
- A Hb molecule contains 4 heme groups and carries 4 molecules of O_2

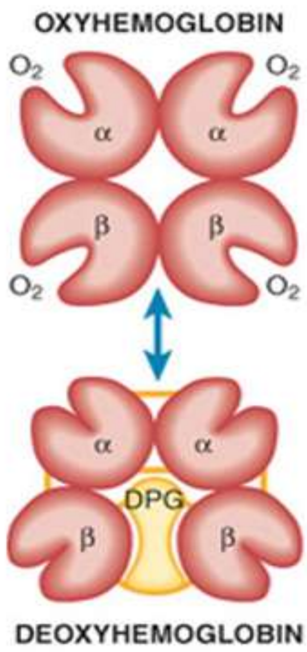
1 dimer = 2 subunits
(thus Hb composed of 4 subunits)

Between α and β **there are hydrogen, Ionic and hydrophobic bonds while between the two dimers there are ionic and hydrogen bonds.** (α and β are held together stronger than the two dimers)



HbA Structure





- ✓ T-form of Hb
  - ❖ The deoxy form of Hb
  - ❖ Taut form (or tense form)
  - ❖ The movement of dimers is constrained
  - ❖ Low-oxygen-affinity form

- ✓ R-form of Hb
  - ❖ The oxygenated form of Hb
  - ❖ Relaxed form
  - ❖ The dimers have more freedom of movement
  - ❖ High-oxygen-affinity form

When Hb reaches the tissue, it becomes more taut so O_2 will be released (like squeezing). While in lungs, Hb will be in relaxed form in which more O_2 will be able to be bound.

Hemoglobin function

- Carries oxygen from the lungs to tissues
- Carries Carbon dioxide from tissues back to the lungs
- Normal level (g/dL):
- Males: 14-16
- Females: 13-15

Factors affecting oxygen binding

- ✓ Three allosteric effectors:
  - pO_2 (Partial oxygen pressure)
  - pH of the environment
  - pCO_2 (partial carbon dioxide pressure)
  - Availability of 2,3-bisphosphoglycerate

Hint: BPG = DPG

Oxygen Dissociation curve

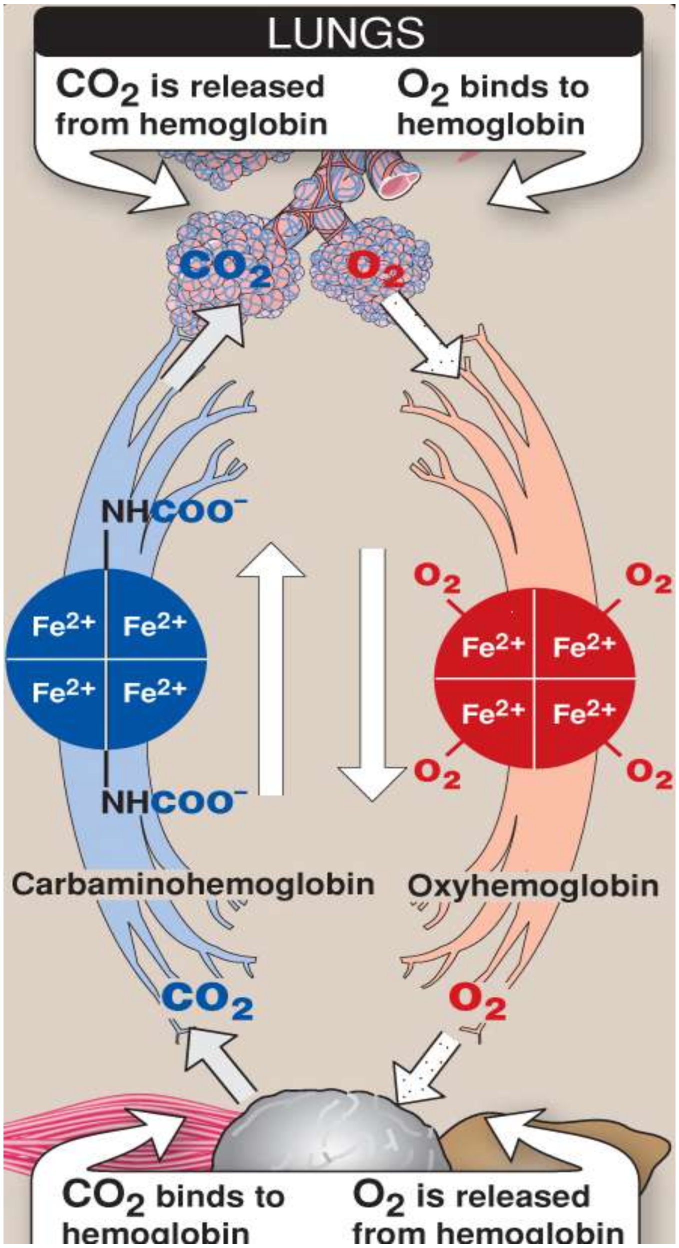
- The curve is sigmoidal (sigmoidal = S-shaped)
- Indicates cooperation of subunits in O_2 binding (cooperation (cooperative binding): when the oxygen binds to hemoglobin it helps the binding of the next oxygen)
- Binding of O_2 to one heme group increases O_2 affinity of others
- Heme-heme interaction

As we know, we have 4 subunits, so when 1 subunit binds to O_2, the other subunits will bind to O_2 also.

If P50 is high = low affinity
Cause: we need more pressure to saturate O_2 within RBCs.
&
Vice versa

pO2 (partial oxygen pressure)

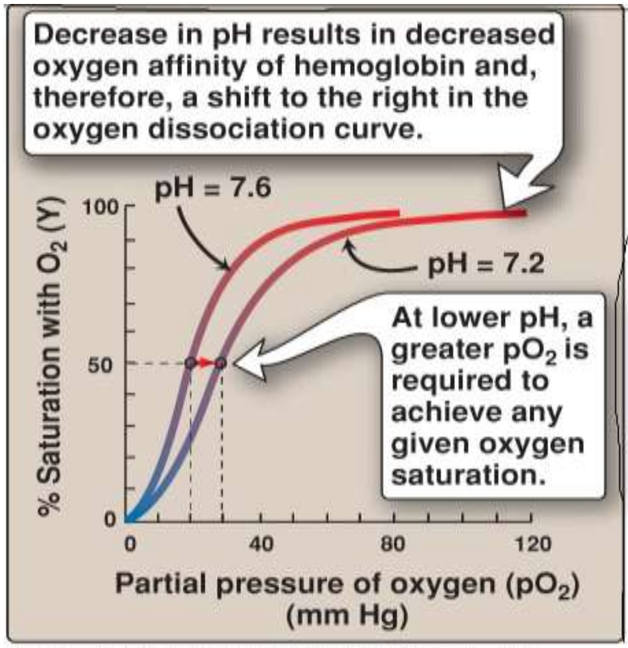
- Indicates affinity of Hb to O_2
- P_{50}(mmHg): the pressure at which Hb is 50% saturated with O_2
- High affinity → slow unloading of O_2 (occur in lungs)
- Low affinity → fast unloading of O_2 (occur in tissues)
- Lung pO_2 is 100 mm → Hb saturation 100%
- Tissue pO_2 is 40 mm → Hb saturation reduces
- Hence O_2 is delivered to tissues



Bohr : scientist name

The Bohr effect

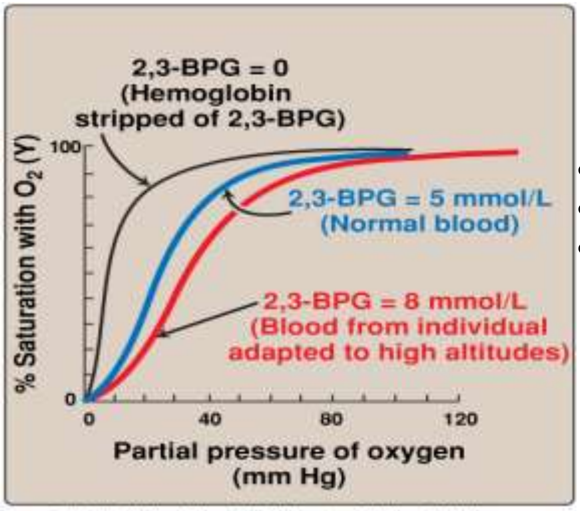
- Effect of pH and pCO_2 on:
- Oxygenation of Hb in the lungs (pH is high in the lung)
- Deoxygenation in tissues (pH is low in the tissues)
- Tissues have lower pH (acidic) than lungs
- Due to proton generation:
- $CO_2 + H_2O \rightarrow HCO_3^- + H^+$ **(H^+ is more than** HCO_3^-, So the environment will be **acidic)**
- Protons reduce O_2 affinity of Hb
- Causing easier O_2 release into the tissues
- The free Hb binds to two protons
- Protons are released and react with HCO^{3-} to form CO_2 gas
- The proton-poor Hb now has greater affinity for O_2 (in lungs)
- The Bohr effect removes insoluble CO_2(in the form of $HCO3^-$) from blood stream
- Produces soluble bicarbonate



Proton generation in the tissue has many sources, thus the net result will be acidic pH in tissue despite HCO_3^- generation.
If the curve shifts to the left (higher PH) = higher affinity; less pressure is required for saturation
If the curve shifts to the right (lower PH) = lower affinity; more pressure is required for saturation
In lungs, pH is high (Alkaline), thus the affinity is high for O_2 binding

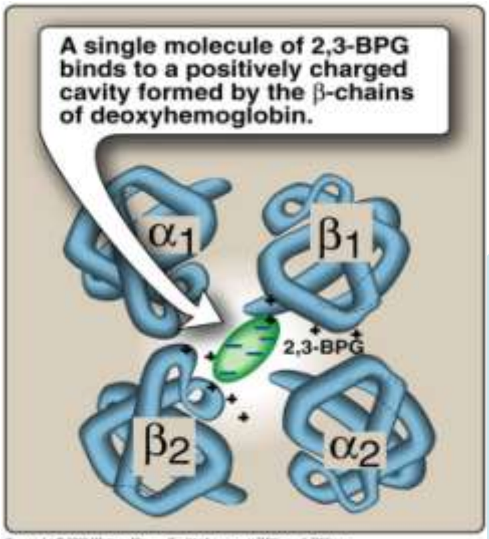
Availability of 2,3 bisphosphoglycerate (one of the glycolysis products)

- Binds to deoxy-hb and stabilizes the T-form (it reduces the affinity)
- When oxygen binds to Hb, BPG is released



At high altitudes:

- RBC number increases
- Hb conc. Increases
- BPG increases → reduces the affinity, why? To ensure O_2 delivery to the tissues.



High altitude and O2 affinity

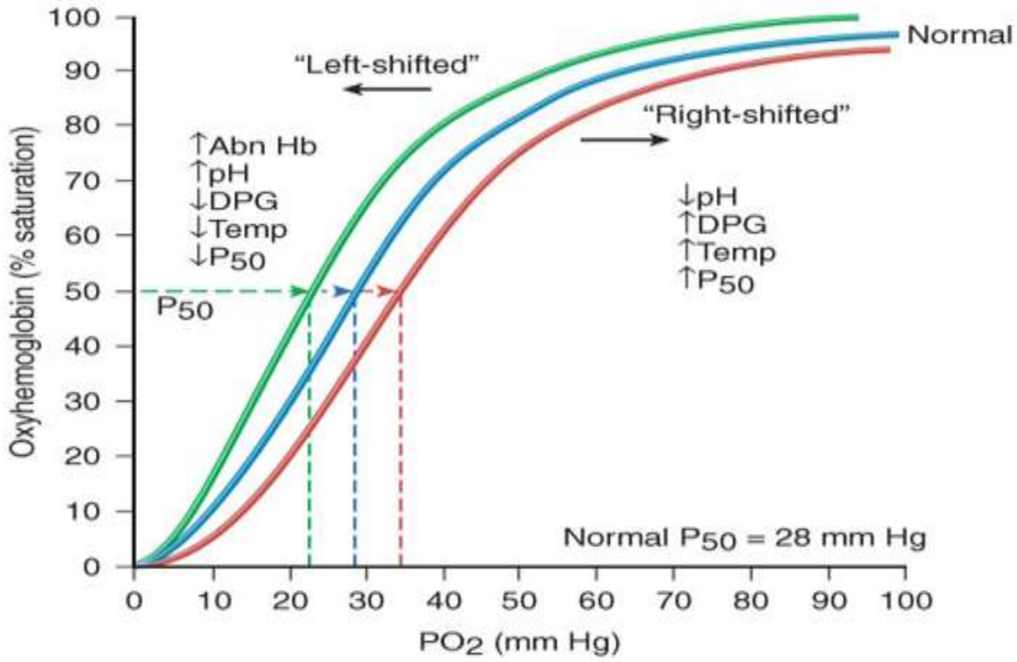
In hypoxia and high altitude

- 2,3 BPG levels rise
- This decreases O_2 affinity of Hb
- Thus increases O_2 delivery to tissues

BPG: is produced by tissues
BPG is not bound to Hb when it reaches the lungs, but once Hb reaches to the tissue, BPG will bind to it causing release of O_2

High O2 affinity is due to:

- Alkalosis
- High levels of Hb F
- Multiple transfusion of 2,3 DPG-depleted blood



Fetal hemoglobin (HbF)

- Major hemoglobin found in the fetus and newborn
- Tetramer with two α and two γ chains
- Higher affinity for O_2 than HBA
- Transfers O_2 from maternal to fetal circulation across placenta

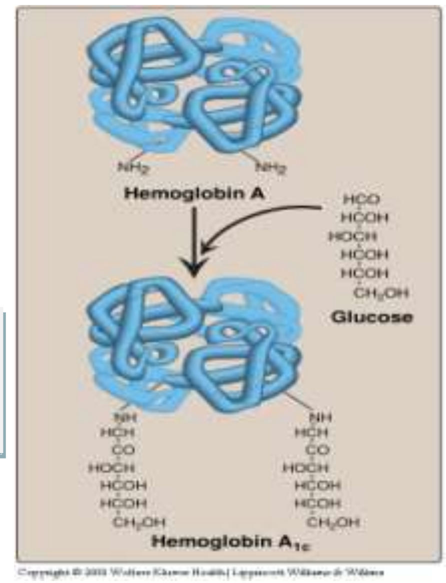
HbA2

- Appears ~12 weeks after birth
- Constitutes ~2% of total Hb
- Composed of two α and two δ globin chains

HbA1c

- HbA undergoes non-enzymatic glycosylation
- Glycosylation depends on plasma glucose levels
- HbA1c levels are high in patients with diabetes mellitus

HbA_{1c} has a half life of 2-3 weeks, so you can tell about the blood glucose level of 3 weeks ago.



Abnormal Hbs

Unable to transport O_2 due to abnormal structure

- Carboxy-Hb: CO replaces O_2 and binds 200X (200 times) tighter than O_2 (in smokers) (reversible)
- Met-Hb: Contains oxidized Fe^{3+} (~2%) that cannot carry O_2 (reversible)
- Sulf-HB: Forms due to high sulfur levels in blood (irreversible reaction)

Questions

1. Which one is the abnormal form of hemoglobin?
A. Oxyhomoglobin
B. Carbaminohemoglobin
C. Deoxyhemoglobin
D. Carboxyhemoglobin

2. A man lives at high altitudes for the past 5 years. What change would you expect in the blood of this person?
A. Lower number of red blood cells
B. Lower amount of hemoglobin in the RBCs
C. Increase in the 2,3-BisPhosphoGlycerate (BPG) levels
D. A shift of oxygen-dissociation curve to the left

3. Which ONE of the following is the major form of adult hemoglobin?
A. HbA2
B. HbA
C. HbF
D. HbA1c

4. Regarding T-form of Hb :
A. Low-oxygen-affinity form
B. The oxygenated form of Hb
C. High-oxygen-affinity form
D. The dimers have more freedom of movement

Answers: 1. D 2. C 3. B 4. A