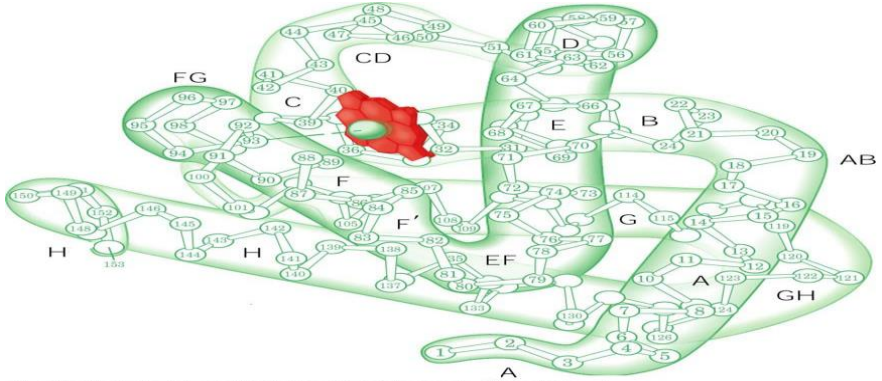
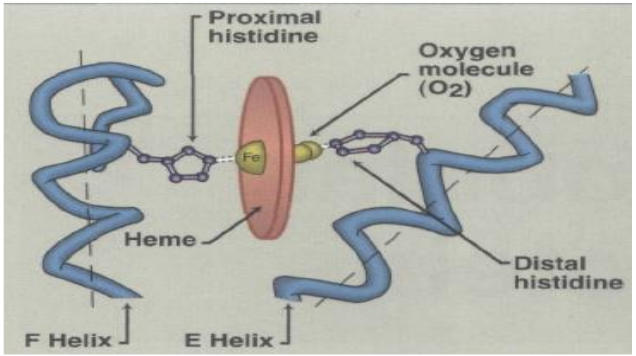
Hemoglobin and Myoglobin

Myoglobin

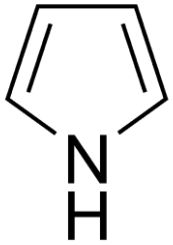
- **Definition :** an intracellular heme protein primarily found in muscle cells. It plays a crucial role in storing oxygen and facilitating its diffusion within these tissues.
  - **Structure :** Composed of a single polypeptide chain of 153 amino acids, Approximately 80% of its structure is made up of α helices, organized into eight segments labeled A–H.
    - The heme group is situated between the E and F helices, within a globular structure that forms a cradle for the heme and oxygen binding.

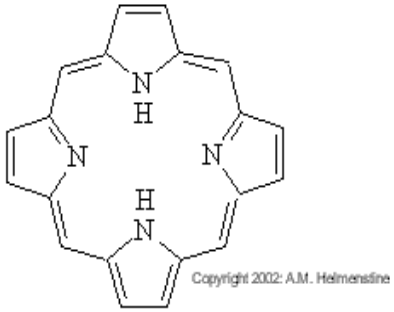




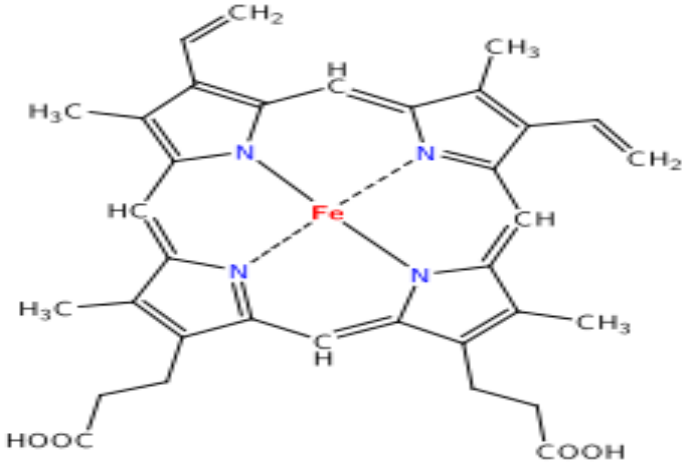
Heme Group

- Both myoglobin and hemoglobin have heme
- Heme is a complex of porphyrin and ferrous iron (Fe^{2+})
  - Porphyrins are a group of organic compound that have four pyrrole subunits interconnected via α-methylene bridges (=CH-)
    - A pyrrole ring is a group of four carbon atoms and a nitrogen atom bonded together in a ring



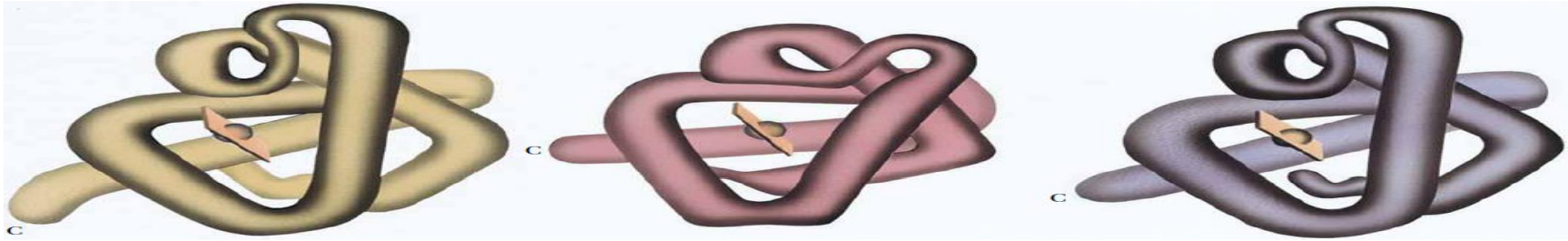


Porphyrin Ring



Hemoglobin

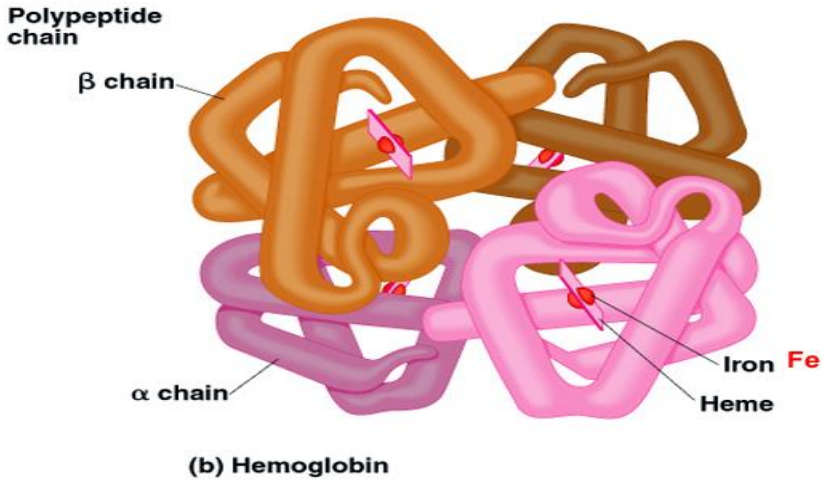
- **Definition :** a globular protein found in red blood cells, with each cell containing around 270 million hemoglobin molecules
  - **Structure :** composed of four polypeptide chains: two alpha (α) chains and two beta (β) chains.
    - The β chain is 146 amino acids long, making it shorter than the myoglobin chain (153 residues) due to a shorter H helix.
    - The α chain has 141 residues, also featuring a shortened H helix and lacking the D helix.



Myoglobin (Mb) α-Globin (Hbα) β-Globin (Hbβ)

Quaternary Structure of Hemoglobin

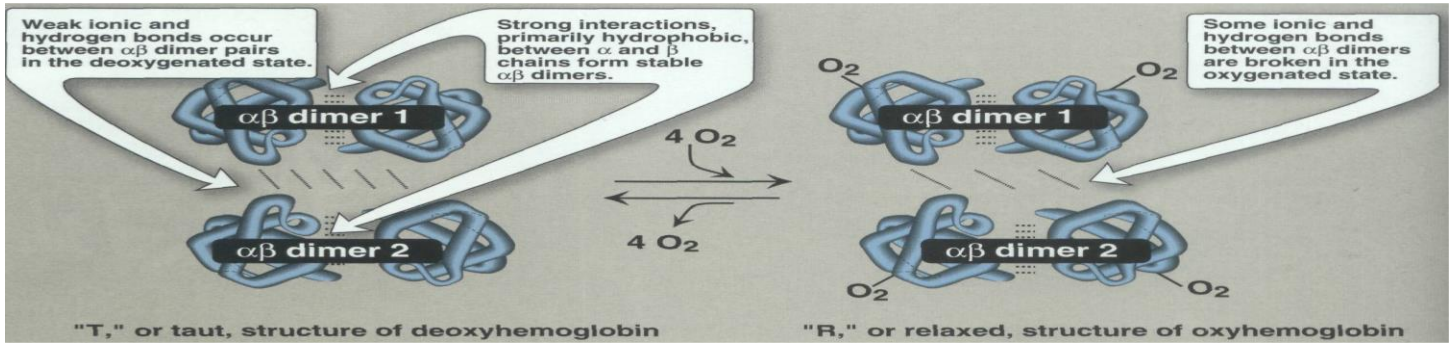
- There are two identical dimmers, dimmer one α1β1 and dimmer two α2β2.
  - The two polypeptide chains within each dimmer are held tightly together, primarily by hydrophobic interactions although Ionic (Salt Bond) and hydrogen bonds play a role.



(b) Hemoglobin

T & R forms of Hemoglobin

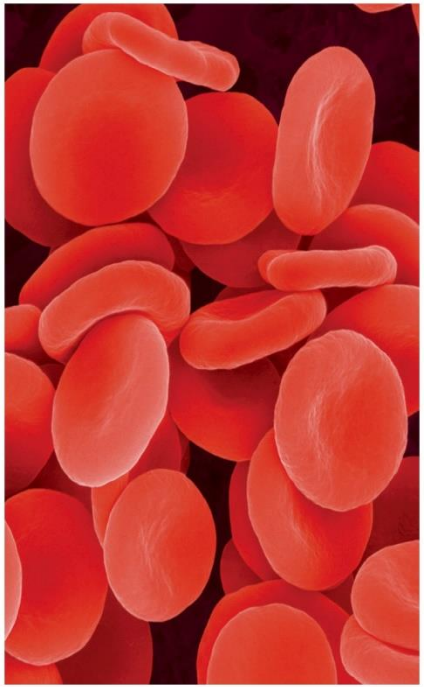
- **T form:** The deoxy form of hemoglobin is called the "T" **(tense)** form
  - The T form is the **low oxygen-affinity form** of hemoglobin
  - the two αβ dimmers interact through a network of ionic bonds and hydrogen bonds
- **R form** : The oxygenated form of hemoglobin is called the (relaxed) form
  - The R form is the **high oxygen-affinity form** of hemoglobin
  - binding of oxygen to hemoglobin causes the rupture of some of the ionic bonds and hydrogen bonds



RBCs

- **Biconcave shape** gives them a much greater surface area & flexibility to squeeze through tiny capillaries

- **Carbon monoxide** binds to heme on the same place as that of O_2
  - Carbon monoxide (CO) has a greater affinity for hemoglobin than oxygen
  - Therefore the haemoglobin is no longer available for oxygen transportation causing hypoxia tissue death
  - To reverse the effects of carbon monoxide, pure oxygen is needed to be introduced



Chapter 7 Opener part 1
Biochemistry, Sixth Edition

Methemoglobin

- **Definition :** a form of hemoglobin where the iron is oxidized from the ferrous (Fe^{2+}) state to the ferric (Fe^{3+}) state
- **Oxygen Binding**: For hemoglobin to bind oxygen, iron must remain in the Fe^{2+} state; when oxidized to Fe^{3+}, it cannot carry oxygen
- **Reduction System**: Red blood cells possess a system to convert Fe^{3+} back to Fe^{2+}, ensuring proper oxygen transport. This system includes:
  - **NADH**: Generated from glycolysis, serving as a reducing agent.
  - **Cytochrome b5 reductase** (methemoglobin reductase): Catalyzes the reduction process.
  - **Cytochrome b5**: Transfers an electron to reduce methemoglobin.

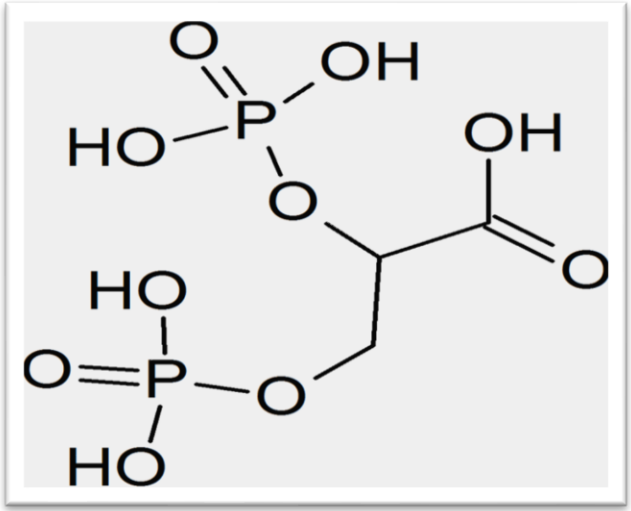
Allosteric effects

- The ability of hemoglobin to reversibly bind oxygen is affected by the pO_2, the **pH** of the environment, the **pCO_2** and the availability of **2,3-bisphosphoglycerate (2,3-BPG)**
  - **Allosteric :** ("other site") effectors , because their interaction at one site on the hemoglobin molecule affects the binding of oxygen to heme groups at other locations on the molecule
  - The binding of oxygen to myoglobin is not influenced by the allosteric effectors of hemoglobin.

2,3-Bisphosphoglycerate (2,3-BPG)

❖**2,3-Bisphosphoglycerate (2,3-BPG) :** is a glycolytic intermediate that plays a crucial role in regulating oxygen binding to hemoglobin

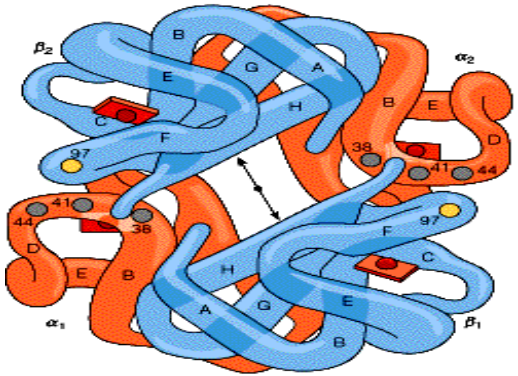
- Low partial pressure of oxygen (pO2) in peripheral tissues stimulates the synthesis of 2,3-BPG in red blood cells (RBCs).
- 2,3-BPG binds to partially deoxygenated hemoglobin, lowering its affinity for oxygen



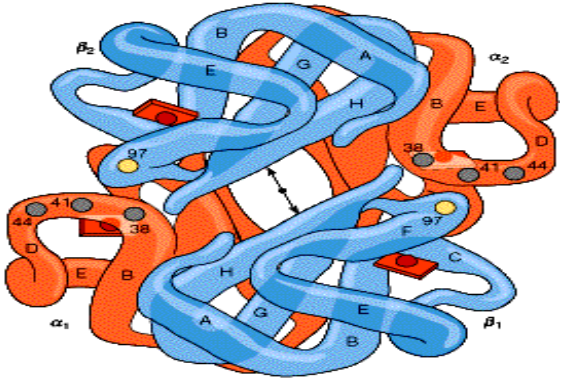
2,3-Bisphosphoglycerate (2,3-BPG)

❖ **Effect on Hemoglobin**:

- There is one binding site for 2,3-BPG located in the central cavity of hemoglobin, formed by interactions between four amino acids
- **Stabilization of Deoxyhemoglobin**: Upon binding, 2,3-BPG cross-links the two β-subunits, forming ionic bonds with key amino acids, including the N-terminus of carbons **1 and 2, 143 histidine, and the carboxyl group of 82 lysine**. This stabilizes the deoxy conformation of hemoglobin, favoring oxygen dissociation.

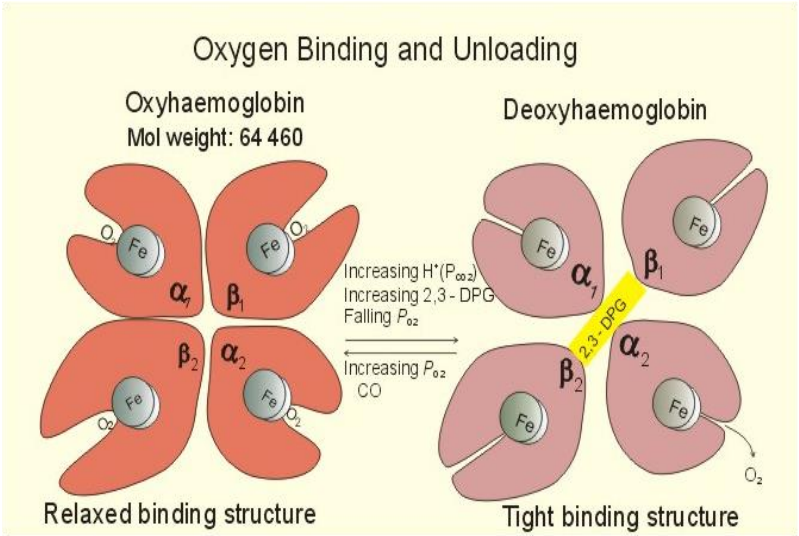


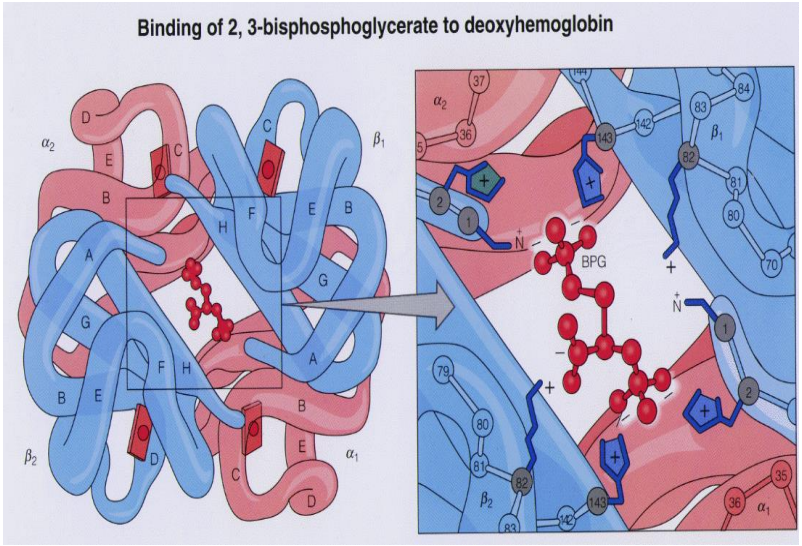
Deoxyhemoglobin



Oxyhemoglobin

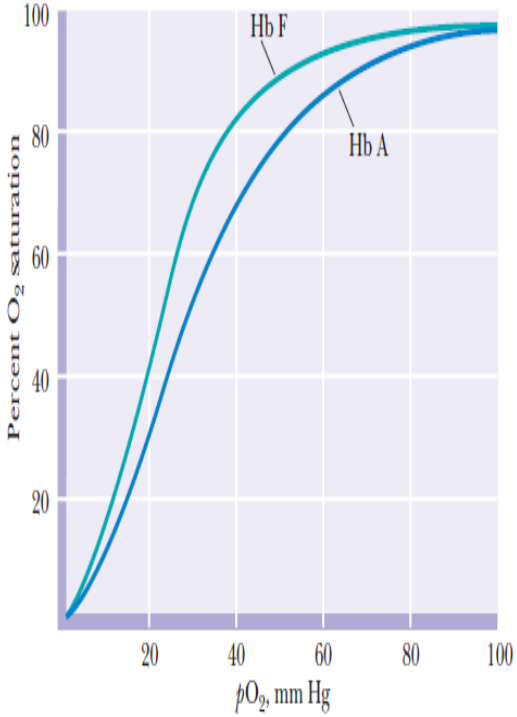
2,3-Bisphosphoglycerate (2,3-BPG)





Fetal Hemoglobin

- Fetal Hemoglobin is **α2γ2**
- **Fetal Hb has a higher affinity for O_2 because it has a lower affinity for 2,3-BPG**
  - the β-chains are replaced by 146-residue subunits called γ chains (gamma chains)
    - 2,3-BPG binds less effectively with the γ chains of fetal Hb
    - Fetal γ chains have Serine (polar uncharged) instead of Histidine at position 143, and thus lack two of the positive charges in the central BPG-binding cavity



Hemoglobin	Myoglobin
In RBCs	In Muscles
Carrier of O2	Reservoir of O2
Has Quaternary Structure	No Quaternary Structure
Can carry CO2	Can’t carry CO2
Can bind 2,3 BPG	Can’t bind 2,3 BPG
Shows Cooperativity	No Cooperativity
O2 affinity is lower than Mb	O2 affinity is higher than Hbg