Derivatives of Hemoglobin

- Normal Derivatives
  - Oxy Hb
  - Deoxy Hb
  - Carbamino Hb
- Abnormal Derivatives
  - Met Hb
  - Sulpha Hb
  - Carboxy Hb (HbCO)

Met Hb

normal level < 1%

Types

1. Inherited
2. Acquired
   - Certain drugs
   - chemicals
   - ox. agents in food

Inherited Methemoglobinemia :-

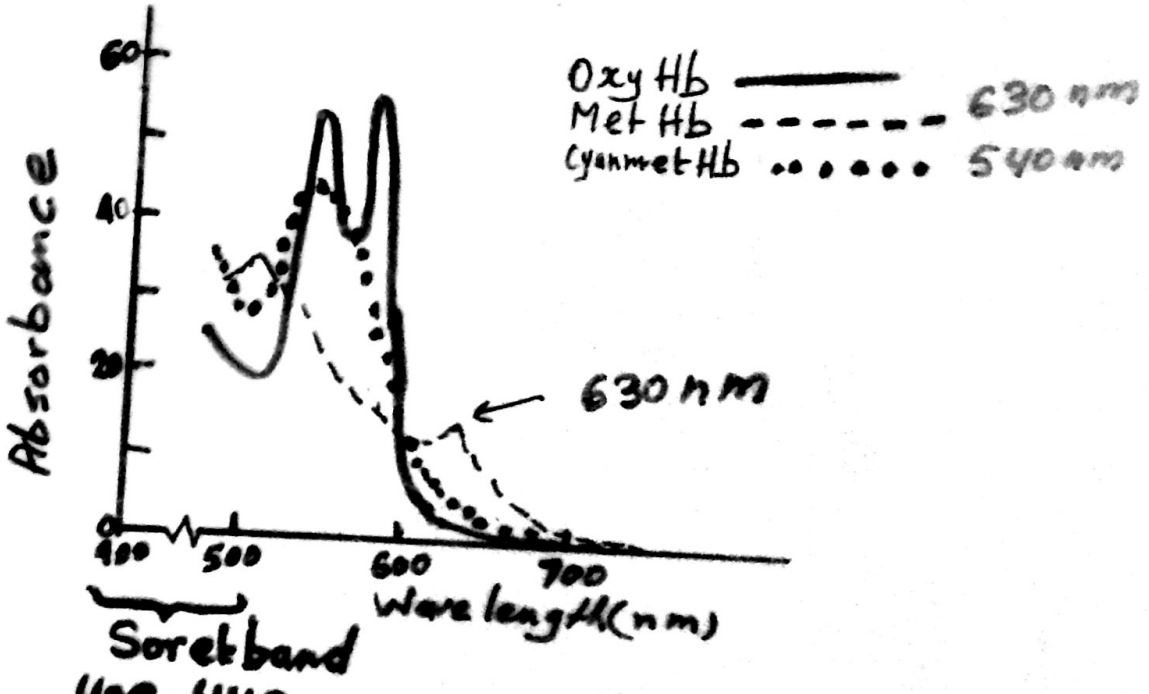
- Deficient MetHb reductase
  NADH-Cytb5 reductase
- Hemoglobinopathies Hb M
  replacement of proximal His by tyr → Hb M

Symptoms

Cyanosis :- bluish discoloration of the skin and mucous membrane

Diagnostic test

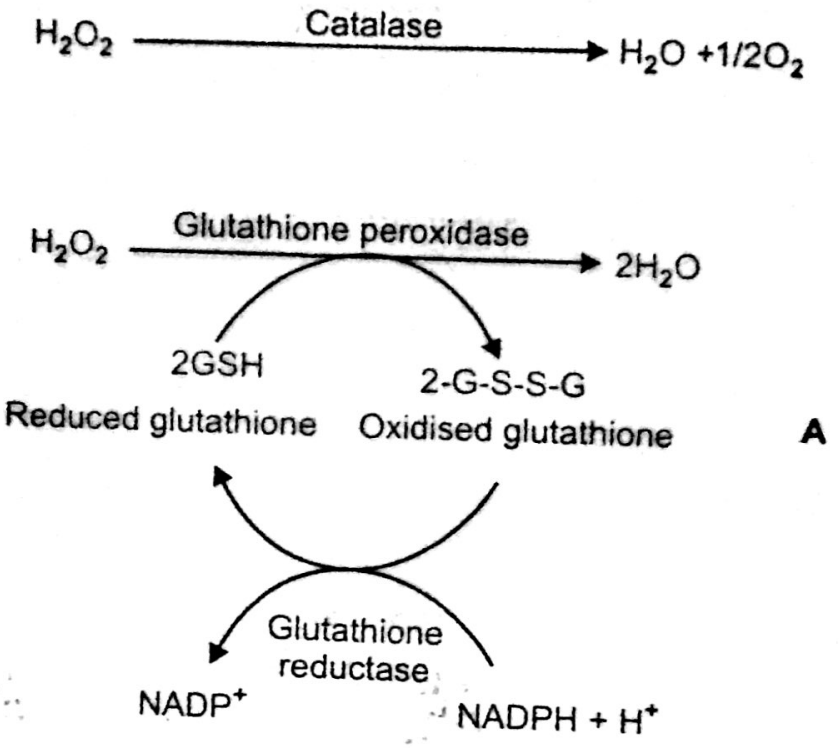
Spectroscopic analysis at 630nm



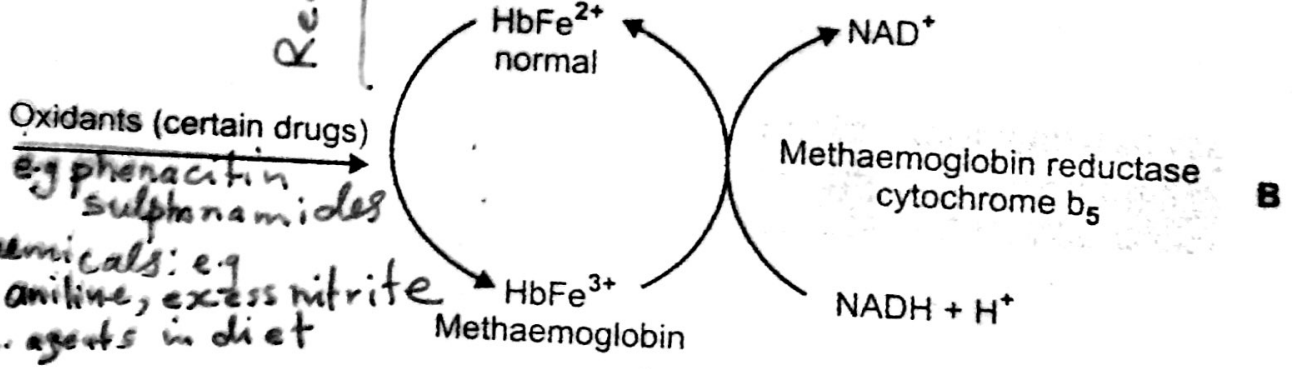
Treatment :- Reducing Agents → Methylene blue, Ascorbic acid

$2O_2^{\cdot-} \xrightarrow[+2H^+]{SOD} H_2O_2 + O_2$

Removal of oxidants



Reduction of Fe



Figures 8.17A and B: Erythrocyte mechanisms for detoxification of methaemoglobin

Sulphahemoglobin

produced by the same substances that cause MetHb, but in presence of sulphur containing compd. e.g H_2S

- SulphaHb & MetHb often present together
- Can not act as O_2 carrier
- Can not be reversed back

CarboxyHb

Affinity 210 > than for O_2

1% of CO in inspired air — fatal in mins.

1% of CO Hb in non-smoker

10% or more CO Hb in smokers

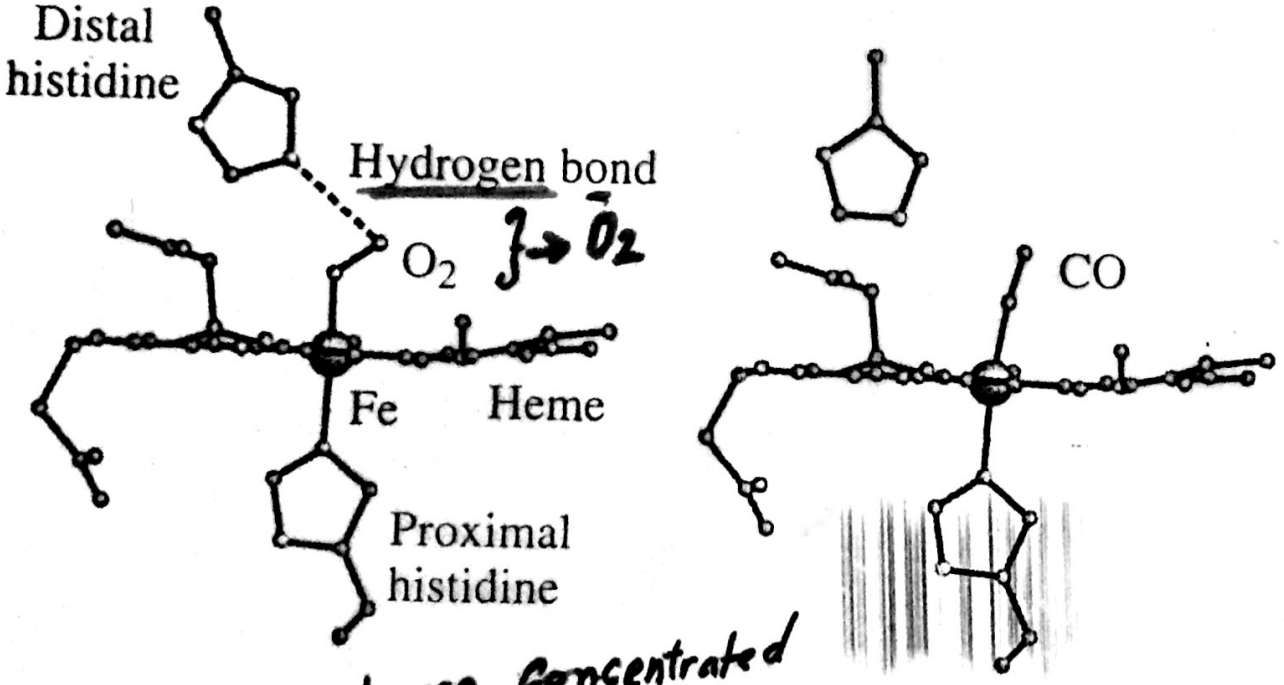
>40% COHb → unconsciousness and fatal

O_2 & CO binding to Hb & Mb

In free heme CO binds 20,000 > O_2

in Mb " " 25 times > O_2

in Hb " " 200 " " "



$\bar{O}_2$, negative charge concentrated on terminal oxygen bound to distal His.

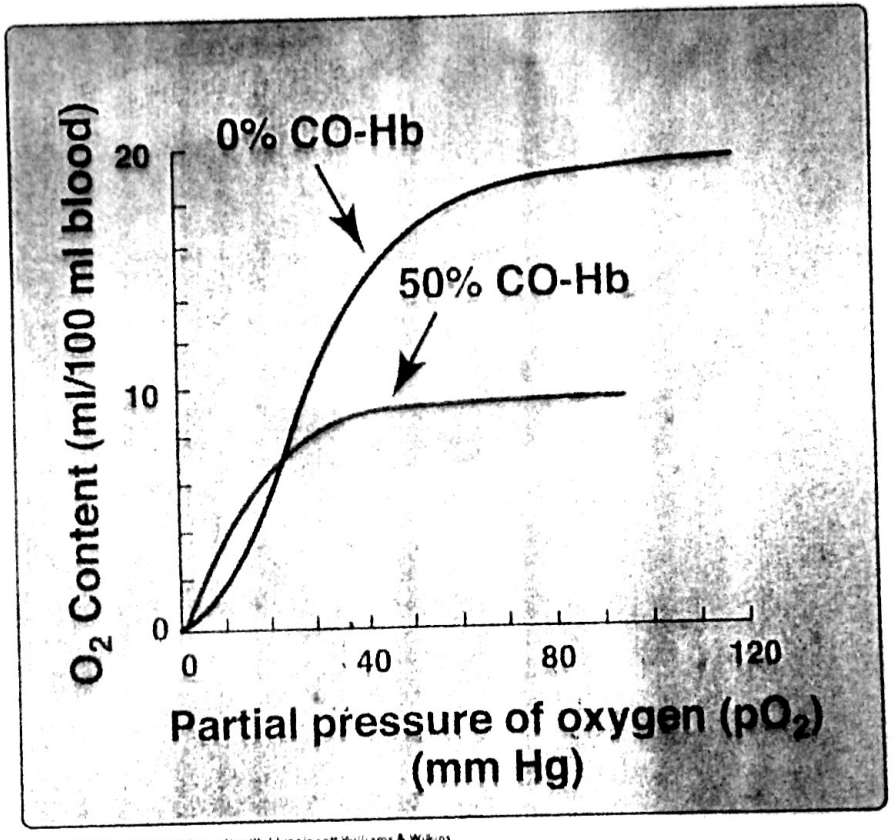
H-bond of O_2 with distal His further stabilize oxygen

Replacement of distal His by non-polar atom decreases affinity of modified heme by 100-fold

Binding of CO

CO binds tightly but reversibly to Hb
CO binding shifts Hb to the R state – remaining sites bind O_2 with high affinity

Binding of NO



CO binding is diminished by distal His

- The function of prosthetic group is modulated by its polypeptide environment
  - Hb & presence of distal His
  - Cyt.C
  - Catalase

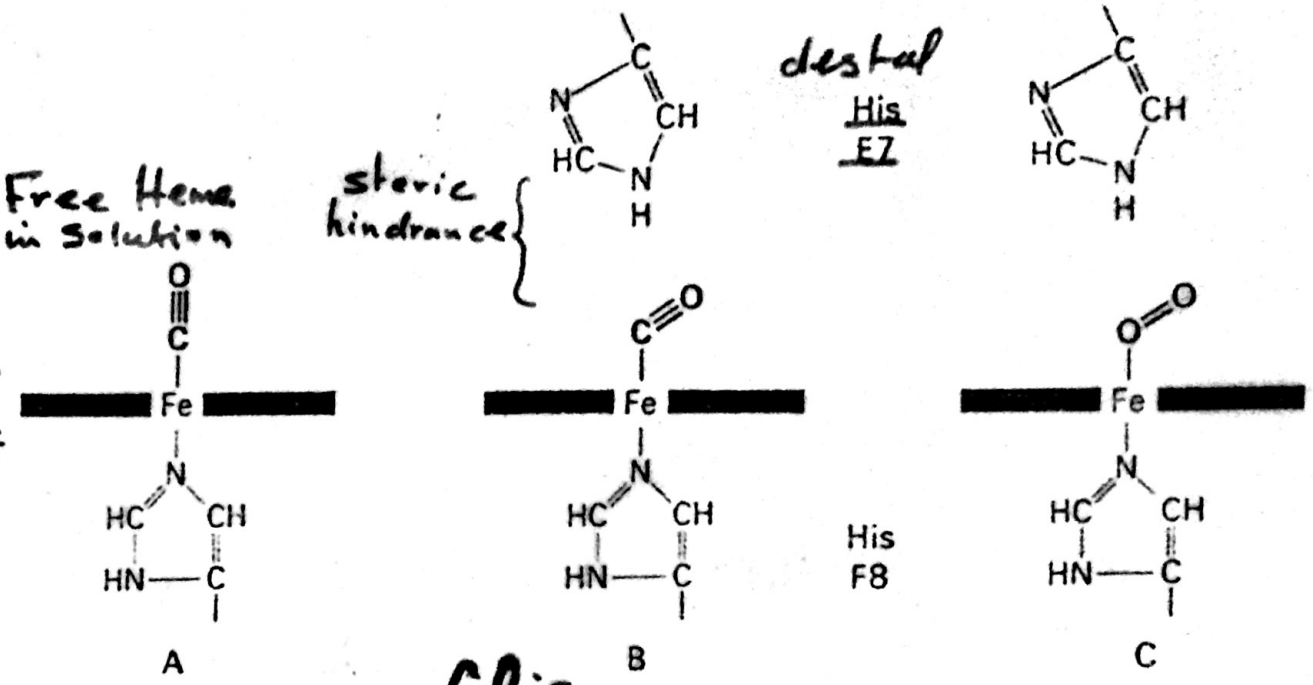


Figure 7-13
Structural basis of the diminished affinity of myoglobin and hemoglobin for carbon monoxide: (A) linear mode of binding of CO to isolated iron porphyrins; (B) bent mode of binding of CO to myoglobin and hemoglobin, in which the distal histidine (E7) prevents CO from binding linearly and so the affinity for CO is markedly reduced; (C) bent mode of binding of O_2 in myoglobin and hemoglobin. Isolated iron porphyrins also bind O_2 in a bent mode.

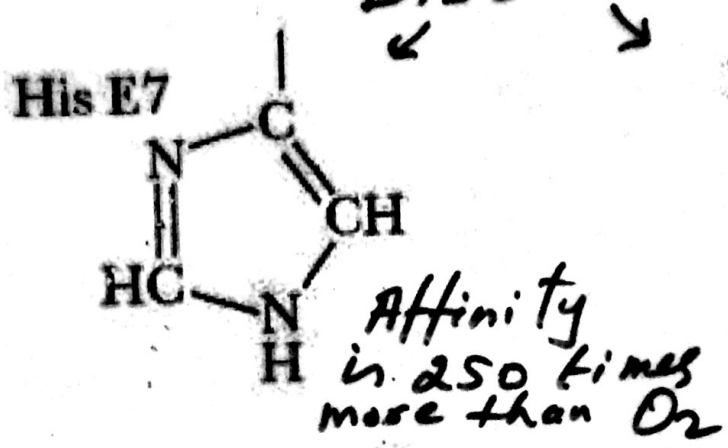
CO affinity is 25000 times > O_2 for free heme in solution

CO:- 200 times more affinity than O_2 for Hb
425 times more than Mb

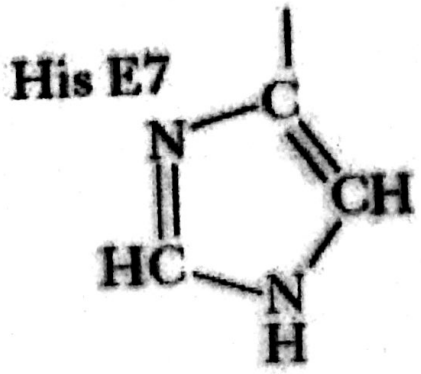
CO and O_2 binding

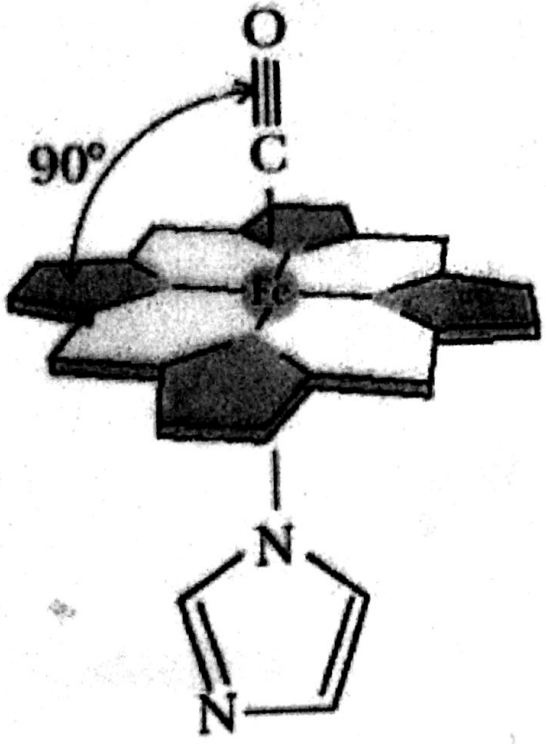
Affinity for CO is 25,000 more than O_2

Distal His

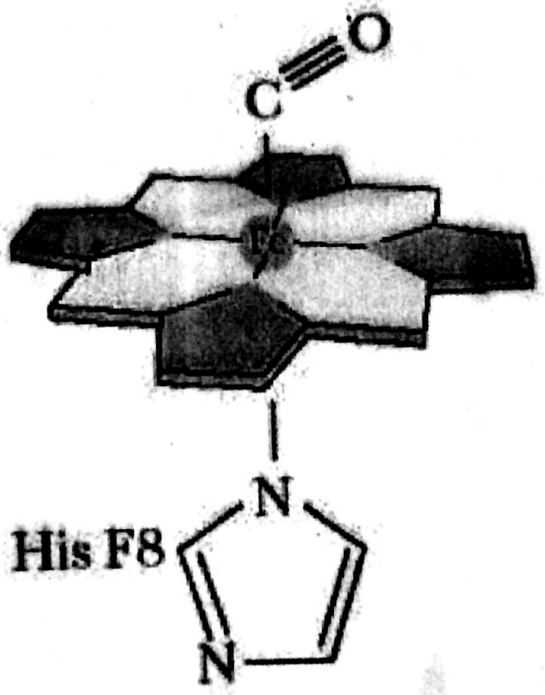


Affinity is 250 times more than O_2

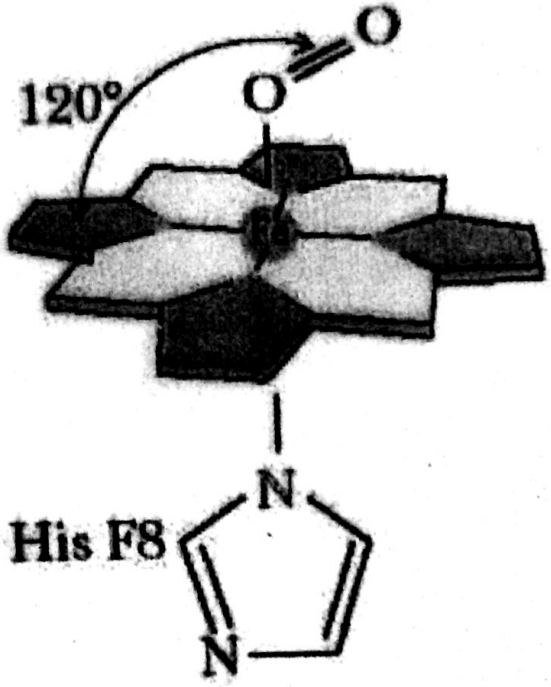




(a) Free heme with imidazole

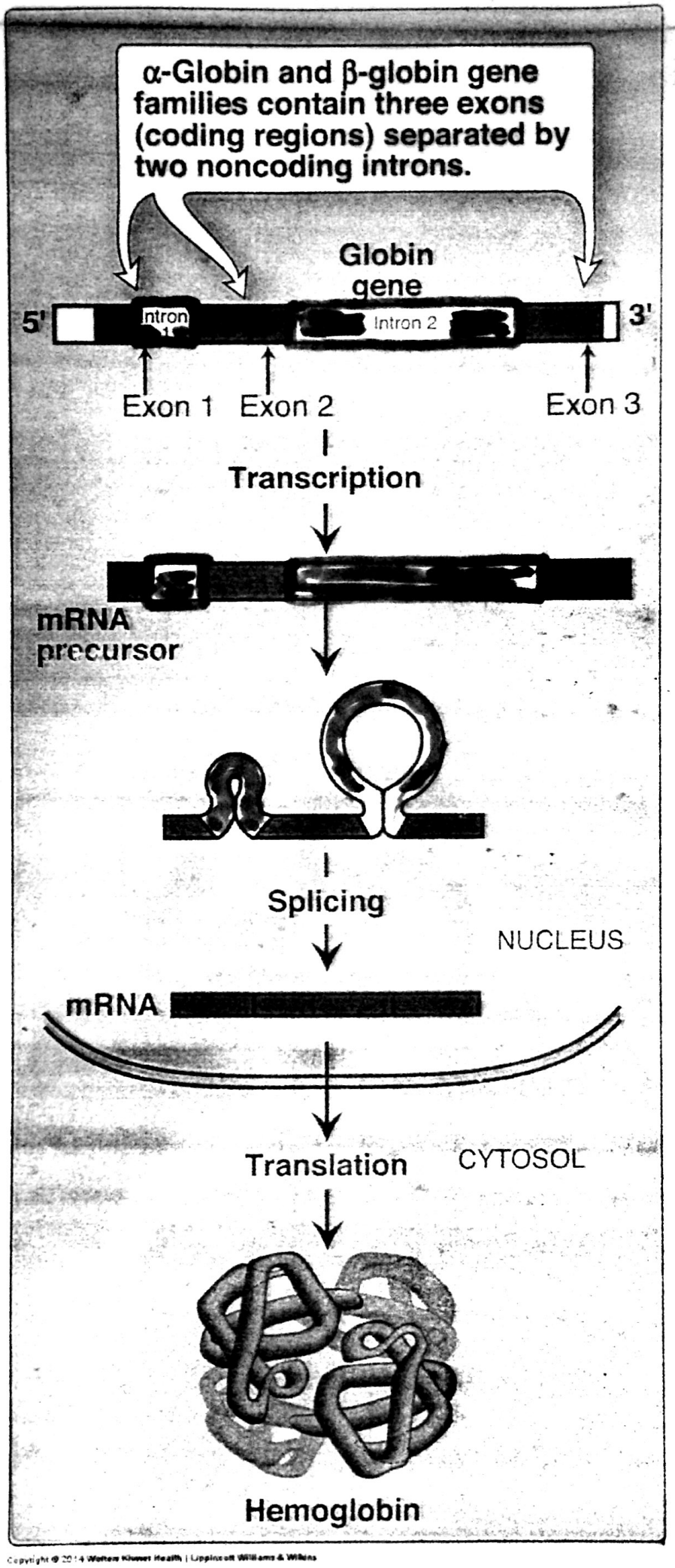


(b) Mb:CO complex



(c) Oxymyoglobin

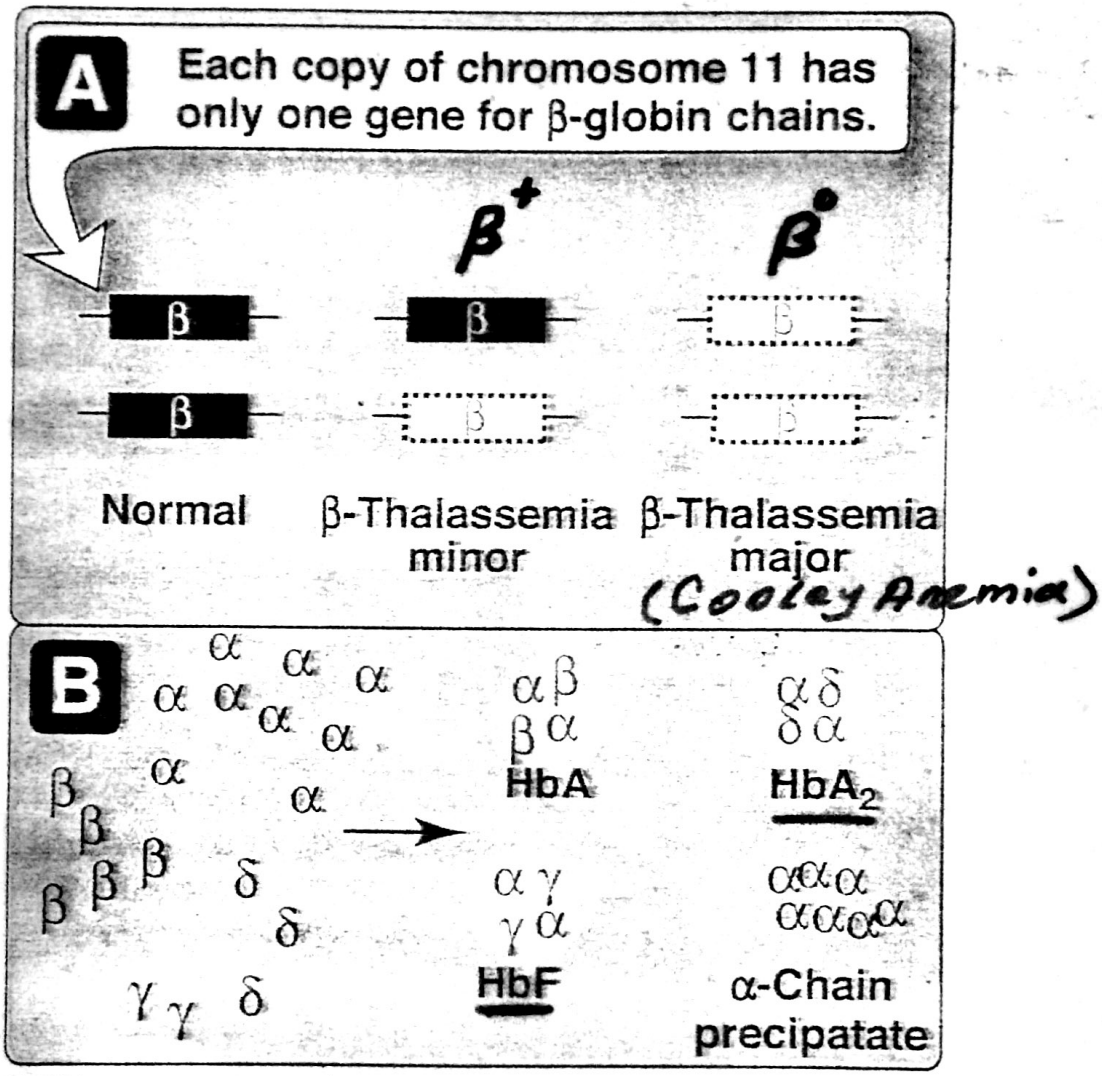
Globin Chains Synthesis



THALASSEMIA

- Decreased Synthesis of α- or β-
  - → Globin chain precipitate
  - → Hemolysis
  - → Hypochromic anemia

β-thalassemia



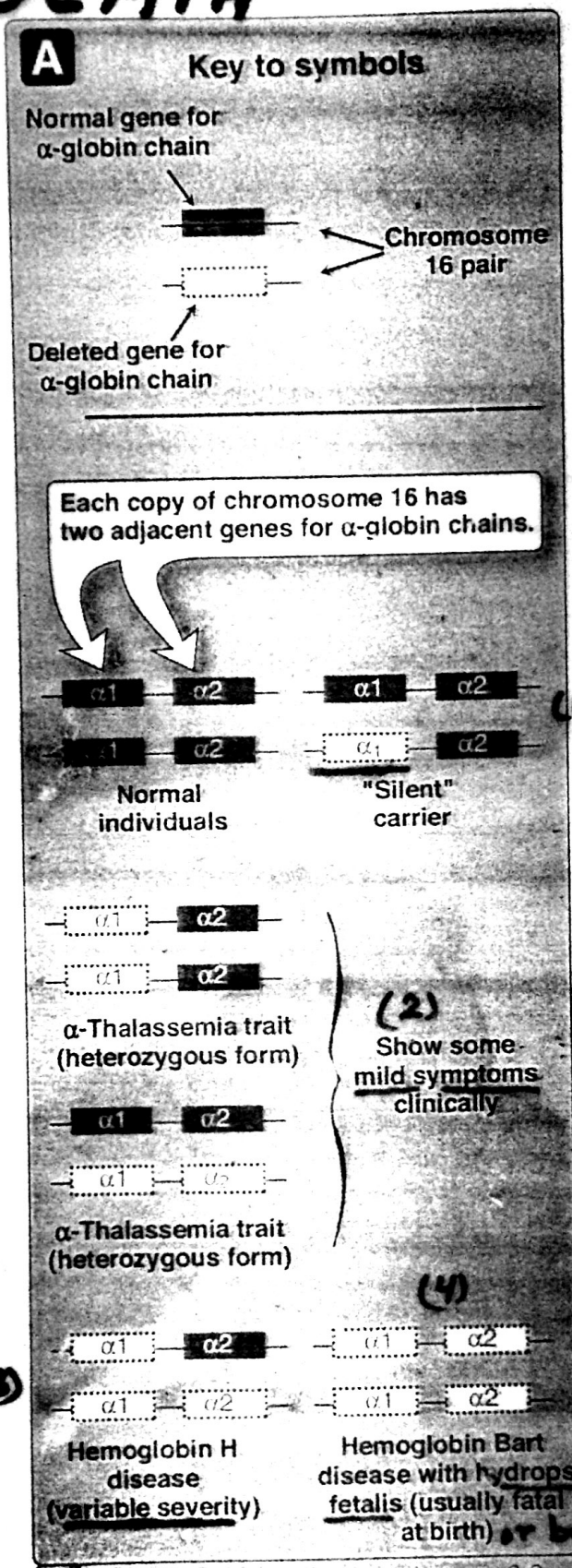
$Hb\,A_2 \uparrow$; $HbF \uparrow$

α chains ⟶ α_4 (Cooley's Hb)

- → α_4 precipitates
- → Heinz bodies
- ⟶ Cell membrane damage → Premature death of erythrocyte

Manifestation of β-thalassemia appears only after birth (because of HbF); becomes severly anemic during the 1st or 2nd year of life.

α-THALASSEMIA



= total loss of α-chain or before

HbH ↑
Hb Bart ↑

Soluble Hb but without sigmoidal kinetics. Useless O_2 deliverer to tissues.

Primary Causes:

α- thalassemia :-
gene deletion

β- thalassemia :-
- Point mutation in the Promotor
- mutation in the translational initiation codon
- point mutation in the Poly-adenylation signal
- mutations → splicing abnormalities

- HbE $\beta^{26 Glu-lys}$
  structural and quantity abnormality
  60% of β-globin is made

- Hereditary persistance of fetal Hb (HPFH)
  → continue to make HbF in adult
  → Benign