HEMATOLOGY

&LYMPH SYSTEM

Biochemistry slides

Number: 1

Doctor: Dr. nayef

Hemoglobin & Myoglobin

- Objectives

- structure – Function relationships in proteins
- Hb – an allosteric protein
- Hb - 4 chains and of two kinds
- Why fetuses have distinctive Hb "Hb F"
- Concept of Molecular Diseases

A. Hb & Mb

(1) Normal Structure of Hb & Mb

(2) Effect of
- pO_2, pH & Temp.
- Mechanism of cooperativity

(3) Effect of 2,3-BPG

(4) CO_2 transport & Mechanism & Bohr effect

(5) Abnormal Hb

(6) Thalassemia

(7) Hb derivatives

B. Heme metabolism

C. Iron Metabolism

D. Metabolism in mature rbc & Genetic disorders

- Globular Heme proteins

- Prosthetic group - HEME

- Apoprotein - provides an environment of three dimensional structure that dictate the role of heme

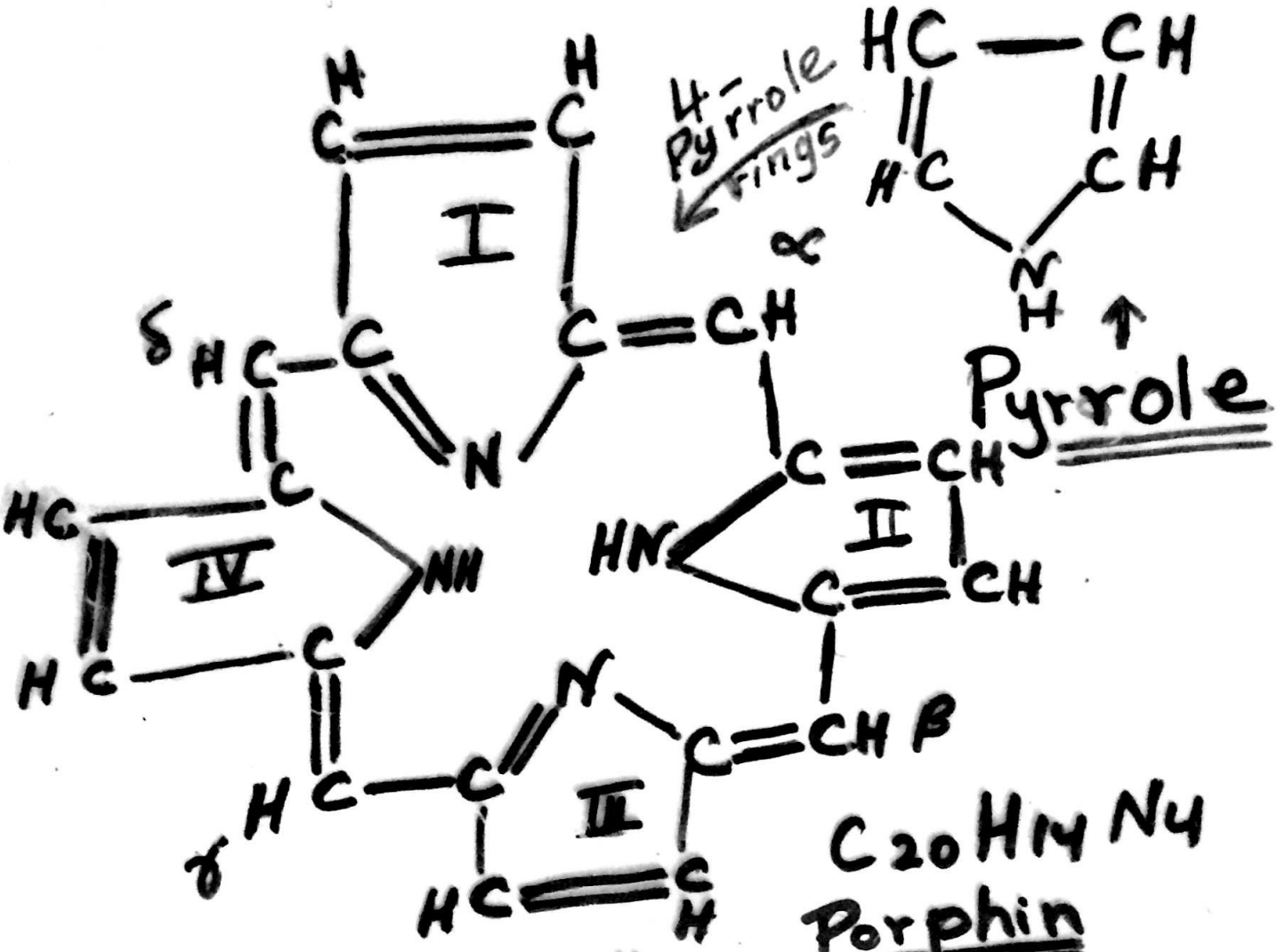
  → Reversible binding of O_2 as in Hb and Mb

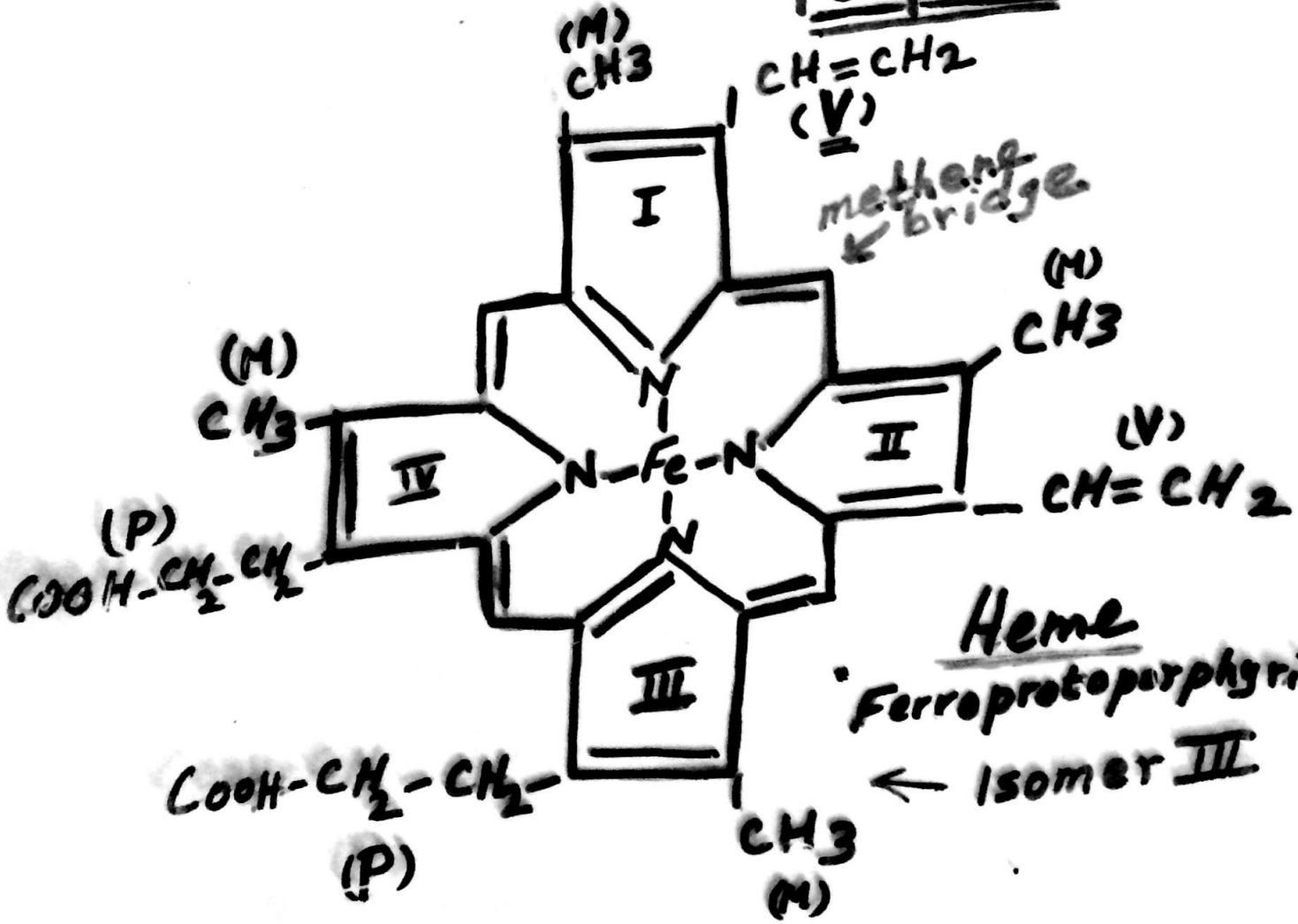
  → Electron carrier as in Cytochromes

  → breakdown of H_2O_2 as in catalase

  → others

HEME STRUCTURE:

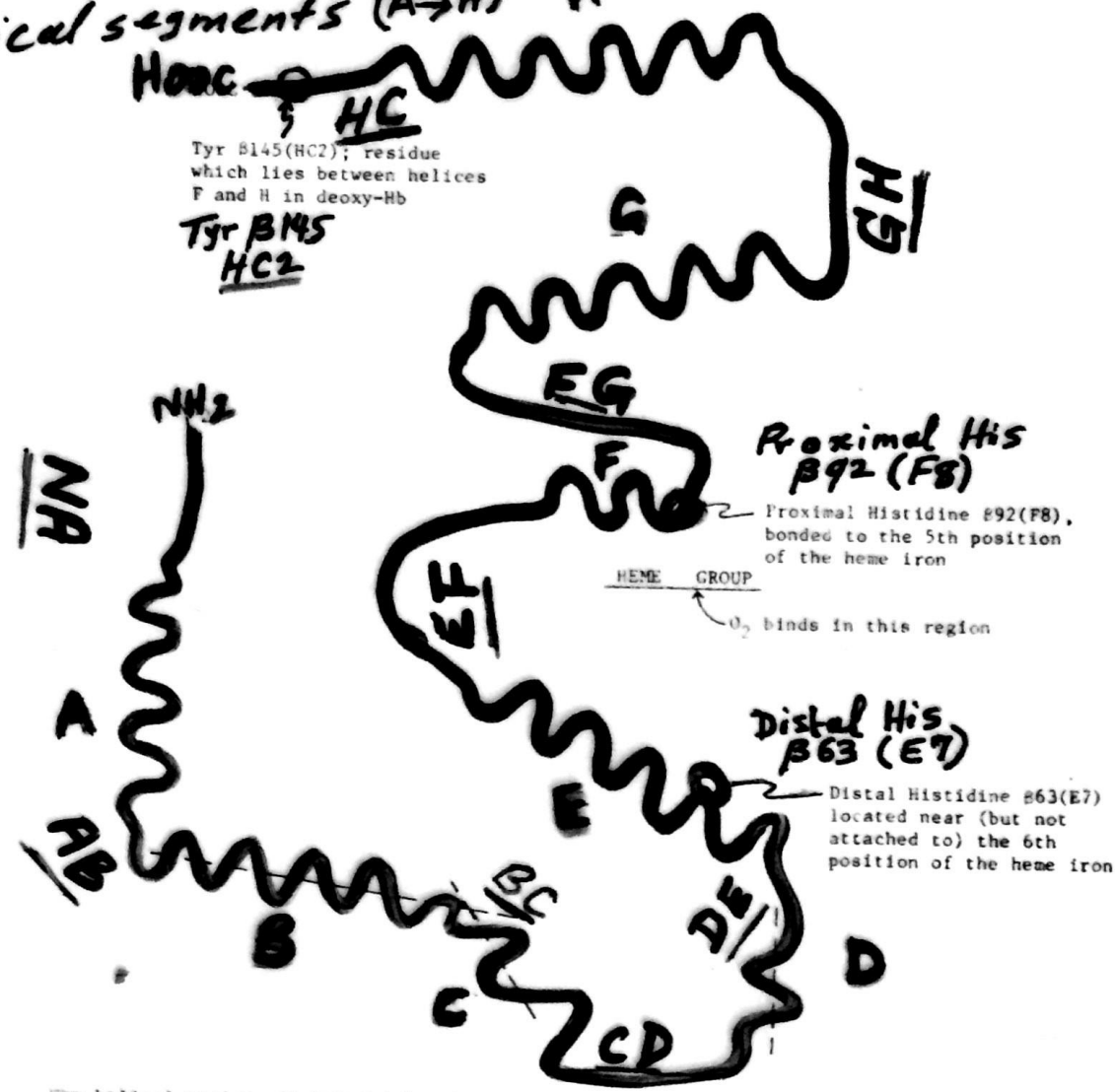




SEC. STRUCTURE OF β-chain of Hb

Figure 81. Secondary Structure of the β-Chain of Human Hemoglobin

146 residues
8 helical segments (A→H)



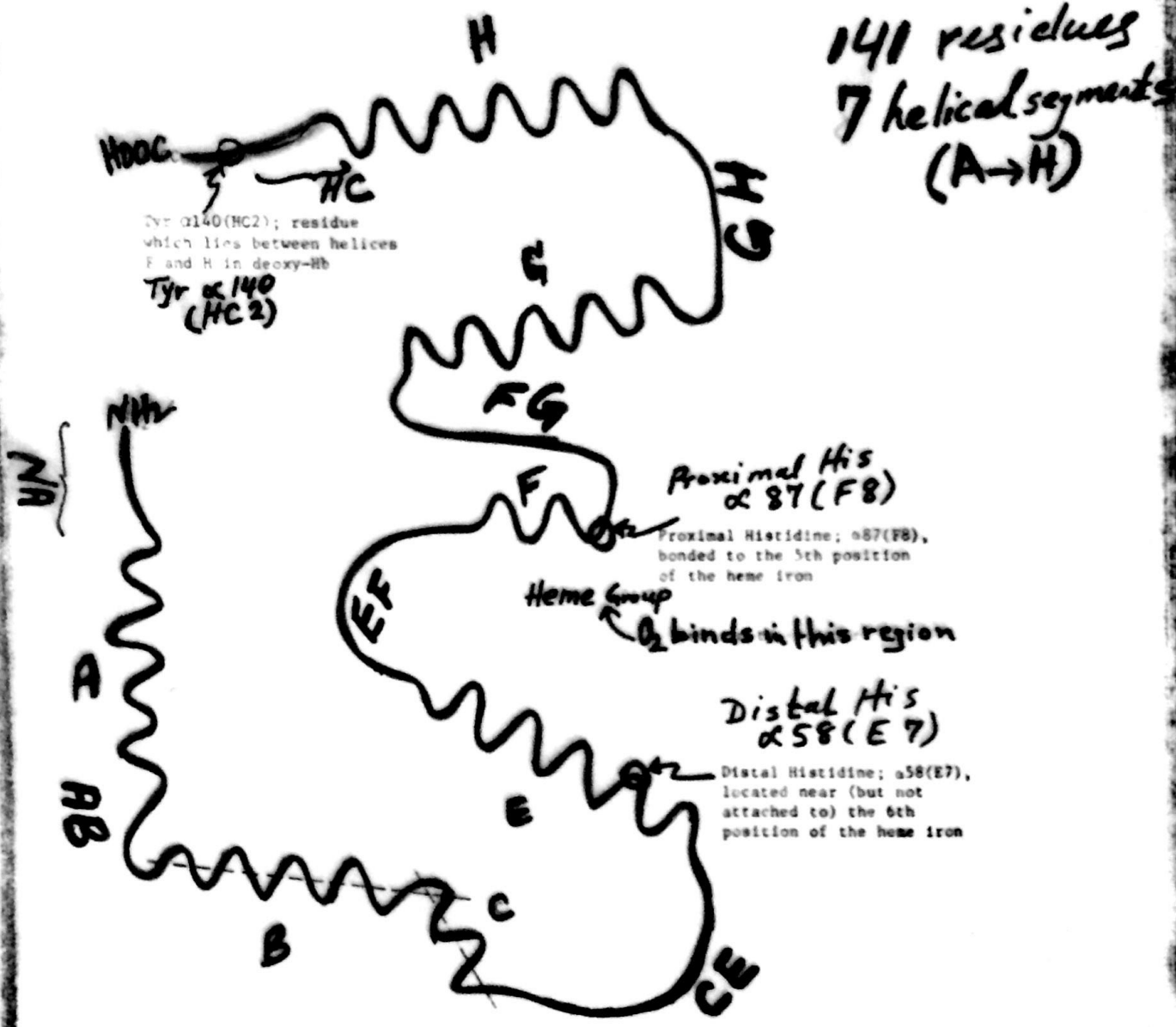
The helical regions (labeled A-H, after Kendrew), N- and C-termini, and the histidines located near the heme group are indicated. The axes of the B, C, and D helices are indicated by dashed lines.

The α-helical regions are terminated by
1- Presence of Proline
or 2- β-bends and loops stabilized by H-bonds and ionic bonds
Electrostatic Interactions or salt bridges

Sec. Structure of α-chain of Hb

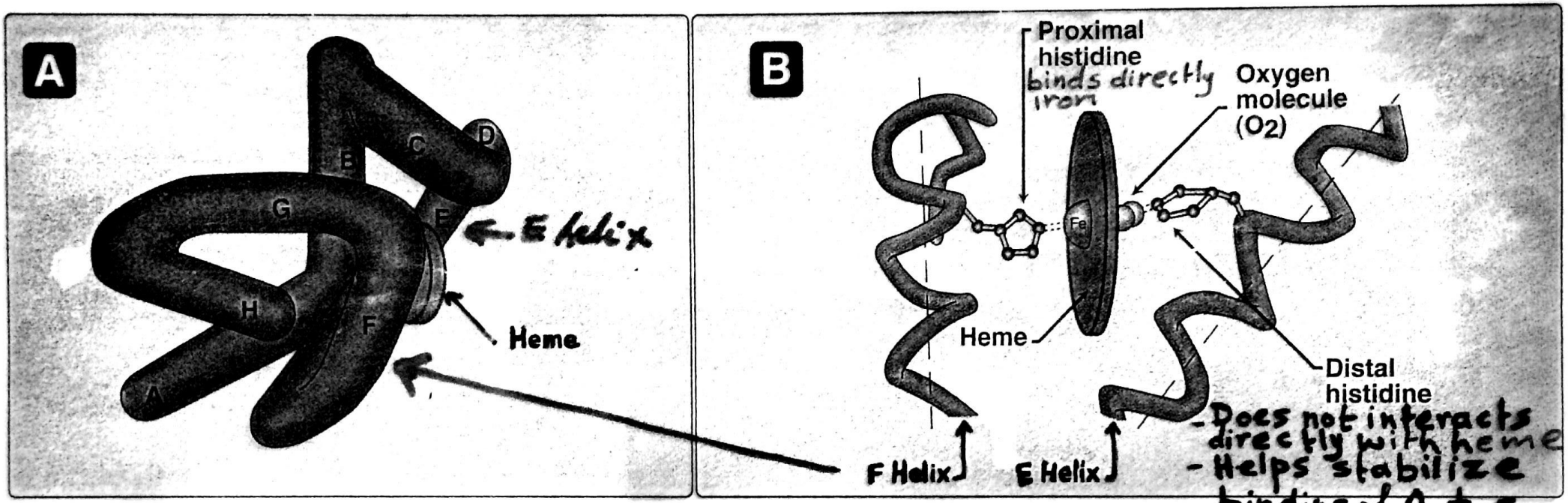
40

Figure 80. Secondary Structure of the α-Chain of Human Hemoglobin



The helical regions (labeled A-H, after Kendrew), N- and C-termini, and the histidines located near the heme group are indicated. The axes of the B and C helices are indicated by dashed lines.

Binding site of heme



- Does not interacts directly with heme
- Helps stabilize binding of O_2 to Ferrous iron

Prosthetic group
Apoprotein
Holoprotein

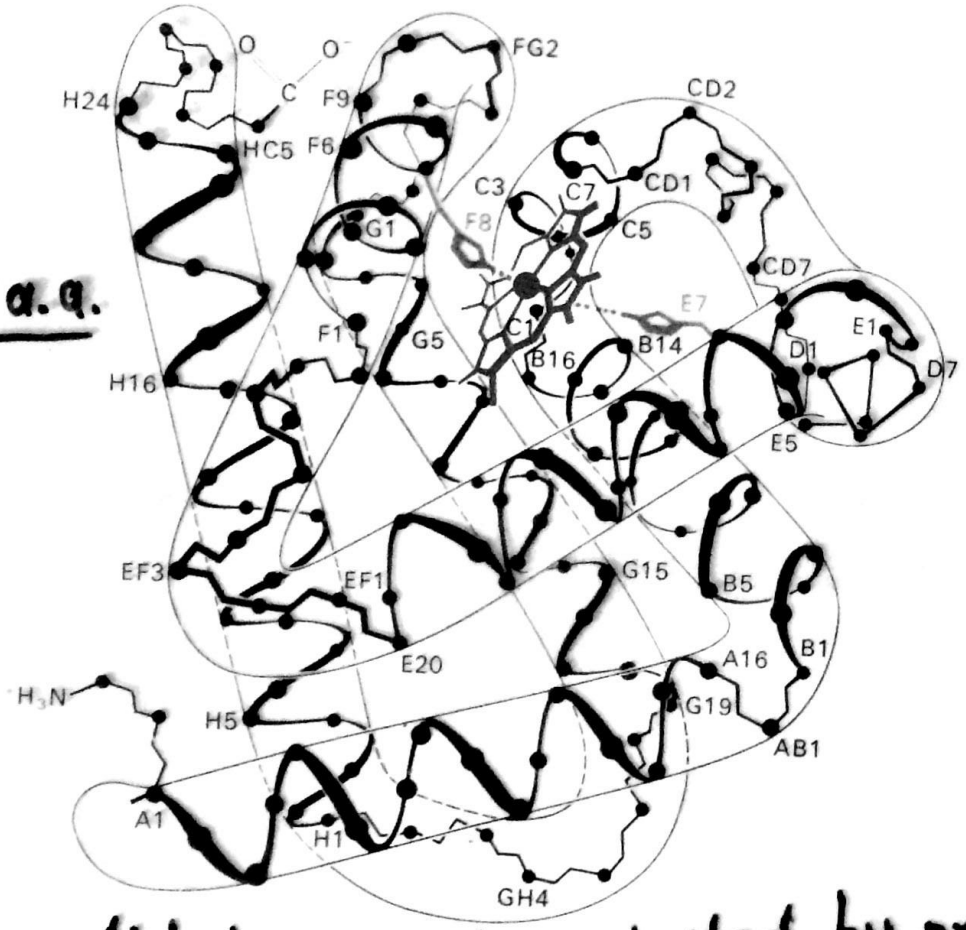
Proximal His
Distal His
Heme Pocket

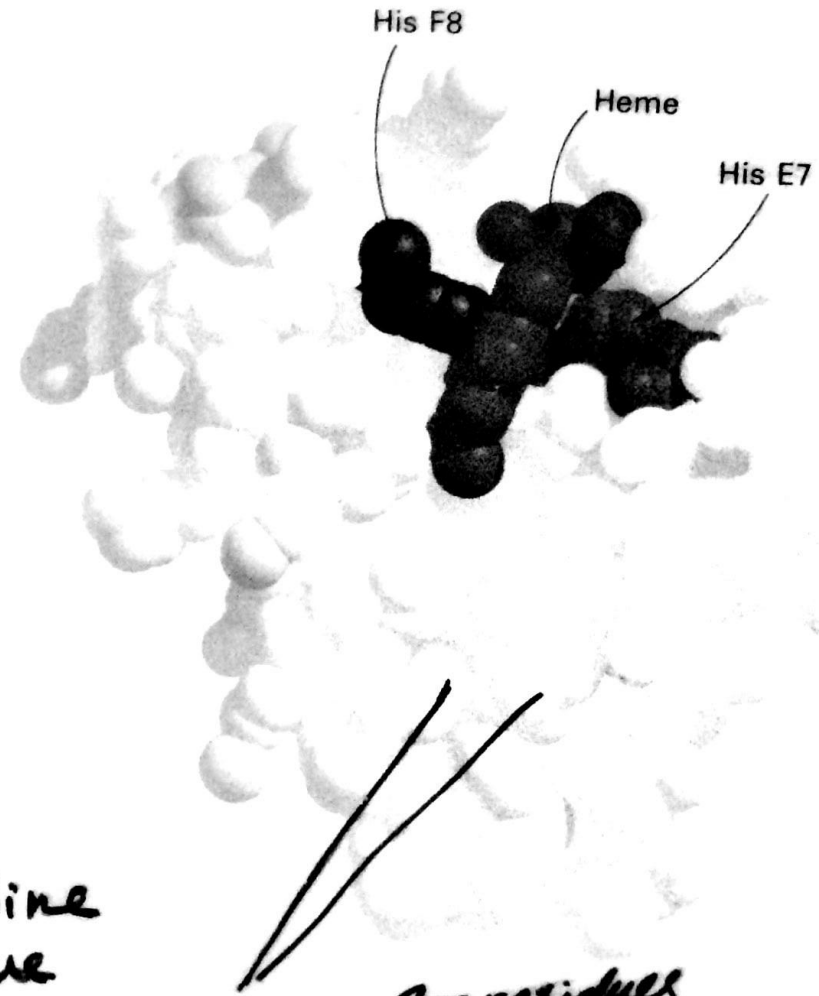
The heme pocket or crevice is lined with non-polar amino acids [except two His] which stabilize hydrophobic heme and permits reversible binding of O_2. Loss of electrons by Fe^{2+} is RARE.

Tertiary Structure Myoglobin, 'Mb' :-

- Mb. is compact 45 X 35 X 25 Å
- ~ 75% helical structure (8-helical segments)

153 a.a.



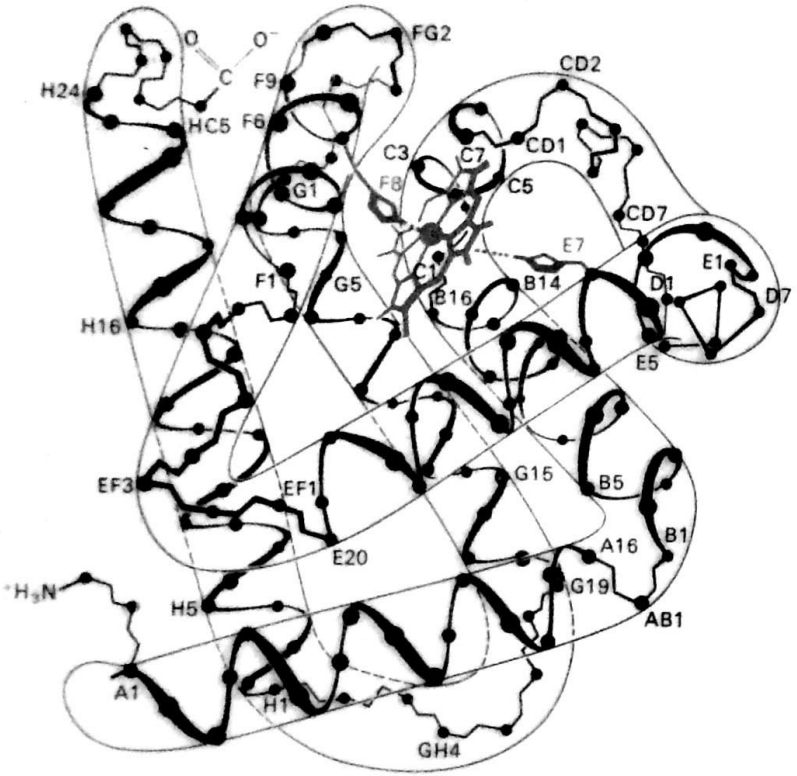


- 4 helices are terminated by proline
- Interior consist of hydrophobic residue except for prox. & dis. his

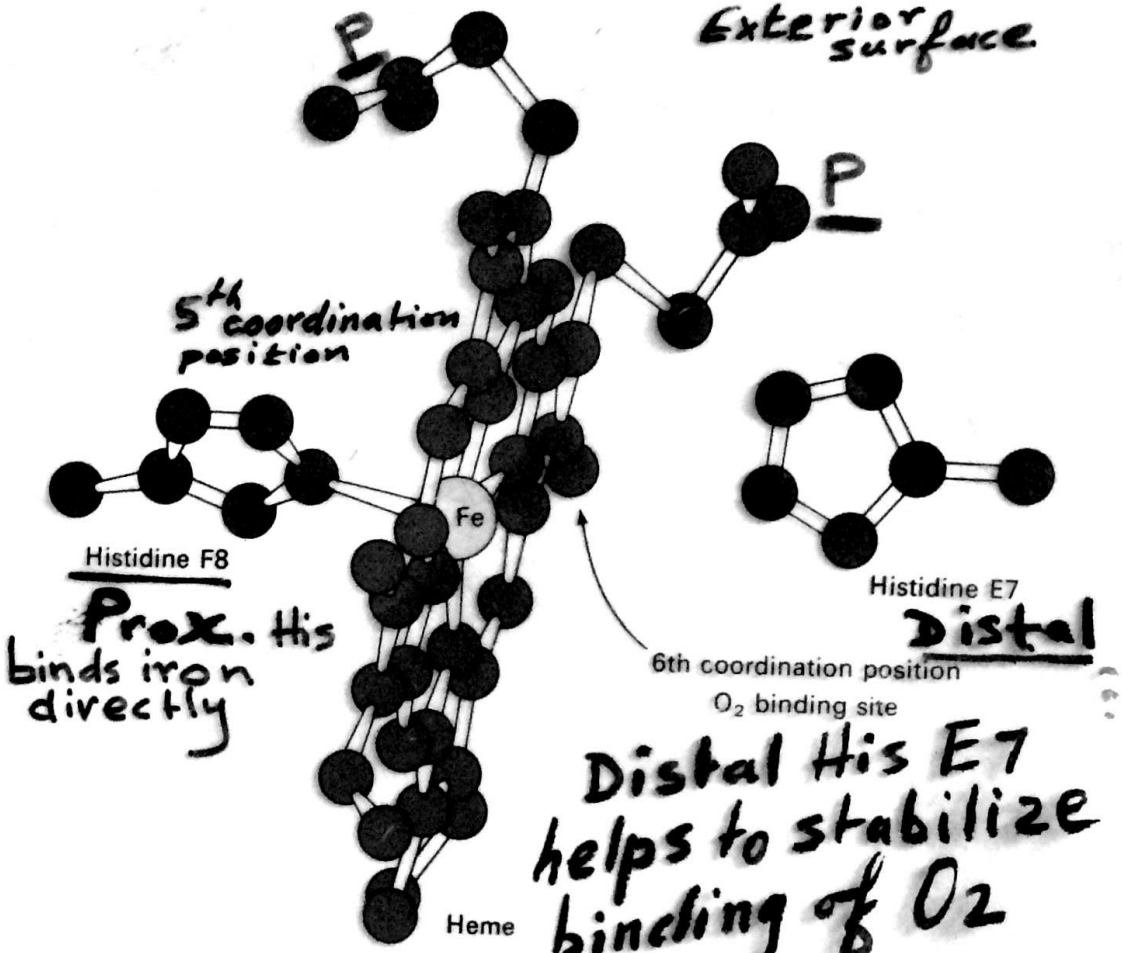
non-polar residues

Figure 7-4, page 149; Figure 7-6, page 150

The O_2-binding site



Tertiary structure



Distal His E7 helps to stabilize binding of O_2 to Ferrous Iron

Figures 7-5 and 7-8

Stryer: *Biochemistry*, Third Edition

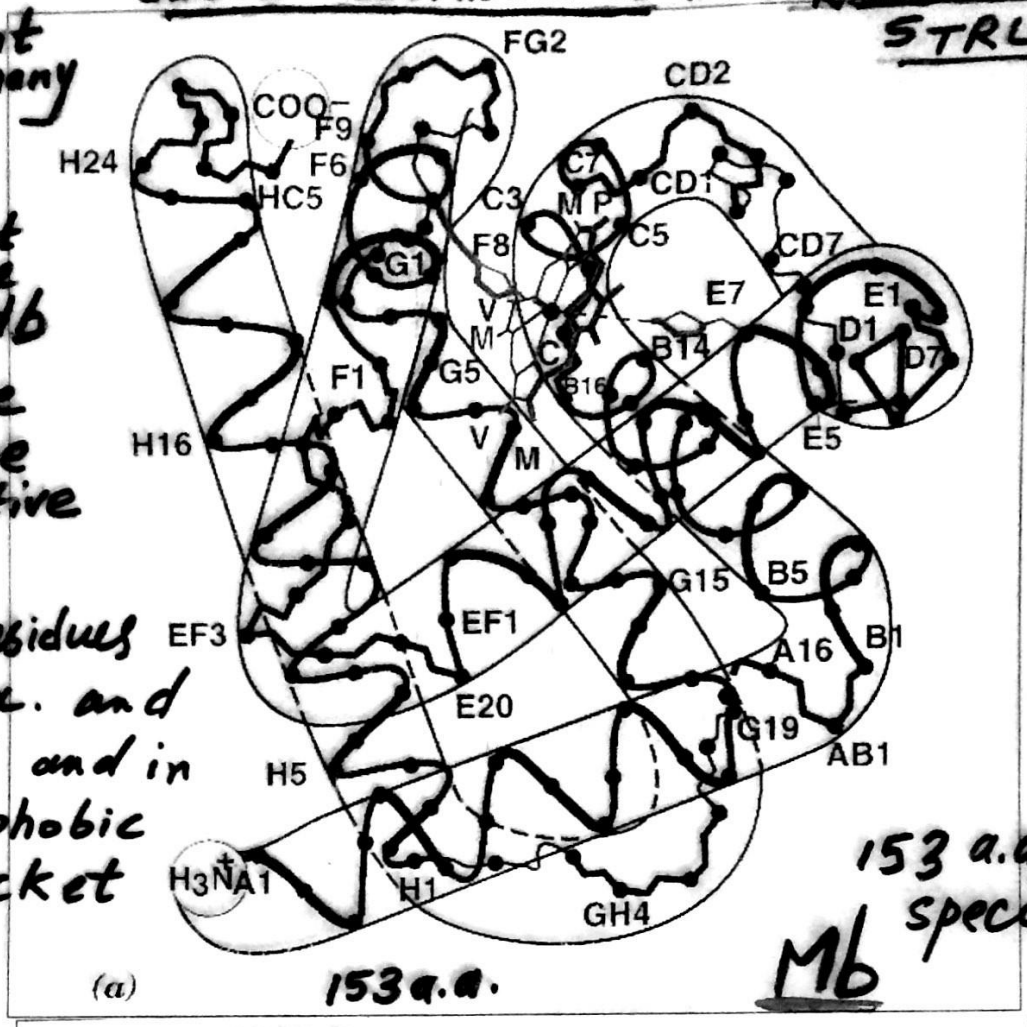
[redacted] W. H. Freeman and Company

7) The Pri, Sec. & Ter. Structures of Mb & Hb chains

CLOSE RESEMBLANCE in THREE-DIMENSIONAL STRUCTURE

- 83 Invariant residues in many Mb
- 15 invariant residues are similar to Hb
- Many of the changes are Conservative

Invariant residues include prox. and distal His and in the hydrophobic heme pocket



153 a.a. in all species

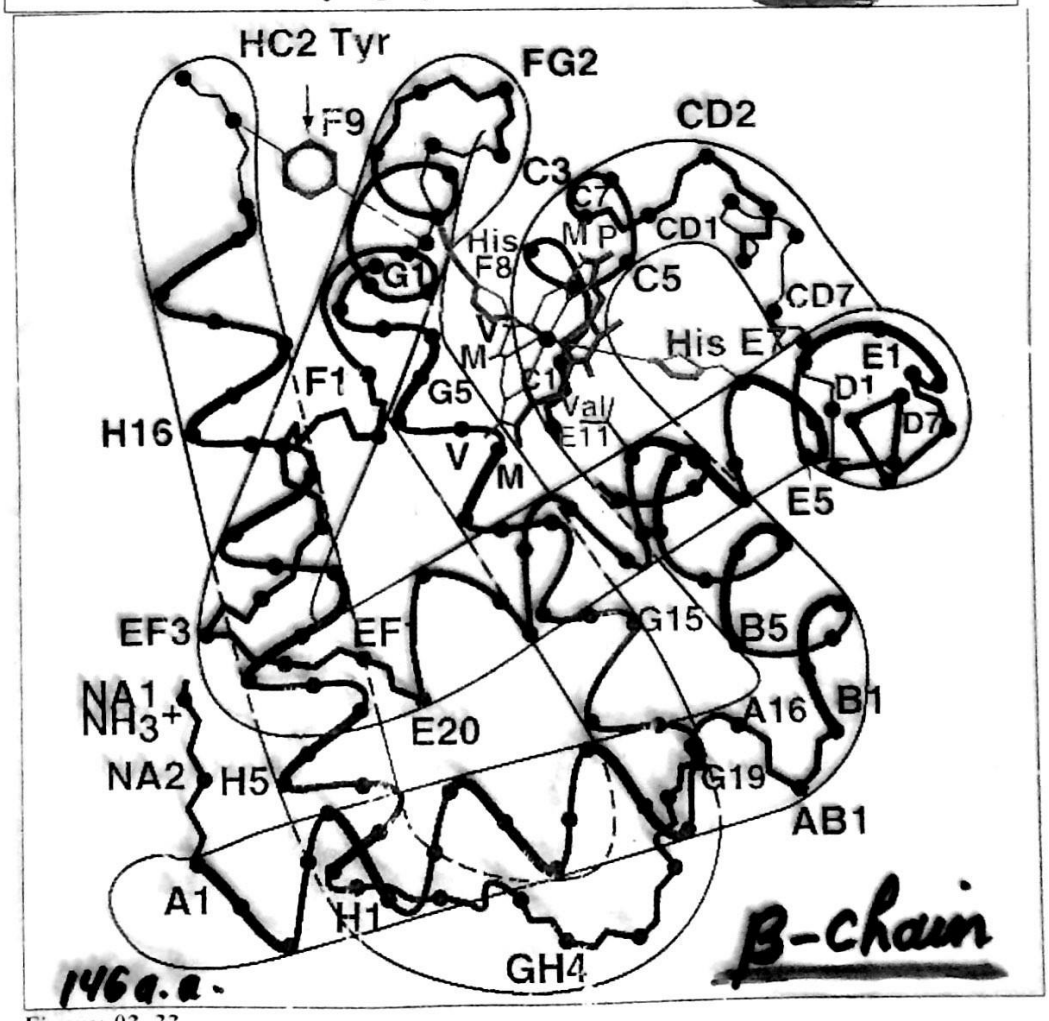
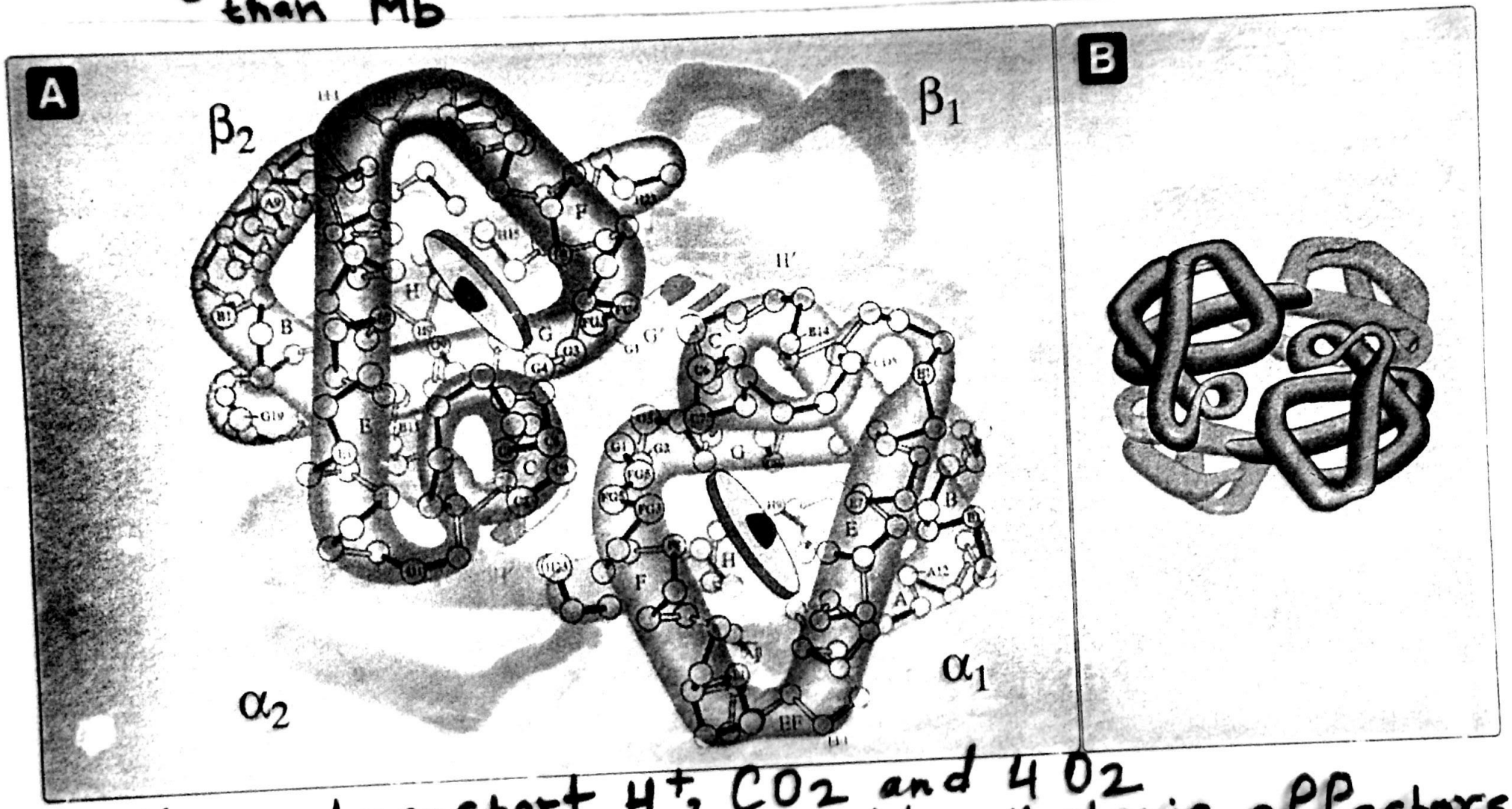


Figure: 03_33
Secondary and tertiary structure characteristics of chains of hemoglobin.

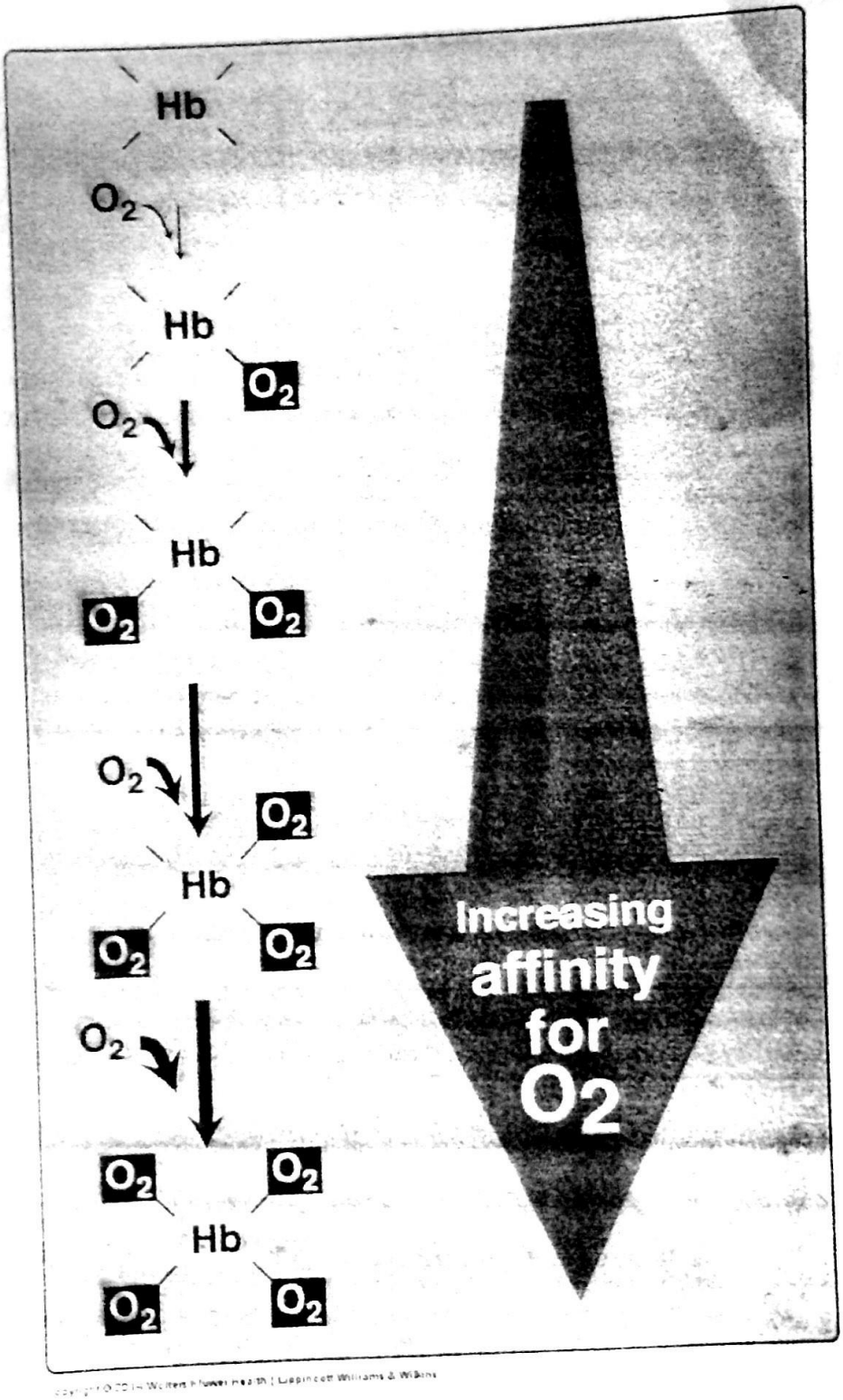
Quaternary Structure of Hb

structure and function of Hb tetramer is more complex than Mb

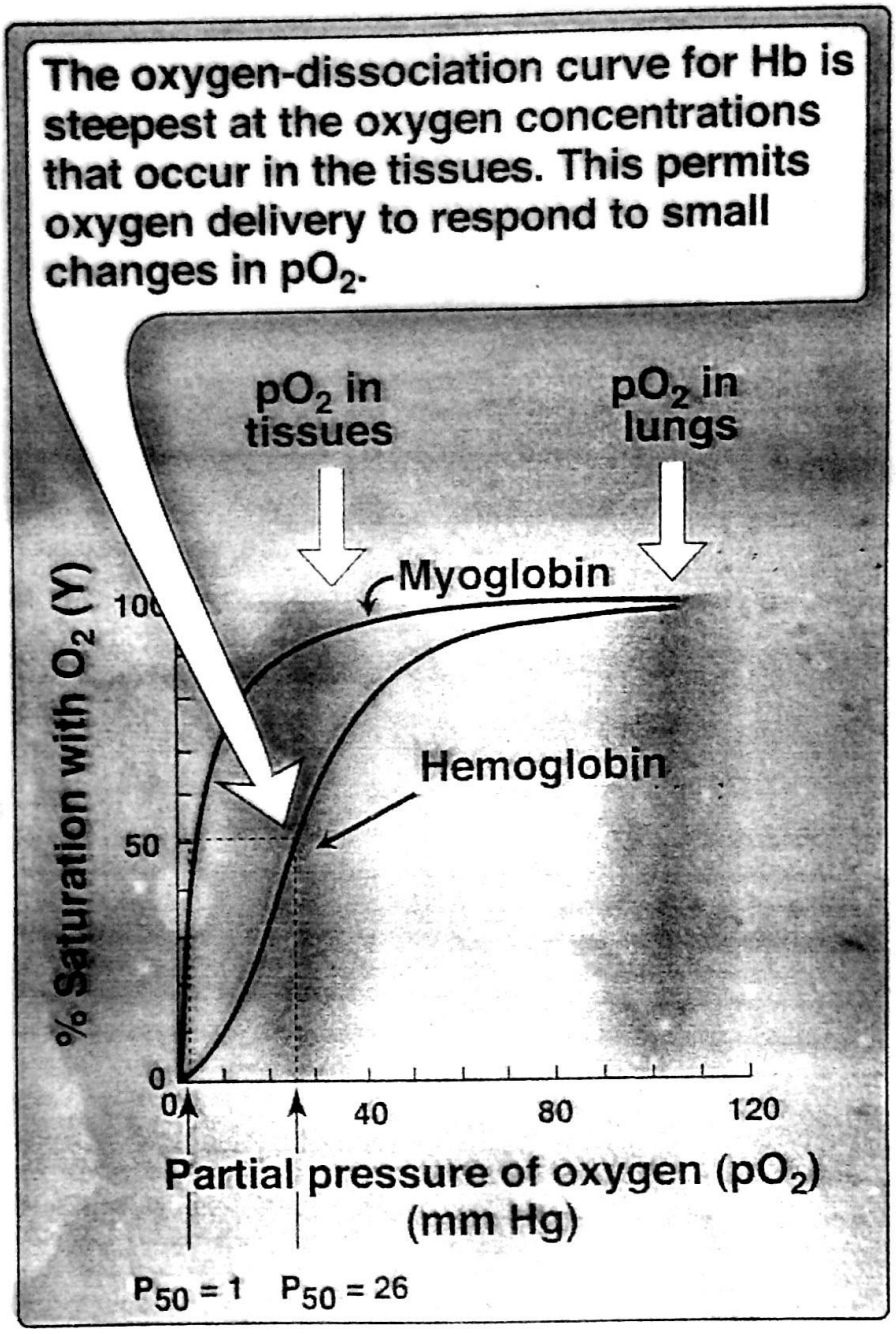


- Hb can transport H^+, CO_2 and 4 O_2
- O_2 binding to Hb is regulated by allosteric effectors while Mb is not

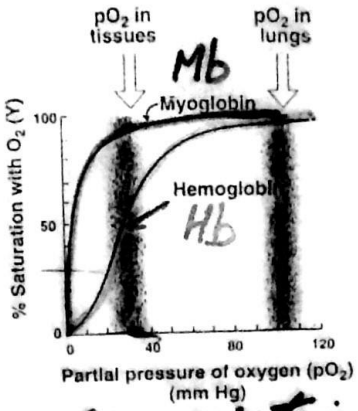
Hb binds successive O_2 molecules with increasing affinity



9a2



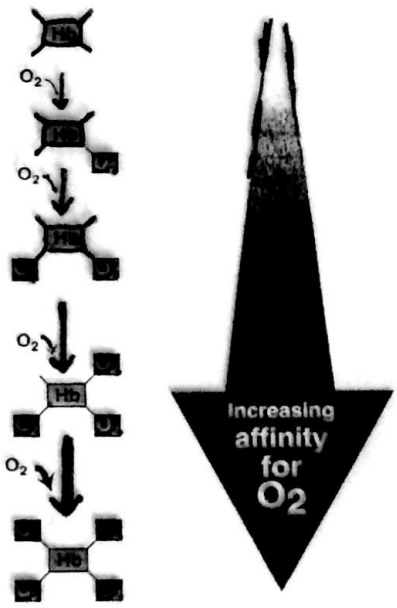
Binding of Oxygen to myoglobin and hemoglobin :-



P_{50} = Mb = 1
P_{50} = Hb = 26

- O_2 - dissociation curve for Hb & Mb
- steepest at $[O_2]$ in tissue which allow O_2 delivery to respond to small changes in pO_2

- O_2 binds cooperatively to Hemoglobin :-



Hb. binds O_2 with increasing affinity

Model for the transition from T to R [Concerted Model of Monod et al]

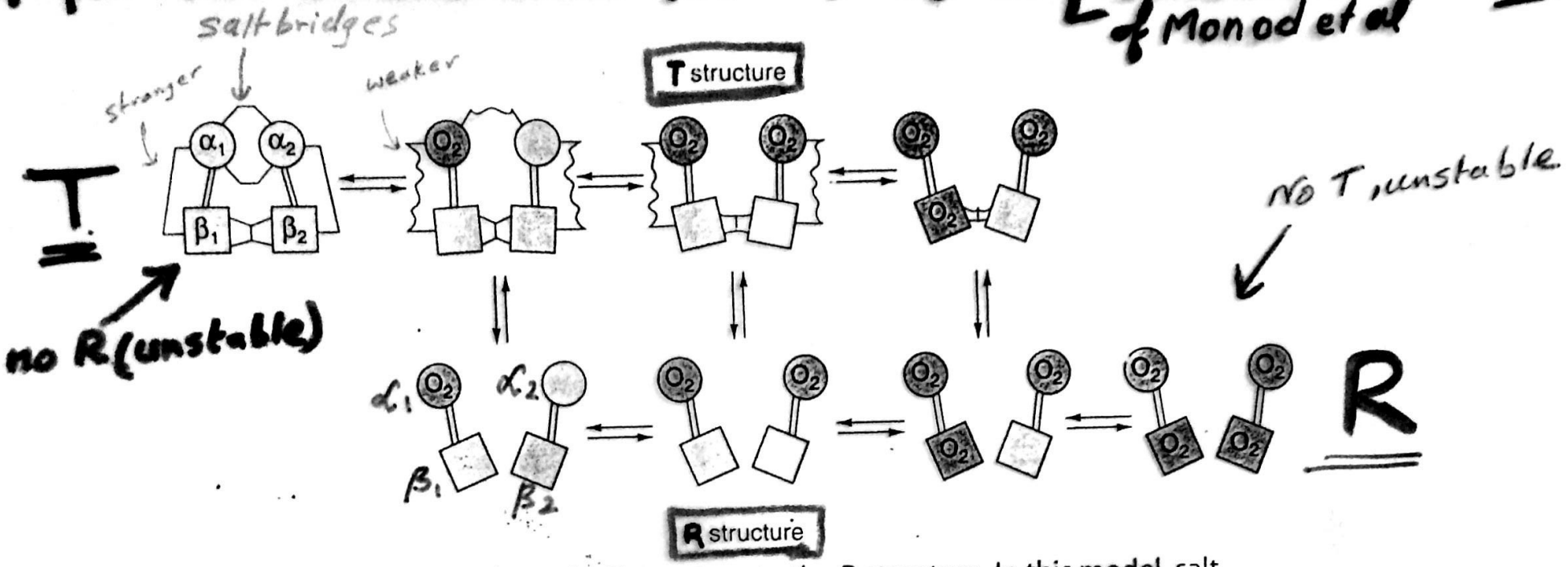
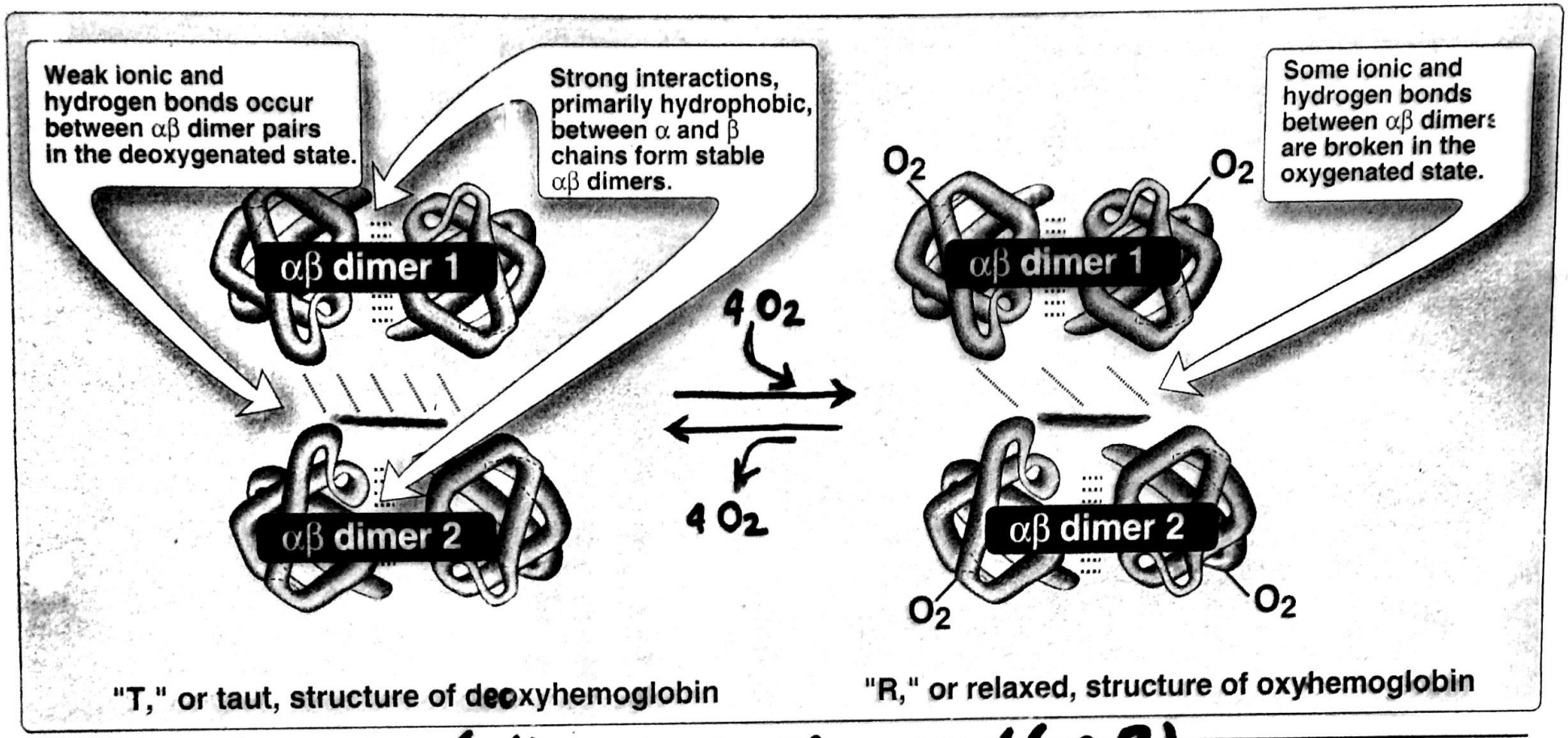


Figure 6–8. Transition from the T structure to the R structure. In this model, salt bridges (thin lines) linking the subunits in the T structure break progressively as oxygen is added, and even those salt bridges that have not yet ruptured are progressively weakened (wavy lines). The transition from T to R does not take place after a fixed number of oxygen molecules have been bound but becomes more probable as each successive oxygen binds. The transition between the two structures is influenced by protons, carbon dioxide, chloride, and BPG; the higher their concentration, the more oxygen must be bound to trigger the transition. Fully oxygenated molecules in the T structure and fully deoxygenated molecules in the R structure are not shown because they are unstable. (Modified and redrawn, with permission, from Perutz MF: Hemoglobin structure and respiratory transport. Sci Am [Dec] [redacted];239:92.)

Transitional or Conformational Change Upon Oxygenation



- Two identical dimers $(\alpha\beta)_1$ and $(\alpha\beta)_2$
- The two polypeptides in each are held mainly by hydrophobic interactions
  - → hydrophobic a.a. in interior and on a certain region on surface → strong hydrophobic interaction between α and β in dimer
  - → The two dimers are held by Polar bonds. Weaker polar interaction allow movement of dimers

The O_2-binding Curve for Hb and Mb

1 KPa = 7.5 torr (mm Hg)

KPa ≡ Kilopascal

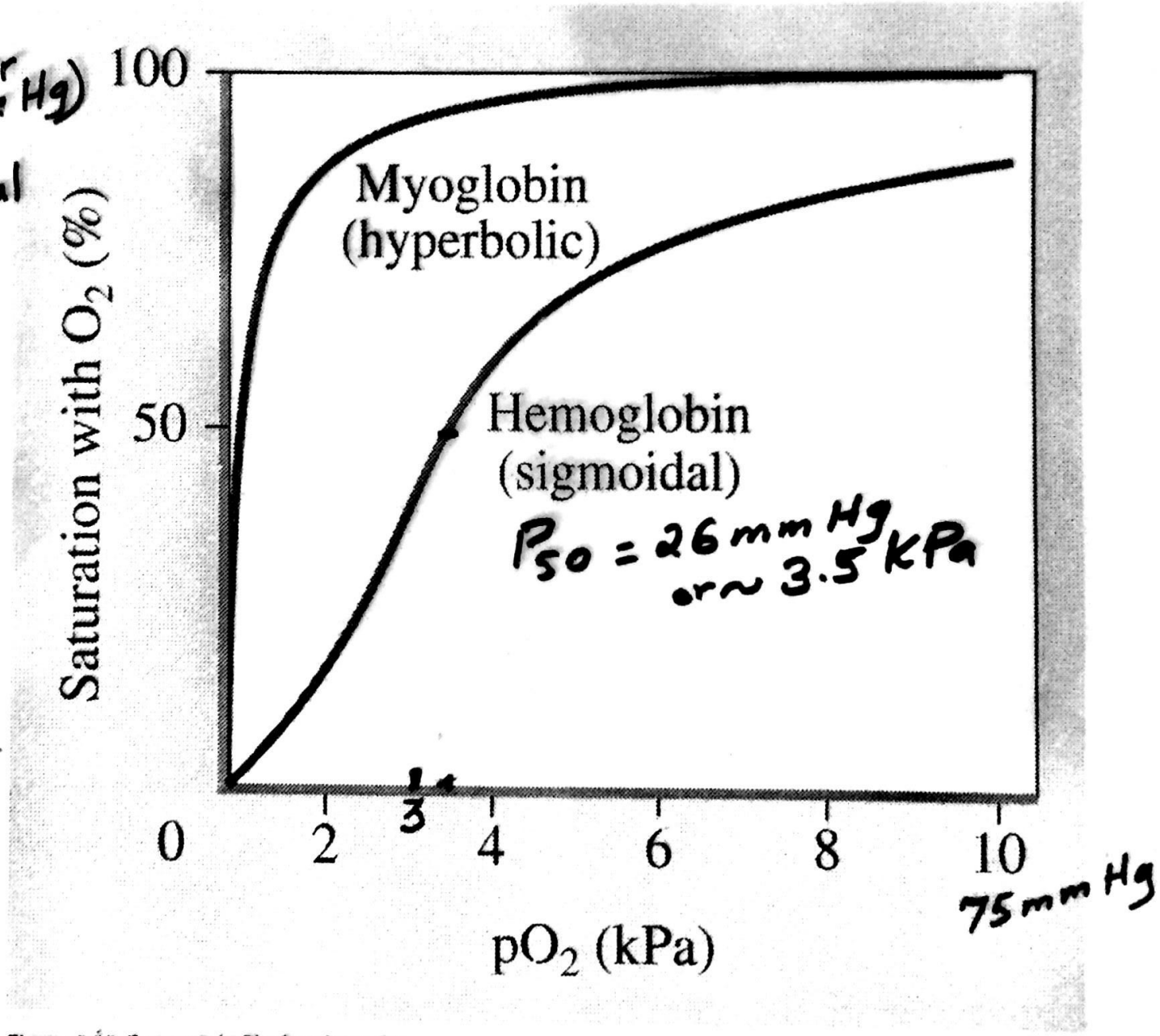


Figure 4-19 Concepts in Biochemistry, 3/e